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Open-label adjunctive creatine for female adolescents with SSRI-resistant major depressive disorder: A 31-phosphorus magnetic resonance spectroscopy study

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Abstract

Background—Adolescent major depressive disorder (MDD) is a life-threatening brain disease with limited interventions. Treatment resistance is common, and the illness burden is disproportionately borne by females. 31-Phosphorus magnetic resonance spectroscopy (^{31}P MRS) is a translational method for in vivo measurement of brain energy metabolites.

Methods—We recruited 5 female adolescents who had been on fluoxetine (Prozac®) for ≥8 weeks, but continued meet diagnostic criteria for MDD with a Children's Depression Rating Scale-Revised (CDRS-R) raw score ≥40. Treatment response was measured with the CDRS-R. ^{31}P MRS brain scans were performed at baseline, and repeated following adjunctive creatine 4 g daily for 8 weeks. For comparison, 10 healthy female adolescents underwent identical brain scans performed 8 weeks apart.

Results—The mean CDRS-R score declined from 69 to 30.6, a decrease of 56%. Participants experienced no Serious Adverse Events, suicide attempts, hospitalizations or intentional self-harm. There were no unresolved treatment-emergent adverse effects or laboratory abnormalities. MDD participants' baseline CDRS-R score was correlated with baseline pH (p=0.04), and was negatively correlated with beta-nucleoside triphosphate (β-NTP) concentration (p=0.03). Compared to healthy controls, creatine-treated adolescents demonstrated a significant increase in brain Phosphocreatine (PCr) concentration (p=0.02) on follow-up ^{31}P MRS brain scans.

Limitations—Lack of placebo control; and small sample size.

Conclusions—Further study of creatine as an adjunctive treatment for adolescents with SSRI-resistant MDD is warranted.

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Conflict of interest

Dr. Renshaw serves as a consultant to Kyowa Hakko, Novartis and Roche. He has received research support from GlaxoSmithKline and Roche. Dr. Renshaw and Dr. Kondo are inventors on a patent application that has been assigned to the University of Utah, and describes the use of creatine as a treatment for depressive disorders. The application was filed after the subjects described in this report completed the research protocol and all aspects of study participation. All other authors declare that they have no conflicts of interest.

Keywords

Female; Adolescent; Depression; Creatine; Magnetic resonance spectroscopy; Combination drug therapy

1. Introduction

Adolescent major depressive disorder (MDD) is associated with significant disability and mortality (Birmaher et al., 2007). Up to 8% of adolescents have MDD at any point in time (SAMHSA, 2008), and MDD eventually effects nearly 1 in 4 American children (Lewinsohn et al., 1993). In the 13–17 age group, mood disorder is the leading cause of hospitalization (Owens et al., 2003), and juvenile MDD predicts depression and psychosocial impairment in adulthood (Fombonne et al., 2001; Pine et al., 1999; Weissman et al., 1999). Pediatric depression also imposes substantial economic costs on society (Lynch and Clarke, 2006). Thus, novel interventions for MDD in the critical adolescent stage of development are urgently needed.

Female adolescents are affected by MDD at twice the rate of males (Merikangas et al., 2010), and this gender disparity continues throughout women's reproductive years (Blazer et al., 1994; Kessler et al., 2003; Nolen-Hoeksema, 1990; Robins and Regier, 1991). The sex-based imbalance is one of the most replicated findings in epidemiology, and is robust to international sampling across continents and cultures (Maier et al., 1999; Seedat et al., 2009; Weissman et al., 1996). Despite the evidence for sex-based differences in MDD pathophysiology (Hyde et al., 2008; Young and Korszun, 2010) and treatment response (Bigos et al., 2009; Dalla et al., 2010), few somatic treatment studies have focused on adolescent females.

Selective serotonin reuptake inhibitors (SSRIs) are first-line medications for adolescent MDD (Birmaher et al., 2007; Ma et al., 2005), and are annually prescribed to 3.9% of American teenagers (Vitiello et al., 2006). However, at least 40% of adolescents with MDD receiving an SSRI show an inadequate response treatment (Brent et al., 2008; Kennard et al., 2009). The response rate in pediatric MDD trials favors SSRIs over placebo by just 10.8% (Usala et al., 2008); even this small margin may be due to publication bias (Whittington et al., 2004). In addition concerns regarding efficacy, meta-analyses and systematic reviews suggest that when prescribed to young people, SSRIs increase the risk for suicidality (Dubicka et al., 2006; Hammad et al., 2006; Hetrick et al., 2007), and attempted or completed suicide (Barbui et al., 2009). Clearly, safe and novel treatments for adolescent MDD are urgently needed.

Converging lines of evidence suggest that mood disorders are associated with changes in cerebral energy metabolism (Kato, 2007; Moretti et al., 2003; Rezin et al., 2009; Shao et al., 2008), that normalize with resolution of a mood episode (Iosifescu et al., 2008; Iosifescu and Renshaw, 2003). 31-Phosphorus magnetic resonance spectroscopy (^{31}P MRS) is the only method for in vivo measurement of these changes (Renshaw et al., 2001). The ^{31}P MRS literature in pediatric MDD is expanding (Kondo et al., 2011), and ^{31}P MRS studies in adults show a distinctive pattern of energy-related metabolites in MDD: decreased beta-

nucleoside triphosphate (β-NTP; largely adenosine triphosphate, or ATP) and increased phosphocreatine (PCr) (Iosifescu et al., 2008; Moore et al., 1997; Volz et al., 1998). This pattern is more common in females (Renshaw et al., 2001), and is associated with increased likelihood of responding to both an SSRI in treatment naïve MDD (Renshaw et al., 2001), and thyroid augmentation in treatment-resistant MDD (Iosifescu et al., 2008). In healthy adults, administration of the dietary supplement creatine induces this pattern in brain chemistry (Lyoo et al., 2003), suggesting the possibility of utilizing creatine to modify brain energy metabolism.

Creatine is an organic acid occurring naturally in vertebrates, where it plays a role in energy homeostasis in tissues with variable energy demands, principally skeletal muscle and brain. Through the reversible creatine kinase reaction, creatine raises cellular PCr levels, which increases capacity for cellular ATP resynthesis (Jost et al., 2002).

Data from preclinical animal studies suggest that creatine may have sex-specific antidepressant properties that favor females. The Porsolt Forced Swim Test (FST) is a widely-used experimental model of depression (Porsolt et al., 1977). Creatine supplementation confers a longer latency to immobility in the FST in female Sprague–Dawley rats, but not males (Allen et al., 2010b). Creatine's sex-specific antidepressant effect in rats is independent of SSRI administration (Allen et al., 2010a).

To date there are no studies of adjunctive creatine in female adolescents with SSRI-resistant MDD. Given the gender-specific effect of creatine in animal studies (Allen et al., 2010a, 2010b), clinical trials in male adolescents must be deferred on until creatine is shown to be safe in adult males with SSRI-refractory MDD. We conducted an open-label study of adjunctive creatine for female adolescents with MDD who had failed an adequate trial of fluoxetine (Prozac®). In addition to standardized clinical assessments, participants underwent ^{31}P MRS brain scans at baseline, and after 8 weeks of creatine augmentation. Healthy female controls were recruited for comparison ^{31}P MRS brain scans.

2. Methods

The University of Utah Institutional Review Board (IRB) approved the study. Informed consent included both written parental consent and written participant assent. An external Data Safety and Monitoring Board with authority to halt the study monitored patient safety outcomes.

Participants were recruited through referrals and IRB-approved advertising. Consecutive patients who met inclusion criteria were enrolled. Inclusion criteria were: females 13–18 years of age with a primary diagnosis of MDD; current fluoxetine treatment for ≥8 weeks with ≥4 weeks at a dose of ≥40 mg/day (if doses higher than 20 mg/day were not tolerated, participants could meet inclusion criteria by taking fluoxetine 20 mg/day for ≥8 weeks); and a current Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski and Mokros, 1996) raw score ≥40. No restrictions were placed on concomitant medications or psychotherapy. Study exclusion criteria were: renal disease; proteinuria; contraindication to magnetic resonance scanning (e.g. ferromagnetic implant); primary diagnosis other than MDD; psychotic symptoms; positive pregnancy test; active use of alcohol or illicit drugs; or

mental retardation. Diagnoses were established with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). A complete blood count, metabolic panel, lipid profile, TSH and urinalysis were obtained at baseline. Laboratory studies were repeated at the conclusion of treatment, to prospectively identify abnormalities associated with creatine administration.

Participants with MDD were treated with fixed-dose Creapure® brand of creatine (AlzChem LLC, Trostberg, Germany) 4 g by mouth daily for 8 weeks. At each visit vital signs and adverse were recorded, and the following rating scales were administered: CDRS-R, the Clinical Global Impressions scale (Guy, 1976) and the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner, 2010). The primary outcome was the change from baseline in CDRS-R raw score.

^{31}P MRS brain scans were acquired with a Siemens 3 Tesla MRI scanner (Siemens AG, Munich, Germany) that is approved for clinical use. A two-dimensional chemical shift imaging free induction decay (2D CSI FID) pulse sequence with an Fourier voxel resolution of 25×25×25 mm^3, Field of View (FOV) = 200 × 200 × 25 mm^3, TR/TE = 3000/2.3 ms, vector size=1024, bandwidth=2500 Hz, data collection time=11.2 min and the number of averages=24 was implemented to collect 2D CSI FID data, using a ^{31}P/^{1}H dual-tuned coil (Clinical MR Solutions LLC, Brookfield, Wisconsin). The high-resolution localization images of CSI data were acquired using an inversion recovery magnetization prepared rapid gradient echo (MPRAGE) pulse sequence with isotropic 1 mm^3 resolution. The imaging parameters were as follows: TR/TE=2000/3.37 ms, FOV=256×192× 144 mm^3, and matrix size=256×192×144, total acquisition time=4.8 min. Participants were instructed that they could discontinue scanning at any time if they experienced discomfort (e.g. claustrophobic anxiety).

^{31}P MRS data were analyzed using the jMRUI software package (jMRUI version 4.0, European Community). A Hamming filter was applied to reduce signal contamination from neighboring voxels, prior to the 2D Fast Fourier Transform (FFT) on the raw data. Nine voxels from a 25 mm slice located at the corpus callosum, anterior commissure and posterior commissure were summed following 2D FFT. Each voxel FID was apodized with a 10 Hz exponential line broadening before zero filling and FFT. Zero-order and first-order phase correction was performed in all spectrums. Signal amplitudes for individual metabolites were calculated with the Advanced Method for Accurate, Robust and Efficient Spectral fitting of MRS data (AMARES), an algorithm in the jMRUI application.

3. Results

3.1. Clinical measures

Summary results for MDD participants are presented in Table 1. All were Caucasian females. No participant initiated or terminated psychosocial treatment or psychotropic medication during the study, and fluoxetine doses were held constant. Five participants completed 8 weeks of adjunctive creatine and the ^{31}P MRS scans. No participant withdrew from the study.

The mean CDRS-R raw score at baseline was 69 (SD 9.69). After 8 weeks of adjunctive creatine the mean CDRS-R score was 30.6 (SD 8.50), an average decrease of 38.4 (56%). The participants' CDRS-R raw scores during 8 weeks of treatment and the 2-week follow-up period are depicted graphically in Fig. 1. After discontinuation of adjunctive creatine, treatment gains were maintained. In fact, the mean CDRS-R raw score two weeks after the end of treatment (Week 10) was lower than at the conclusion of treatment.

3.2. ^{31}P MRS neuroimaging results

MDD participants' ^{31}P MRS scans were performed prior to the first dose of creatine, and repeated following 8 weeks of treatment. We also recruited ten healthy control adolescents, six of whom returned 8 weeks later for a follow-up scan. Statistical analyses were performed using JMP 8 (SAS Inc., Cary, North Carolina USA). Neuroimaging analyses were considered exploratory, and no correction for multiple testing was applied.

Table 2 displays repeated measures of ^{31}P MRS metabolites in MDD participants and controls. Following 8 weeks of treatment with creatine, depressed adolescents demonstrated a significant increase in PCr (p=0.02; paired *t*-test; 2-tailed) compared to controls. There was no change in creatine-treated participants' mean β-NTP, pH or PCr/β-NTP concentrations.

Using the technique of a previous report (Renshaw et al., 2001), correlations between baseline depression rating scale scores and baseline neurometabolite levels were assessed using Spearman rank correlation and generalized two-tailed least squares modeling methods. CDRS-R baseline score was correlated with baseline pH (correlation=0.8919; 95% CI 0.045–0.993; p=0.04). CDRS-R baseline score was negatively correlated with β-NTP concentration (Spearman's p=−0.90; p=0.03). (Data not shown.)

3.3. Adverse events

Adverse events, summarized in Table 1, were self-limited with no unresolved treatment-emergent side effects. There was no attempted suicide, self-injurious behavior or psychiatric hospitalization during the study. There were no significant changes in vital signs or laboratory tests; no participant developed proteinuria or an abnormal serum creatinine.

3.4. Suicidality

All but one participant endorsed a history of suicidality, highlighting the severity of MDD in this population. Three participants had attempted suicide, and four participants reported suicidal ideation during the 2 weeks prior to their initial visit. During the treatment phase of the study, two participants reported no suicidality. Three participants reported suicidal ideation lasting from 2 to 6 weeks during treatment. In all cases, suicidal ideation resolved during the study and did not recur during the treatment phase, or at the Week 10 follow-up visit. The participant who reported suicidal ideation during the first 6 weeks of treatment endorsed chronic suicidal ideation for the 22 months prior to study entry.

4. Discussion

The authors report the results of an open-label study of adjunctive creatine for female adolescents with SSRI-resistant MDD. The aims of the study were twofold: 1) to obtain pilot

data for creatine augmentation in this population; and 2) to demonstrate the feasibility of pre- and post-treatment ^{31}P MRS brain scans for in vivo measurement of bioenergetic neurometabolites. Eight weeks of creatine augmentation was associated with a mean decrease in CDRS-R score from 69 to 30.6. Because brain tissue is unavailable for pathologic sampling, the lack of non-invasive assessment tools is a critical barrier to research in the neurobiology of mood disorders (Drevets et al., 2008). Cerebral ^{31}P MRS is the only method capable of in vivo measurement of energy-related metabolites such as PCr and β-NTP, proved to be acceptable to participants and was well-tolerated.

Multiple lines of evidence implicate mitochondrial dysfunction in the pathophysiology of mood disorders. In adults with primary mitochondrial disorders, the rate of MDD is 54% (Fattal et al., 2007), and altered brain energy metabolism has been proposed as the etiology of MDD in pediatric mitochondrial illness (Koene et al., 2009). Mice with neuronal mitochondrial DNA mutations display a depressive phenotype (Kasahara et al., 2006). Support also comes from molecular biology research: in a post-mortem study of MDD and suicide, altered expression of genes involved in ATP synthesis and utilization was found in prefrontal cortex (Klempan et al., 2009). The Genetics of Recurrent Early-Onset Depression (GenRED) project found that matrilineal relatives, i.e. those with the same mitochondrial genome as the proband, were more likely to suffer from a mood disorder than non-matrilineal relatives (Bergemann and Boles, 2010).

We found that brain PCr concentration was increased after 8 weeks in creatine-treated participants compared with untreated controls. During neuronal activation, PCr is rapidly depleted in order to maintain ATP levels at a constant (Rango et al., 1997; Sappey-Marinier et al., 1992). Creatine supplementation reduces levels of cerebral oxygenated hemoglobin during mental tasks, indicating increased oxygen utilization (Watanabe et al., 2002). Creatine also improves working memory and intelligence testing results ($p<0.0001$) in healthy subjects (Rae et al., 2003). Previous work from our group showed that creatine increases brain PCr concentration in healthy volunteers (Lyoo et al., 2003), and that pre-treatment PCr is a robust predictor of treatment response in MDD (Iosifescu et al., 2008). The creatine kinase reaction utilizes PCr to synthesize ATP at 12 times the rate of oxidative phosphorylation, and over 70 times faster than de novo synthesis (Wallimann et al., 1992).

This study is limited by the lack of a placebo control. The placebo response rate in SSRI-resistant adolescent MDD is unknown, but there are two reasons to speculate that the rate could be lower than the placebo response in treatment-naïve MDD: first, it is thought that the placebo response in MDD is inversely proportional to the severity of depression (Fournier et al., 2010). A second reason is that by definition, SSRI-resistant adolescents have already had the opportunity to exhibit the placebo response. In the TORDIA trial, the medication response rate was 40.5% (Brent et al., 2008). If the difference between active drug and placebo response rates in SSRI-resistant adolescent MDD is similar to that found in treatment-naïve patients, we would expect a placebo response of ~29.7% (Brent et al., 2008; Usala et al., 2008). In our open-label study, 3 of 5 participants (60%) experienced a reduction in CDRS-R score of ≥50%. For the Pearson chi-square statistic from a multinomial sample under general conditions (Agresti, 1989), with alpha set at 0.05, a sample size of n=86 (43 subjects per group) would provide a power of 0.803 to detect the

between-group difference. This provides an estimate of the sample size required for a placebo-controlled study of creatine's efficacy in this population.

Our study was limited to female participants, and offers an opportunity to point to the disproportionate burden-of-illness imposed on girls and women by MDD. By the middle teenage years, females experience double the rate of depressive disorders found in males (Garrison et al., 1997; Wade et al., 2002). This 2:1 gender disparity continues throughout women's reproductive years (Kessler et al., 1993). In addition, initial episodes of depression are longer and symptoms more severe in girls compared to boys (McCauley et al., 1993). Girls with MDD also have a longer risk of recurrence, compared with women who experience their first depressive episode in adulthood (Kovacs, 1996, 1997). Depression is the leading cause of disability among females between the ages of 15 and 44 (Murray and Lopez, 1996), implying that adolescent 'window of vulnerability' to depression (Andersen and Teicher, 2008; Hankin et al., 1998) represents a singular opportunity to reduce the burden of illness in MDD.

Polypharmacy is commonplace in the treatment of pediatric MDD (McIntyre and Jerrell, 2009). In fact, multiclass psychotropic treatment occurs in 32.2% of children's physician office visits in which psychotropic medicine is prescribed (Comer et al., 2010). Yet the medical knowledge that is available to guide augmentation psychopharmacology in adolescent MDD is sparse. The updated 2007 *Texas Children's Medication Algorithm* for juvenile MDD states that the best augmentation agent for SSRI partial- or non-responders has not been determined (Hughes et al., 2007). Even in adult MDD, there is little medical scientific evidence to support augmentation with lithium, thyroid hormone, buspirone, stimulants or pindolol (Connolly and Thase, 2011). Given the reality of pediatric polypharmacy and the sizeable proportion of SSRI non-responders, augmentation studies of adolescent MDD are important research priorities (Szigethy, 2011).

An unexpected finding from this study is the resolution of suicidal ideation associated with adjunctive creatine. The related problems of adolescent MDD and suicidality are pressing public health concerns. Data from the Youth Risk Behavior Surveillance System show that 26.1% of U.S. high school students report feeling "*so sad or hopeless almost every day for 2 or more weeks in a row*" during the past year that they stopped some of their usual activities, 13.8% report having "*seriously considered attempting suicide*," and 6.3% endorse having made one or more actual suicide attempts (Eaton et al., 2010). These data are made more striking by the fact that respondents are asked to report on the previous 12 months only — not on their lifetime history. Another study found that 21.9% of adolescents with MDD report having made a suicide attempt (Kessler and Walters, 1998). Further, treatment with antidepressant medication is associated with both suicide attempts and suicide deaths in patients 6–18 years of age with severe depression (Olfson et al., 2006).

At a time when ethicists have argued that antidepressant prescription to pediatric patients should be "severely restricted" (Shearer and Bermingham, 2008), interventions with potential to reduce depressive symptoms and suicidality in adolescent MDD are urgently required. Long studied as an ergogenic supplement for athletic skeletal muscle performance, it is now clear that creatine plays a vital role in brain function (Brosnan and Brosnan, 2007).

Based on these results and evidence from multiple disciplines implicating mitochondrial dysfunction in depression, further study of adjunctive creatine for adolescent females with SSRI-resistant MDD is warranted.

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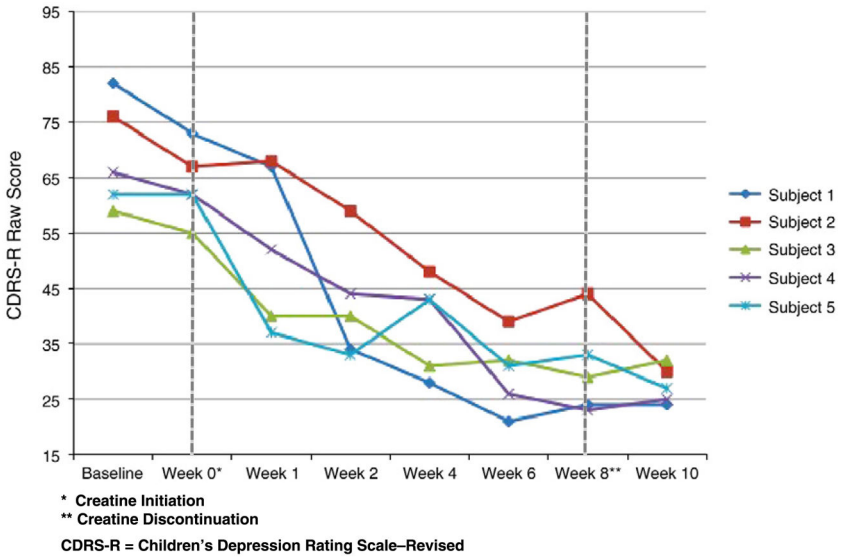

Fig. 1.
CDRS-R scores during adjunctive creatine treatment.

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Table 1

Summary of results for open-label adjunctive creatine treatment for 8 weeks.

#	Age sex	Diagnoses	Duration of MDD episode (weeks)	CDRS-R baseline	CDRS-R final	Adverse events	C-SSRS baseline	C-SSRS during treatment with creatine (weeks)	Concomitant medications
1	16 F	MDD social phobia	32	82	24	Tremor† (Multi-year history of tremor prior to study)	–Active suicidal ideation with plan and intent 5 months prior to study entry –Wish to be dead 2 weeks prior to study drug	None during treatment	Fluoxetine 40 mg Aripiprazole 2.5 mg Clonidine 0.1 mg Clonazepam 0.5 mg
2	15 F	MDD dysthymic disorder social phobia	24	76	44	Suicidal ideation† Sinus congestion† Dyspepsia*	–Suicide Attempt-Overdose 11 months prior to study entry –Wish to be dead 2 weeks prior to study drug	Active suicidal ideation (1–2) Resolved at week 3 No recurrence	Fluoxetine 40 mg Ethinyl estradiol/ levonorgestrel 20 μg/0.1 mg
3	18 F	MDD social phobia	190	59	29	Suicidal ideation† H1N1 influenza† Headache* Nausea/Vomiting*	–Suicide attempt-overdose 5 years prior to study entry –Wish to be dead 1 week prior to study drug	Wish to be dead (1) Resolved at week 2 No recurrence	Fluoxetine 40 mg Norgestimate/ethinyl estradiol 0.25 mg/0.035 mg
4	14 F	MDD	18	66	23	Suicidal ideation† Bruising† Headache* Acne† URI†	–Two suicide attempts-overdose 22 months prior to study entry 5 months prior to study entry –Wish to be dead 1 week prior to study drug	Wish to be dead (1–5) Resolved at week 6 No recurrence	Fluoxetine 20 mg
5	15 F	MDD generalized anxiety disorder	92	62	33	URI† Epistaxis† Headache*	–No lifetime suicidal ideation or suicide attempts	None during treatment	Fluoxetine 40 mg

CDRS-R: Children's Depression Rating Scale-Revised Raw Score.

C-SSRS: Columbia Suicide Severity Rating Scale.

MDD: major depressive disorder.

URI: upper respiratory infection.

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* Adverse event possibly or probably related to study drug.

† Adverse event unrelated to study drug.

Table 2

Baseline and week 8 ^{31}P-MRS results for female adolescents with MDD vs. healthy controls.

	Major depressive disorder (n=5)			Healthy controls (n=6)		
Phosphorus metabolite	**Mean baseline (SD)**	**Mean 8 weeks (SD)**	**p-value**	**Mean baseline (SD)**	**Mean 8 weeks (SD)**	**p-value**
PCr/TP	0.1513 (0.0137)	0.1610 (0.0165)	0.020	0.1556 (0.0086)	0.1558 (0.0154)	0.969
β-NTP/TP	0.1254 (0.0087)	0.1280 (0.0125)	0.729	0.1203 (0.0048)	0.1253 (0.0109)	0.329
pH	7.059 (0.1383)	7.0712 (0.0359)	0.648	7.0526 (0.0290)	7.0294 (0.0143)	0.054
PCr/β-NTP	1.221 (0.0528)	1.2700 (0.1380)	0.528	1.2962 (0.1005)	1.2584 (0.2172)	0.645

Paired *t*-test, 2-tailed.

PCr: Phosphocreatine.

β-NTP: beta-Nucleoside Triphosphate.

TP: Total Phosphorus Resonance.

^{31}P MRS: 31-Phosphorus Magnetic Resonance Spectroscopy.

SD: Standard Deviation.