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Brief Report

Creatine monohydrate in resistant depression: a preliminary study

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Objectives: Creatine plays a pivotal role in brain energy homeostasis, and altered cerebral energy metabolism may be involved in the pathophysiology of depression. Oral creatine supplementation may modify brain high-energy phosphate metabolism in depressed subjects.

Methods: Eight unipolar and two bipolar patients with treatment-resistant depression were treated for four weeks with 3–5 g/day of creatine monohydrate in an open add-on design. Outcome measures were the Hamilton Depression Rating Scale, Hamilton Anxiety Scale, and Clinical Global Impression scores, recorded at baseline and at weeks 1, 2, 3 and 4.

Results: One patient improved considerably after one week and withdrew. Both bipolar patients developed hypomania/mania. For the remaining seven patients, all scale scores significantly improved. Adverse reactions were mild and transitory.

Conclusions: This small, preliminary, open study of creatine monohydrate suggests a beneficial effect of creatine augmentation in unipolar depression, but possible precipitation of a manic switch in bipolar depression.

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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). Recent studies have also suggested increased brain utilization of oxygen following oral creatine supplementation (2). Creatine enters the brain (3) via a specialized sodium-dependent transporter, as has been shown by advanced imaging methods (4). Recently, creatine supplementation (5 g/day for six weeks) demonstrated a positive effect on cognitive function in normals (5). This suggests that creatine supplementation may enhance the performance of certain brain areas and might be useful in brain disorders exhibiting hypoactive metabolism, including depression.

Accumulated evidence suggests the possible involvement of altered cerebral energy metabolism in the pathophysiology of depression (6). Functional brain imaging studies (positron and single-photon emission tomography) have shown decreased blood flow and metabolism in the frontal lobes and basal ganglia in unipolar depression (7, 8). Fewer data are available regarding bipolar depression, although Ketter et al. (9) did observe a pattern of prefrontal hypometabolism in depressed bipolars.

Dager et al. studied depressed or mixed-state bipolar patients using two-dimensional proton echo-planar spectroscopic imaging, reporting an inverse correlation between severity of depression and white matter creatine levels (10).

Magnetic resonance spectroscopy (MRS) studies have studied brain levels of creatine-containing compounds. Kato et al. (11) reported that phosphocreatine was significantly decreased in severely (as opposed to mildly) depressed patients. Several studies have used proton MRS in the study of

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brain levels of creatine + phosphocreatine (CRE) in affective patients. (It should be noted that this method does not enable specifying the *ratio* between the two metabolites.) While studies of the dorsolateral prefrontal cortex of adult unipolar patients (12), adult bipolar patients (13) and young bipolar patients (14) show no evidence of CRE levels that significantly differ from those in controls, CRE levels have been shown to be disrupted in the hippocampus of adult patients undergoing a first affective episode (compared to those in controls) (15) and to be significantly lower in euthymic adult male bipolar patients with a family history of bipolar disorder (16). Creatine + phosphocreatine levels in the cerebellar vermis of children with both a mood disorder and at least 1 bipolar parent were about 8% lower than the levels in matched controls (17). It may be, therefore, that decreased CRE levels are area-specific.

Finally, there is evidence that agents with reported antidepressant activity cause changes in brain levels of creatine-containing compounds. Sartorius et al. (18) used MRS to study metabolic changes in the hippocampus of rats and demonstrated a significant creatine level rise induced by electroconvulsive treatment (ECT) occurring specifically in the group of animals which had exhibited depression-like (learned helplessness) behavior before the ECT. In humans, *S*-adenosyl-L-methionine (SAM) and acetyl-L-carnitine, respectively, have increased phosphocreatine brain levels in healthy subjects (19) and in geriatric depressed patients (20).

Taken together, these findings suggest the possibility of using oral creatine supplementation to increase brain levels of creatine-containing compounds and thereby, most likely by modifying the high-energy phosphate metabolism in hypoactive brain areas, treating subjects with depression.

Methods

The study was an open, four-week, clinical add-on trial examining the effect of creatine monohydrate in the treatment of resistant depression.

Subjects

Patients with resistant depression were eligible for inclusion regardless of whether they had a history of unipolar or bipolar depression. Patient characteristics are presented in Table 1. Ten patients participated in the study: seven were outpatients and three (ID nos. 4, 7 and 10) were hospitalized at the time of the study. All patients had been treated with antidepressants and/or mood stabilizers in adequate doses for at least six weeks prior to participation in the study, without any clinically significant improvement. Patient age averaged 49.3 years [± standard deviation (SD) 9.5 years], and on average patients had been ill for 19.6 years (± SD 10.0 years). Three patients had comorbid hypertension, which was medically stable, and two of these also suffered from diabetes mellitus type II. Three patients had psychiatric comorbidity (see Table 1).

Patients with a known history of alcohol or drug abuse were excluded.

Procedure

All patients were evaluated using the Mini International Neuropsychiatric Interview (21) for the

Table 1. Patient characteristics

ID no.	Diagnosis	Status	Sex	Age	Years	Medication
1	MDD	Outpatient	M	49	16	Venlafaxine 150 mg/day
2	MDD	Outpatient	M	30	4	Citalopram 60 mg/day
3	MDD	Outpatient	F	58	42	Sertraline 200 mg/day Reboxetine 8 mg/day Lamotrigine 100 mg/day
4	MDD/Panic disorder	Inpatient	F	54	30	Clomipramine 225 mg/day
5	MDD	Outpatient	F	44	4	Paroxetine 20 mg/day
6	MDD/GAD	Outpatient	M	41	15	Fluoxetine 40 mg/day Carbamazepine 600 mg/day
7	BPD-D	Inpatient	M	45	20	Valproic acid 600 mg/day
8	BPD-D	Outpatient	F	59	32	Nortriptyline 250 mg/day Mirtazepine 30 mg/day
9	MDD	Outpatient	M	60	8	Clomipramine 300 mg/day
10	MDD/GAD	Inpatient	M	53	26	Paroxetine 20 mg/day Valproic acid 600 mg/day Risperidone 1 mg/day

MDD = major depressive disorder; GAD = generalized anxiety disorder; BPD-D = bipolar disorder-current depressive episode; M = male; F = female.

Table 2. Patient scores on outcome measures at baseline and at weeks 1, 2, 3 and 4

	HAM-D scores					HAS scores					CGI Scale scores				
ID no	B/l	W 1	W 2	W 3	W 4	B/l	W 1	W 2	W 3	W 4	B/l	W 1	W 2	W 3	W 4
1	26	21	18	15	10	16	17	12	17	14	4	4	3	3	3
2	22	11	11	14	9	19	8	13	14	11	4	2	2	3	2
3	20	7	11	18	15	15	10	13	16	13	4	2	3	4	3
4	22	12	23	14	9	24	14	23	13	10	5	3	5	3	2
5[a]	16	8	Withdrew			10	8	Withdrew			3	2	Withdrew		
6	19	13	6	4	4	17	7	4	4	4	4	3	2	2	2
7[a]	20	4	8	4	Manic	19	3	7	4	Manic	5	2	3	3	Manic
8[a]	18	15	7	Hypomanic		14	11	4	Hypomanic		4	4	3	Hypomanic	
9	28	26	17	30	30[b]	21	19	20	24	24[b]	5	5	4	6	6[b]
10	25	16	14	11	11	19	14	14	8	8	5	4	4	3	3

[a]Not included in data analysis; [b]Last value was carried forward.
HAM-D = Hamilton Depression Rating Scale; HAS = Hamilton Anxiety Scale; CGI = Clinical Global Impression; B/l = baseline; W = week.

presence of comorbidity and diagnosed by DSM-IV-TR (22). All patients signed informed consent forms. This study was approved by the appropriate institutional ethics review board.

All patients were treated with creatine monohydrate for four weeks (administered as tablets of 1 g each), 3 g/day in the first week, followed by 5 g/day for another three weeks. Ongoing psychotropic treatment was not changed during the study. The Hamilton Depression Rating Scale 21-item version (HAM-D) (23), Hamilton Anxiety Scale (HAS) (24), and Clinical Global Impression (CGI) (25) scores were recorded at baseline and at weeks 1, 2, 3 and 4.

Statistical analysis

Changes in HAM-D, HAS and CGI scores at 1, 2, 3 and 4 weeks after baseline were analyzed using one-way repeated measures ANOVA. Regression analysis was used to assess the relationship between background information and baseline scale scores.

Results

Individual HAM-D, HAS and CGI scores are presented in Table 2.

Seven patients completed at least three weeks of the study. The two bipolar patients (ID nos. 7 and 8) developed hypomania or mania and withdrew from the study before completion of week 4. Their results are not included in the analysis because we did not feel it appropriate to equate manic switch with improvement in depression. The third patient to withdraw early (ID No. 5) improved considerably during the first week and discontinued treatment; his results are not included in the analyses.

One-way repeated measures ANOVA showed significant improvement on all scales: mean ($\pm$ SD) CGI scores decreased from 4.43 (SD 0.5) at baseline to 3.00 (SD 1.4) at week 4 [$F(4,24) = 3.442$, $p = 0.02$]; HAM-D scores from 23.14 (SD 3.3) at baseline to 12.57 (SD 8.3) at week 4 [$F(4,24) = 5.994$, $p = 0.002$]; and HAS scores from 18.71 (SD 3.1) at baseline to 12.00 (SD 6.2) at week 4 [$F(4,24) = 3.789$, $p = 0.016$]. Least significant difference post hoc testing revealed that each of the outcome measures improved significantly ($p \leq 0.012$) over baseline by week 1. None of the demographic or historical parameters were significantly correlated with baseline scores on the outcome scales (data not shown).

One patient (ID no. 9) did not improve while on creatine treatment and withdrew from the study after week 3. He is included in the data analysis with last observations carried forward.

Adverse reactions were mild. Two patients complained of transient nausea, in one case including transient flatus and constipation. These complaints disappeared by week 4. No other adverse reactions were reported.

Discussion

This preliminary, open-label augmentation study of creatine monohydrate – an agent which enhances brain energy metabolism – demonstrated a beneficial effect in the treatment of resistant depression. Five out of the seven completers (71%) reduced their HAM-D scores by more than 50% from baseline, comparing favorably to the placebo response rates of 27–50% cited in two major reviews of clinical trials in depression (26, 27). These results suggest a novel strategy for the treatment of depression, a strategy based on modifying brain energy metabolism.

Two female patients (ID nos. 3 and 4) showed transient increases in HAM-D scores following a creatine dose increase to 5 g/day. In both cases, when the creatine dose was returned to 3 g/day, improvement was seen again. This suggests that there may be an inverted, U-shaped dose–response curve for creatine.

In follow-up, two weeks after termination of the study, three of the seven completers reported a worsening of their depressive and anxiety symptoms. They then restarted creatine, with considerable improvement in their condition within 1–2 weeks.

This study included two bipolar I patients. Each developed mania or hypomania while treated with creatine. Is the induction of mania associated with the enhancement of brain energy by creatine in certain key brain structures? It is interesting that SAM, an antidepressant and a precursor of creatine, was reported to be associated with high rates of manic/hypomanic switch in bipolar patients (28).

It may be noted from Table 2 that most of the improvement occurred after only one week of creatine augmentation. Does adding creatine rapidly enhance the antidepressant effect of other agents, as with lithium augmentation of antidepressants, or is it an antidepressant in its own right?

This study has several important limitations. The sample size was small and the formal study period was short (although there was non-quantitative follow-up for the study completers). In future studies, a more homogeneous sample would be preferable [only unipolar patients, all patients in the same treatment setting (in- or outpatient)]. Finally, a placebo control group will be necessary in order to rule out the possibility that these patients, although they had not shown adequate response to medication before inclusion in the study, either improved as a delayed reaction to their ongoing medications or from other non-specific elements of the study (researcher attention, repeated measures, placebo effect of a new medication).

Within the confines of its limitations, this small, preliminary study suggests that creatine, a brain energy metabolism enhancer, may be an efficacious, well tolerated and fast-acting treatment for depression. We hope that larger, controlled trials will continue to explore the potential of this treatment, whether as monotherapy or as an augmentation to standard antidepressant medications.

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