Depressed Adolescents with Bipolar Disorder Treated with Open-Label Uridine: A (1H-MRSI) and Phosphorus (31P-MRSI) Magnetic Resonance Spectroscopic Imaging Study

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OBJECTIVES
This study had three objectives: (1) to initiate testing of the nutritional supplement uridine as a treatment for depressed adolescents with bipolar disorder, and (2) to compare the concentrations of brain chemical metabolites using 1H-MRSI and 31P-MRSI between adolescents with bipolar depression and healthy controls. 

BACKGROUND
The World Health Organization ranks bipolar disorder (BD) as the 4th most disabling condition among persons 10-24 years of age (Gureje et al., 2011). Adolescents with BD commonly report their symptoms and impairment begin in adolescence. Experts including Husseini Manji have implicated both brain chemistry abnormalities and uridine administration. 

METHODS
The University of Utah IRB approved the study. Written consent & assent were both obtained prior to study procedures. A Data Safety and Monitoring Board met quarterly to monitor data.

Inclusion criteria: female and males ages 13-19 with a primary diagnosis of BD I or BD II and currently untreated. A negative side-effect rated new score > 40. Medication-free and medicated adolescents were enrolled.

Exclusion criteria: history of serious medical illness or psychiatric illness and history of self-harm or suicide attempt.

Controls, including N-acetyl aspartate (NAA), choline, and the phosphocreatine (PCr) ratio > 10; psychotic symptoms; increased pH; and suicidal ideation.

Baseline neuroimaging and HC, performed 6 weeks from start of treatment.

RESULTS: Clinical Measures
We enrolled 22 depressed adolescents with BD and 24 HC. There were no medication-related adverse events among BD participants. No suicide attempts or suicides in the BD group. As shown in FIGURE 3, the mean CORS-R score during 6 weeks of treatment with uridine was 32.3 (SD = 0.3), a decrease of 49%

FIGURE 3 CORS-R Scores During 6 Weeks of Open-Label Uridine in Depressed Adolescents with Bipolar Disorder

We found improved phospholipid metabolism. 

1. Increased synthesis of monoamines, improved mitochondrial function, increased pH, and improved phospholipid metabolism.

2. Despite the fact that more than 50% of pediatric BD patients experience a major depressive episode, there are no FDA-approved treatments for bipolar depression.

3. Antipsychotics (SGAs).

4. Despite the fact that more than 50% of pediatric BD patients experience a major depressive episode, there are no FDA-approved treatments for bipolar depression.

5. It is important to note that the mean CDRS-R score during 6 weeks of treatment with uridine was 32.3 (SD = 0.3), a decrease of 49%.

Baseline neuroimaging was acquired on 14 BD and 24 HC. No intracranial abnormalities were detected on anatomic MRIs. There were no significant between-group differences between BD and HC in age, educational level, or handedness.

The BD participants included both unmedicated (n=8) and medicated (n=6) adolescents. Four unmedicated BD participants were medication-naive. The remaining 4 uridine-treated BD participants had a median medication-free period of 27.4 (range: 3-60) days at study entry.

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