A Pilot Open Study of Long Term High Dose Creatine Augmentation in Patients with Treatment Resistant Negative Symptoms Schizophrenia

Uri Levental, MD, Yuly Bersudsky, MD, Tzvi Dwalatzky, MD, Vladimir Lerner, MD, Sophie Medina, MA, and Joseph Levine, MD

Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheva, Israel

ABSTRACT

Background: The effects of creatine on brain metabolism and the potential cognitive enhancing properties of this compound raise the possibility of developing a new augmentation therapeutic strategy in schizophrenia especially in patients demonstrating negative and cognitive symptomatology.

Methods: Seven inpatients with chronic schizophrenia presenting with treatment resistant negative symptoms were enrolled into exploratory treatment study with creatine monohydrate augmentation at a daily high-dose of 10 grams, administered for 6 months. Several clinical rating scales and a computerized cognitive assessment battery were applied.

Results: Creatine treatment mildly improved the schizophrenia symptomatology but there were no significant changes in cognitive functions. Several ward behaviors were also improved. Tardive parkinsonism improved numerically by above 40% in 4 out of 6 patients.

Conclusion: This small, open design study of high dose creatine add-on for 6 months in chronic inpatients with schizophrenia demonstrated only mild positive effects on the patients' symptomatology and behavior and might have beneficial effect on tardive parkinsonism.

Sources of financial and material support: NARSAD Independent Investigator Award Grant for Joseph Levine

INTRODUCTION

Creatine is a substrate of creatine kinase and serves as a temporal and spatial buffer for cytosolic and mitochondrial pools of the cellular energy currency adenosine triphosphate. As such it plays a pivotal role in brain energy homeostasis. Creatine also demonstrates neuroprotective qualities in a variety of experimental models (1-6). Creatine enters the brain via a specialized sodium dependent transporter leading to a significant increase in concentration of creatine and phosphocreatine across brain region (7, 8).

Imaging studies – not using creatine as an internal reference (9) – suggest the possible involvement of altered creatine/phosphocreatine/creatine kinase energy metabolism in the pathophysiology of schizophrenia. Thus, Burbaeva et al. (10) reported a drastic drop of creatine kinase (CK, the enzyme converting creatine to phosphocreatine) activity and CK BB immunoreactivity in all the examined brain areas in schizophrenic patients compared to controls. Jayakumar et al. (11) in examining the volumetric and metabolic correlates of the caudate nucleus in antipsychotic-naïve patients with schizophrenia compared with healthy controls, showed that phosphocreatine (PCr)/total phosphorous and PCr/total adenosine tri-phosphate ratios of both caudate nuclei were significantly lower in patients compared with controls. A significant negative correlation was found between the left caudate volume and left PCr/total phosphorus ratio in the patients. Chang et al. (12) studied elderly schizophrenic patients and controls for neurometabolite concentrations in several white matter regions. Interactions between age and schizophrenia on total creatine were observed and only participants with schizophrenia showed an age-related creatine decrease in the right frontal region.

Address for Correspondence: ✉ Dr. Joseph Levine, Beersheva Mental Health Center, POB 4600, Beersheva, Israel yossilevine@gmail.com

These findings may suggest a decreased activity of the brain creatine/phosphocreatine/creatine kinase energy metabolism system in schizophrenia. However, there are also reports of an increase of creatine/phosphocreatine concentrations in certain brain areas in this disorder, possibly suggesting abnormal local cell-energy demands. Thus, O'Neill et al. (13) using proton magnetic resonance spectroscopic imaging showed that in children and adolescents with schizophrenia, creatine was 14% higher in the superior anterior cingulate region than in controls. Lutkenhoff et al. (14) reported that in the medial prefrontal gray matter, creatine plus phosphocreatine (Cr+PCr), did not differ significantly between patients with schizophrenia, their unaffected co-twins or healthy controls whereas in the left hippocampus, Cr+PCr was higher in schizophrenic patients compared both to controls and to their unaffected co-twins. Wood et al. (15) in assessing patients with a first episode of psychosis reported significant elevations of creatine/phosphocreatine (Cr/PCr) in the medial temporal lobe bilaterally in the treated group compared to controls, perhaps suggesting that these are treatment-related changes. The authors also note that seemingly illness-related Cr/PCr elevations were also specific to the diagnosis of schizophrenia-spectrum disorder.

These findings of altered creatine/phosphocreatine/creatine kinase energy metabolism in schizophrenia are corroborated by the reports of Volz et al. (16) who demonstrated reduced ATP in the frontal and left temporal lobe of schizophrenic patients. There are also reports of alterations in metabolic rates in a variety of brain regions, including the frontal lobes (hypofrontality), temporal lobes, the thalamus and the basal ganglia, suggesting an impairment in fronto-striatal-thalamic circuitry in schizophrenia (17). These findings of either a decrease in the activity of creatine/phosphocreatine/creatine kinase energy metabolism, or abnormal local cell-energy demands in schizophrenia raise the possibility of developing a treatment strategy by enhancing brain energy metabolism in schizophrenia.

A previous double-blind cross-over treatment study from our research group (18), comparing the effects of 3 months of creatine at a dose of 5 grams daily compared to placebo in schizophrenia failed to detect efficacy in treating symptoms, including negative symptoms and cognition, but supported the need for further research. Reported side effects of creatine treatment were few, and included mild transient nausea and vomiting.

An initial placebo-controlled clinical trial in patients with Huntington's disease – another brain disorder associated with psychotic symptomatology – in which creatine was administered in a similar dose (namely 5 grams daily) for 1 year failed to detect significant effects (19). However, later studies in this disorder using higher doses of creatine showed beneficial brain biochemical changes including the lowering of glutamate levels (20) as well as that of serum 8-hydroxy-2'-deoxyguanosine levels – the latter suggested to reflect oxidative injury to DNA (21). Moreover, creatine at a high dose of 10 g daily administered for longer periods of time, such as 12 months (22) and 24 months (23) was associated with the stabilization of neuropsychiatric function. Thus, this raises the possibility that higher doses (i.e., 10 grams daily) administered for periods longer than 3 months, may show beneficial effects in augmentation strategies in schizophrenia. A dose of creatine 10 grams daily was reported to be safe and to be associated with few side effects (22-24).

We thus conducted an exploratory pilot observational study to evaluate the effect of a daily high dose of 10 grams of creatine as augmentation strategy to ongoing psychotropic treatment administered for 6 months on the illness-related symptomatology of inpatients with schizophrenia showing treatment resistant negative symptoms. Since creatine was previously reported to exert beneficial effects on cognition (25-27) and perhaps on extrapyramidal symptomatology (24), we also assessed these parameters.

METHODS

This study, approved by the local Helsinki (IRB) committee, is a small open 6 months long clinical trial examining the effect of creatine monohydrate added to ongoing psychotropic treatment for inpatients with schizophrenia – demonstrating a lack of response of their negative symptoms to at least 2 antipsychotic psychotropic treatments, each administered for at least 6 weeks. We defined these as patients with "treatment resistant negative symptoms" rather than patients with "treatment resistant schizophrenia."

Creatine monohydrate was purchased from Solgar Ltd., Israel, where 1 tablet contains 1 gram.

Inclusion criteria were: Sex: male or female; Age: 18-65 years old; Diagnosis: primary diagnosis of schizophrenia according to DSM-IV-TR; a history of at least 2 previous years with predominant negative symptoms and at least 3 negative items of the Positive and Negative Symptoms Scale (PANSS), with a score equal to or above 4 points each at baseline; no change in the patients' clinical status for at least 6 months prior to study entry.

We examined each one of the candidate patients as to their understanding following repeated detailed explanations in plain language of four components related to their

ability to sign informed consent: a. general understanding of the study design, the fact that there will be questionnaires and scales to fill, the expected benefits from creatine add-on, the expected possible side effects and risks involved in this treatment; b. the patient's understanding that he or she is influenced by a mental illness; c. the patients' ability to consider alternative modes of treatment each with its advantages and disadvantages; d. the patients' ability to utter his decision as to his participation in the study verbally without any fear or hesitation. Only patients who fulfilled these 4 components and agreed to sign an informed consent were recruited into the study.

Exclusion criteria were: pregnant or lactating female patients; patients with clinically significant or unstable medical conditions, epilepsy, or a history of alcohol or substance abuse in the last 6 months prior to study entry; a history of liver or kidney disorders or disturbances in liver or kidney function or blood count and differential as reflected by baseline blood test; creatine use 90 days prior to study entry; known sensitivity to creatine use.

Criteria for removal from the study were: any request from the patient to be withdrawn from the study; the development of hypersensitivity to creatine administration; exacerbation in the patients' clinical condition (increase in the PANSS score equal to or above 20%).

Seven consenting inpatients with chronic schizophrenia demonstrating treatment-resistant negative symptoms, 6 males and 1 female, mean (S.D.) age 45.5 (8) years, range 35-55 years, mean (S.D.) years of education 10.1 (1.5), range 8-12 years. All with more than 15 years of illness with basically no change in clinical presentation in the last 6 months as judged by the patient's psychiatrist. All were residents of a hospital psychiatric ward for at least 10 years where they had ongoing follow-up by certified psychiatrists and nursing staff.

Patients were treated with creatine monohydrate (administered by the nursing staff twice daily in equal doses) for 6 months (3 g daily in the first 2 weeks, 5 g daily in the next 2 weeks, 7 g in the next 2 weeks and finally 10 g daily for up to 6 months of treatment). Patients' neuroleptic treatment was not be affected by study participation. Real life treatment with mood stabilizers, benzodiazepines and anticholinergic medications were allowed but doses were documented throughout the study. No changes were made in the patients' neuroleptic treatment throughout the study, and small changes in the use of benzodiazepines were recorded. One change was made in the dose of a mood stabilizer as required in order to maintain levels within the therapeutic range (carbamazepine dose was raised from 600mg/d to 800mg/d after 4 months of creatine treatment). Routine blood tests including kidney function and liver function were monitored at baseline, and at 3 and 6 months, and were all within the normal range. In practice the 7 patients were treated respectively with the following antipsychotics and mood stabilizers (the latter were administered as these patients were not responding to antipsychotic drug therapy): 1. clozapine 500mg/d along with valproic acid 800mg/d; 2. amisulpiride 700mg/d along with chlorpromazine 200mg/d; 3. olanzapine 20 mg/d along with chlorpromazine 200 mg/d and valproic acid 800mg/d; 4. perphenazine 24 mg/d along with haloperidol decanoate 100mg IM every 3 weeks and valproic acid 800 mg/d; 5. perphenazine 20 mg/d along with carbamazepine 800 mg/d; 6. risperidone 6 mg/d along with lithium 750mg/d; 7. perphenazine 12 mg/d along with haloperidol decanoate 100mg IM every 3 weeks

The Positive and Negative Symptoms Scale (PANSS), Clinical Global Impressions (CGI), The Nurse Observation Scale for Inpatient Evaluation (NOSIE; a sensitive rating scale for ward behavior), the Extrapyramidal Symptom Rating Scale (ESRS; this scale is designed to rate the severity of four types of drug-induced movement disorders – both acute and delayed-onset – including parkinsonism, akathisia, dystonia and tardive dyskinesia [28-30], the Mindstreams computerized cognitive battery (see below) were administered at baseline and at 3 and 6 months, and adverse effects were recorded. The assessment scales and the cognitive battery were performed by highly trained personnel with previous experience in delivering the specific assessment scales (Cognitive battery by TD, ESRS by VL, PANSS & CGI by UL and JL, NOSIE by SM).

COGNITIVE BATTERY

The Mindstreams Severe Impairment Battery (MSIB) (31) was appropriate for use for these patients with chronic schizophrenia. It consists of six technician-administered tests and one patient-administered interactive test (Go-NoGo Basic test) sampling the cognitive domains of orientation (to time and place), memory, executive function, visual spatial processing, and verbal function.

Following is a brief description of the tests included in this battery. Orientation to Time and Place: the participant is asked three basic questions regarding orientation to time and place. Accuracy is weighted such that partial credit is awarded for responses that are almost correct.

Language Skills: the participant is asked to comply with simple verbal commands and to name pictures of

common objects; partial credit is awarded for responses that are nearly correct.

Nonverbal Memory: the participant is presented with pictures of common objects followed by an immediate recognition test; a delayed recognition test for the same objects is administered after 5 minutes.

Similarities and Judgment: a multiple-choice test in which the participant is asked simple questions relating to similarities and differences of common objects, as well as basic knowledge and praxis.

Reality Testing: the participant is presented with a series of pictures in which a particular aspect of the scene is either incomplete or inconsistent with context; following the presentation of each picture, the participant is asked to determine which aspect is aberrant; if he is unable to identify the aberrant aspect, multiple choices for the correct answer are provided and partial credit is awarded if a correct response is made.

Spatial Orientation: computer-generated scenes containing a red pillar are presented; the participant is asked to select the view of the scene from the vantage point of the red pillar. Go-NoGo Basic: a timed, patient-administered test consisting of two parts; in the simple reaction time (SRT) portion, large green squares are presented at pseudo-random intervals, and the participant is required to press the mouse button as quickly as possible whenever a square appears; in the inhibition stage, either a red circle or a white square is presented, and the participant responds only to a white square but not to a red circle.

For the technician-administered tests, a test supervisor reads the instructions and verbal test stimuli to the participant and enters the participant's response according to instructions given in small italicized text at the bottom of the screen. Only accuracy outcome parameters (scale: 0 to 100%) are recorded for these tests. For the patient-administered Go-NoGo Basic test, the patient's own responses are recorded, and reaction time (RT) and standard deviation of RT outcome parameters are recorded in addition to accuracy. Tests are always administered in the same fixed order.

All assessments were made between 9:00-11:00 AM in the morning in order to rule out diurnal fluctuations that may influence symptoms.

STATISTICAL ANALYSIS

Statistical analysis: Descriptive statistics were used to describe all study variables at baseline, at 3 and 6 months from the beginning of the study. To evaluate change over time we used ANOVA with repeated measures (with post hoc LSD test). Throughout our calculations, age and education were used as co-variants. Statistical significance was set at .05.

RESULTS

There was a significant change in the total PANSS with treatment, although this was of only minimal clinical value mainly due to mild improvement of the general psychopathology PANSS subscale. There was no significant improvement in PANSS negative and PANSS positive subscales with treatment. CGI severity and cognitive function as assessed by the Mindstreams Severe Impairment Battery did not change significantly as a result of treatment. On NOSIE there was a significant improvement in the total score, and in particular in personal neatness, psychomotor retardation and social competence (see Table 1).

Table 1. *Results for the cognitive battery, PANSS, CGI and the NOISE scales****

	Baseline		Month 3		Month 6		F	
Scale	mean	SD	mean	SD	mean	SD	(2,12)	p
Global cognitive score	75.2	18.9	76.3	19.3	73.1	13.6	0.4	0.7
Orientation score	78.6	23.0	73.9	27.0	61.9	30.2	1.3	0.3
Verbal Function score	86.7	14.1	87.9	18.3	83.6	18.9	0.3	0.7
Memory score	75.9	30.3	76.1	30.4	72.1	21.4	0.4	0.7
Executive Function score	69.6	21.9	73.0	16.3	74.9	16.2	0.6	0.5
Visual Spatial score	73.6	17.8	76.4	17.0	71.7	20.3	0.1	0.9
PANSS Total score	92.6	9.1	89.3*	8.3	87.4*	8.4	8.8	0.004
PANSS Positive subscale score	20.6	6.2	20.0	5.7	20.1	6.8	0.8	0.5
PANSS Negative subscale score	25.1	4.8	24.4	5.6	23.4	6.1	3.4	0.067
PANSS General subscale score	46.9	5.9	44.9	4.8	43.9*	6.3	5.4	0.021
CGI Severity score	4.9	0.9	4.7	0.8	4.7	0.8	1.0	0.4
NOSIE total score	108.6	30.5	112.6*	21.7	134.3*	11.7	4.15	0.043
NOSIE social competence score	12.6	9.3	13.1*	8.3	22.9*	4.3	5.27	0.023
NOSIE social interest score	27.1	8.6	24.9	4.5	26.6	5.5	0.49	0.626
NOSIE personal neatness score	20.6	5.4	21.1*	5.3	25.7*	1.8	4.37	0.038
NOSIE irritability score	22.0	11.4	19.4	8.5	17.1	8.5	3.58	0.060
NOSIE manifest psychosis score	14.0	5.7	12.9	4.0	17.1	13.8	0.67	0.532
NOSIE psychomotor retardation score	11.7	5.3	10.3	3.9	6.9*	1.6	4.15	0.043

**Applied by One Way Repeated Measures Analysis of Variance with time as repeated measure
*Post hoc LSD test: $p<0.05$

The patients demonstrated TD (tardive dyskinesia) and TP (tardive parkinsonism) and no other extrapyramidal syndromes. Six patients had TP, four of them showed improvement of 40-51% whereas the other two showed no improvement. Six patients had TD, one showed improvement of 50% whereas five showed no improvement.

No side effects were reported except for transient nausea in one patient.

DISCUSSION

The current study is a small size pilot open design with its inherent shortcomings and thus its modest results should be taken with caution. Although others have suggested that creatine may benefit some cognitive functions (25), in our study the use of a computerized cognitive assessment battery appropriate for patients with schizophrenia failed to demonstrate any beneficial effect on cognitive functions.

We did find an improvement, although of minimal clinical value, in the patients' symptomatology as measured by the general psychopathology subscale of the PANSS, yet no improvement in the PANSS negative syndrome subscale. However, there was a significant improvement in the patients' personal neatness, social competence and psychomotor retardation as measured by the NOSIE. Personal neatness and social competence may suggest that there was some improvement of negative symptomatology detected by the highly sensitive ward behavior rating scale: the NOSIE (32, 33) but not by the PANSS negative subscale. In this regard, this beneficial effect of creatine administered for 6 months on behavioral and social parameters was also reported recently in females with Rett syndrome, although this finding did not reach statistical significance (34). However, as we stated previously one should take with caution our results concerning the above NOSIE items as no change was noted in the PANSS negative subscale and such NOSIE improvement may also be attributed to non-specific factors of being enrolled in a study with multiple encounters and staff care.

Recently creatine was administered in a high dose of 30 grams daily in patients with amyotrophic lateral sclerosis (ALS) with few side effects (35) and an unpublished open-label pilot study explored creatine in doses of up to 40 g daily in patients with Huntingdon's disease (36). It may thus be of interest to administer creatine in even higher doses and for longer periods while following behavioral and social parameters.

In our study tardive parkinsonism was improved in 4 out of 6 patients and the subscale of the NOSIE also showed a statistically significant improvement of psychomotor retardation. Creatine was previously suggested to have beneficial effects on extrapyramidal symptomatology in animal models (37) and a large scale futility study (24) suggested that creatine could not be rejected as futile in Parkinson disease. It is thus of interest to study this effect of creatine in future studies.

Interestingly, Burbaeva et al. (10) reported a substantial decrease of creatine kinase (CK) activity and CK BB immunoreactivity in all the examined brain areas in patients with schizophrenia compared with controls. The decreased activity of this key enzyme may suggest that creatine administered to schizophrenic patients may not be converted sufficiently to creatine phosphate. This may be overcome by either increasing the dose of creatine administered (as suggested above as warranting further study) or alternatively by the administration of creatine phosphate high energy derivatives thus sparing the need to phosphorylize creatine to phophocreatine. Creatine phosphate derivatives were previously administered intravenously in certain medical conditions (i.e., cardiovascular disorders) to animals and humans (38-40). Interestingly, phosphocreatine-Mg-complex acetate (PCr-Mg-CPLX), one of these phosphocreatine compounds, was able to increase in vitro neuronal creatine independently of the creatine transporter (41) and has also shown neuroprotection in animal models in vivo (42). With regard to this finding, further research in animal models of schizophrenia is warranted.

References

1. Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiol Rev 2000; 80: 1107-1213.
2. Persky AM, Brazeau GA. Clinical pharmacology of the dietary supplement creatine monohydrate. Pharmacol Rev 2001; 53: 161-176.
3. Adcock KH, Nedelcu J, Loenneker T, Martin E, Wallimann T, Wagner BP. Neuroprotection of creatine supplementation in neonatal rats with transient cerebral hypoxia-ischemia. Dev Neurosci 2002;24:382-388.
4. Baker SK, Tarnopolsky MA. Targeting cellular energy production in neurological disorders. Expert Opin Investig Drugs 2003;12:1655-1679.
5. Chaturvedi RK, Beal MF. Mitochondrial approaches for neuroprotection. Ann N Y Acad Sci 2008;1147:395-412.
6. Adhihetty PJ, Beal MF.Creatine and its potential therapeutic value for targeting cellular energy impairment in neurodegenerative diseases. Neuromolecular Med 2008;10:275-290.
7. Dechent P, Pouwels PJ, Wilken B, Hanefeld F, Frahm J. Increase of total creatine in human brain after oral supplementation of creatine-monohydrate. Am J Physiol 1999; 277: R698-704.
8. Lyoo IK, Kong SW, Sung SM, Hirashima F, Parow A, Hennen J, et al. Multinuclear magnetic resonance spectroscopy of high-energy phosphate metabolites in human brain following oral supplementation of creatine-monohydrate. Psychiatry Res 2003; 123: 87-100.
9. Ongür D, Prescot AP, Jensen JE, Cohen BM, Renshaw PF. Creatine abnormalitiesin schizophrenia and bipolar disorder. Psychiatry Res 2009;172:44-48.

10. Burbaeva GSh, Savushkina OK, Boksha IS. Creatine kinase BB in brain in schizophrenia. World J Biol Psychiatry 2003;4:177-183.

11. Jayakumar PN, Venkatasubramanian G, Keshavan MS, Srinivas JS, Gangadhar BN. MRI volumetric and 31P MRS metabolic correlates of caudate nucleus in antipsychotic-naïve schizophrenia. Acta Psychiatr Scand 2006;114:346-351.

12. Chang L, Friedman J, Ernst T, Zhong K, Tsopelas ND, Davis K. Brain metabolite abnormalities in the white matter of elderly schizophrenic subjects: Implication for glial dysfunction. Biol Psychiatry 2007;62:1396-1404.

13. O'Neill J, Levitt J, Caplan R, Asarnow R, McCracken JT, Toga AW, Alger JR. 1H MRSI evidence of metabolic abnormalities in childhood-onset schizophrenia. Neuroimage 2004;21:1781-1789.

14. Lutkenhoff ES, van Erp TG, Thomas MA, Therman S, Manninen M, Huttunen MO, Kaprio J, Lönnqvist J, O'Neill J, Cannon TD. Proton MRS in twin pairs discordant for schizophrenia. Molecular Psychiatry 2010;15:308-318.

15. Wood SJ, Berger GE, Wellard RM, Proffitt T, McConchie M, Velakoulis D, McGorry PD, Pantelis C. A 1H-MRS investigation of the medial temporal lobe in antipsychotic-naïve and early-treated first episode psychosis. Schizophr Res 2008;102:163-170.

16. Volz H, Gaser C, Sauer H. Supporting evidence for the model of cognitive dysmetria in schizophrenia--a structural magnetic resonance imaging study using deformation-based morphometry. Schizophr Res 2000; 46: 45-56.

17. Andreasen NC, O'Leary DS, Flaum M, Nopoulos P, Watkins GL, Boles Ponto LL, et al. Hypofrontality in schizophrenia: Distributed dysfunctional circuits in neuroleptic-naive patients. Lancet 1997; 349: 1730-1734.

18. Kaptsan A, Odessky A, Osher Y, Levine J Lack of efficacy of 5 grams daily of creatine in schizophrenia: A randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2007;68:881-884.

19. Verbessem P, Lemiere J, Eijnde BO, Swinnen S, Vanhees L, Van Leemputte M, Hespel P, Dom R. Creatine supplementation in Huntington's disease: A placebo-controlled pilot trial. Neurology 2003;61:925-930.

20. Bender A, Auer DP, Merl T, Reilmann R, Saemann P, Yassouridis A, Bender J, Weindl A, Dose M, Gasser T, Klopstock T. Creatine supplementation lowers brain glutamate levels in Huntington's disease. J Neurol 2005;252:36-41.

21. Hersch SM, Gevorkian S, Marder K, Moskowitz C, Feigin A, Cox M, Como P, Zimmerman C, Lin M, Zhang L, Ulug AM, Beal MF, Matson W, Bogdanov M, Ebbel E, Zaleta A, Kaneko Y, Jenkins B, Hevelone N, Zhang H, Yu H, Schoenfeld D, Ferrante R, Rosas HD. Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG. Neurology 2006;66:250-252.

22. Tabrizi SJ, Blamire AM, Manners DN, Rajagopalan B, Styles P, Schapira AH, Warner TT. Creatine therapy for Huntington's disease: Clinical and MRS findings in a 1-year pilot study. Neurology 2003;61:141-142.

23. Tabrizi SJ, Blamire AM, Manners DN, Rajagopalan B, Styles P, Schapira AH, Warner TT. High-dose creatine therapy for Huntington disease: A 2-year clinical and MRS study. Neurology 2005;64:1655-1656.

24. NINDS NET-PD Investigators. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. Neurology 2006; 66:664-671.

25. Rae C, Digney AL, McEwan SR, Bates TC. Oral creatine monohydrate supplementation improves brain performance: a double-blind, placebo-controlled, cross-over trial. Proc R Soc Lond B Biol Sci 2003; 270: 2147-2150.

26. McMorris T, Harris RC, Swain J, Corbett J, Collard K, Dyson RJ, Dye L, Hodgson C, Draper N. Effect of creatine supplementation and sleep deprivation, with mild exercise, on cognitive and psychomotor performance, mood state, and plasma concentrations of catecholamines and cortisol. Psychopharmacology (Berl) 2006;185:93-103.

27. McMorris T, Harris RC, Swain J, Corbett J, Collard K, Dyson RJ, Dye L, Hodgson C, Draper N. Effect of creatine supplementation and sleep deprivation, with mild exercise, on cognitive and psychomotor performance, mood state, and plasma concentrations of catecholamines and cortisol. Psychopharmacology (Berl) 2006;185:93-103.

28. Chouinard G, Ross-Chouinard A, Annable L, Jones B. Extrapyramidal Symptom Rating Scale. Can J Neurol Sci (abstract) 1980;7:233.

29. Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). Schizophr Res 2005;76:247-265.

30. Hyde TM, Egan MF, Brown RJ, et al. Diurnal variation in tardive dyskinesia. Psychiatry Res 1995; 56:53-57.

31. Ritsner MS, Blumenkrantz H, Dubinsky T, Dwolatzky T. The detection of neurocognitive decline in schizophrenia using the Mindstreams Computerized Cognitive Test Battery. Schizophr Res 2006;82:39-49.

32. Honigfeld G, Gillis RD, Klett CJ. NOSIE-30: A treatment-sensitive ward behavior scale. Psychol Rep 1966; 19: 180-182.

33. Philip AE. A note on the nurses' observation scale for inpatient evaluation. Brit J Psychiat 1973; 122: 593-596.

34. Freilinger M, Dunkler D, Lanator I, Item CB, Mühl A, Fowler B, Bodamer OA. Effects of creatine supplementation in Rett syndrome: A randomized, placebo-controlled trial. J Dev Behav Pediatr 2011;32:454-460.

35. Atassi N, Ratai EM, Greenblatt DJ, Pulley D, Zhao Y, Bombardier J, Wallace S, Eckenrode J, Cudkowicz M, Dibernardo A. A phase I, pharmacokinetic, dosage escalation study of creatine monohydrate in subjects with amyotrophic lateral sclerosis. Amyotroph Lateral Scler 2010; 11: 508-513.

36. Hersch SM. Creatine safety, tolerability, and efficacy in Huntington's disease: CREST-E. http://www.labome.org/grant/u01/at/creatine/safety/creatine-safety--tolerability--and-efficacy-in-huntington-s-disease--crest-e-7374072.html

37. Yang L, Calingasan NY, Wille EJ, Cormier K, Smith K, Ferrante RJ, Beal MF. Combination therapy with coenzyme Q10 and creatine produces additive neuroprotective effects in models of Parkinson's and Huntington's diseases. J Neurochem 2009;109:1427-1439.

38. Cafiero M, Strumia E, Pirone S, Pacileo S, Santoro R. [The efficacy of creatine phosphate in the treatment of patients with heart failure. Its echographic evaluation after acute and protracted treatment]. Clin Ter 1994;144:321-328.

39. Weber P, Vlasicová Y, Lábrová R, Semrád B. [Use of creatine phosphate in treatment of cardiocerebral syndrome associated with acute myocardial infarct in the aged]. Cas Lek Cesk 1995;134:53-56.

40. Prabhakar G, Vona-Davis L, Murray D, Lakhani P, Murray G. Phosphocreatine restores high-energy phosphates in ischemic myocardium: Implication for off-pump cardiac revascularization. J Am Coll Surg 2003;197:786-791.

41. Lunardi G, Parodi A, Perasso L, Pohvozcheva AV, Scarrone S, Adriano E, Florio T, Gandolfo C, Cupello A, Burov SV, Balestrino M. The creatine transporter mediates the uptake of creatine by brain tissue, but not the uptake of two creatine-derived compounds. Neuroscience 2006;142:991-997. Epub 2006 Sept. 1.

42. Perasso L, Adriano E, Ruggeri P, Burov SV, Gandolfo C, Balestrino M. In vivo neuroprotection by a creatine-derived compound: phosphocreatine-Mg-complex acetate. Brain Res 2009;1285:158-163.