

# Brain 31P-MRS at 4.0 Tesla: Effects of Triacetyluridine (TAU) in the treatment of mood disorders

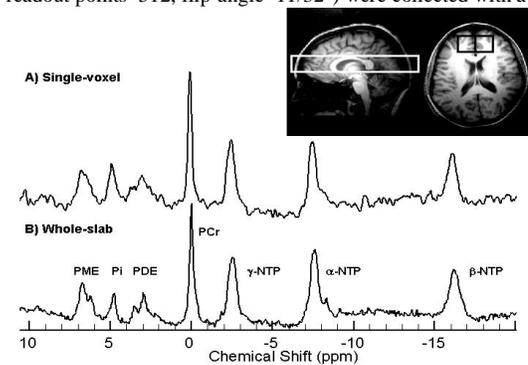
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**Abstract:** Eleven patients diagnosed with major depression (N=6) and bipolar disorder (N=5) in an ongoing study were treated with oral doses of Triacetyluridine (TAU), a pro-drug that is converted to uridine in the body (1). Subjects were assessed with mood rating scales throughout the course of the study. Depressed subjects showed improvement from baseline (mean score 24.5±10.3) to week 6 (mean score 15.5±10.5) as indicated by Montgomery-Asberg Depression Rating Scale (MADRS) scores (p<0.05). Bipolar subjects improved as shown by decreases in Young Mania Rating Scale (YMRS) scores from baseline (mean score 6.2±4.09) to week 6 (mean score 3.0±4.2) (p<0.05). Eight subjects also completed phosphorus MRSI scans, which were conducted immediately pre and 6 weeks post-treatment with TAU. B-NTP and total NTP levels were reduced in the right frontal-cortex in all subjects post-treatment compared to baseline by 35±13% and 17±4%, respectively (p<0.05). PCr/B-NTP ratio was increased in this region after treatment by 47±23% (p<0.05). Total NTP was reduced in the left-temporal lobe by 14±2% (p<0.01).

**Introduction:** Past studies suggest a link between high-energy phosphate levels in the frontal lobe and depression (2, 3), and it has been suggested that treatment with uridine could provide a possible medication strategy. Aside from being a major structural and informational component of RNA, uridine can be converted into high-energy phosphate compounds (1). A past study showed that patients with various types of depression synthesize less uridine than controls, and that administration of uridine acts as an antidepressant (4). Another study administering uridine to rats indicates that it has antidepressant effects (5). Triacetyluridine (TAU), a pro-drug (Repligen – Waltham, MA) is converted to free uridine in the body. It is therefore hypothesized that treatment with TAU will affect B-NTP levels in the brains of patients with mood-disorder, compared to baseline.

**Methods:** Patients undergoing TAU (Repligen, Waltham, MA) therapy for major depression (N=6) or bipolar disorder (N=5) were recruited from the greater Boston area (age: 49±10yrs, 3 male, 8 female). Subjects received an increasing dose of TAU over the course of the study as follows: wks 1-2: 6 grams/day; wks 3-4: 12 grams/day; wks 5-6: 18 grams/day. The Montgomery-Asberg Depression Rating Scale (MADRS) (6), 11-item Young Mania Rating Scale (YMRS) (7), and the Global Assessment of Functioning (GAF) (8) were administered and completed by all subjects at baseline, week 1, 2, 3, 4, and 6. Eight patients (4 major depression, 4 bipolar) also participated in MRSI examinations and were scanned prior to commencing treatment at baseline and after 6 weeks of therapy. All data were collected on a Varian/UnityINOVA 4 Tesla(T) whole-body MR imaging system. High-resolution T<sub>1</sub> and T<sub>2</sub>-weighted axial image sets (TE/TR=6.2/11.4ms, field-of-view (FOV)=24x24x16cm, readout-duration=4ms, receive bandwidth= ±32kHz, data matrix size=128x256x32, in-plane resolution=0.94x1.88mm, slice thickness=5mm, readout points=512, flip-angle=11/32°) were collected with a 3D-FLASH sequence for post-acquisition voxel placement and partial-volume analysis. An optimized 2D-MRSI, pulse-acquire sequence acquired <sup>31</sup>P-MRSI data from a 3cm thick slab placed axially through the basal ganglia and frontal cortex (matrix size=8x8, TR=3s; tip-angle=80°; Rx bandwidth=±2 kHz; complex-points=1024; readout duration=256ms; NEX=k-space weighted; pre-acquisition delay=1.2ms; field of view (FOV)=24x24cm; nominal volume=27ml, scan-time=23min). The spectroscopic imaging data were Fourier-transformed to localize spectra. Spectra were extracted from the following regions for each patient for baseline and post-treatment scans: bilateral frontal-cortex, basal-ganglia, thalamus, temporal-cortex, as well as phase-corrected/whole-slab summed spectra. Metabolite peak areas were obtained using an iterative, time-domain fitting routine with prior knowledge. Repeated measures



**Figure 2** – Right: Mean 31P metabolite ratios pre and post treatment (A). PCr/B-NTP ratios pre(1) and post(2) treatment with TAU plotted for each subject (B). PCr/b-NTP ratio in (B) scaled x10 for visual display. (\* p<0.05).

**Results/Discussion:** Depressive symptoms for depressed subjects improved from baseline (mean score 24.5±10.3) to week 6 (mean score 15.5±10.5) as indicated by MADRS (p<0.05). In addition, an encouraging trend was seen in GAF scores of depressed subjects (mean scores baseline: 58.3±9.3; wk 6: 64.2±10.2; p=.18). Mania symptoms for bipolar subjects improved as shown by decreases in Young Mania Rating Scale (YMRS) scores from baseline (mean score 6.2±4.09) to week 6 (mean score 3.0±4.2) (p<0.05). Brain metabolite levels for the right frontal cortex are given in figure 1-B. B-NTP was reduced on average by 35±13% after treatment with TAU and total NTP was reduced by 17±4%, (p<0.05). The PCr/B-NTP ratio increased in all 8 subjects (p<0.05) studied on average by 47±23% in the right frontal cortex (figure 1-A). Total NTP was also reduced in the left-temporal lobe (14±2% - p<0.01). No energy metabolite level changes were detected in any other region studied with treatment. Although PCr did not show any change in these, or any other region, PCr/B-NTP ratio suggests a strong and consistent shift in brain energetics with TAU across all subjects in the right frontal lobe. This trend in altered energy metabolism should become more apparent as more subjects are included in this ongoing study.

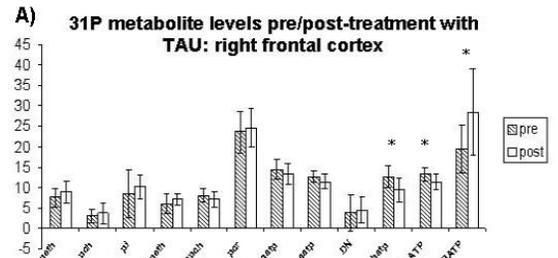
**Conclusions:** Oral administration of TAU demonstrates mood-stabilizing effects in both depressed and bipolar subjects. TAU also causes a consistent and detectable shift in brain energetics in mood disorder patients in the right frontal cortex, manifested by an increase in PCr/B-NTP ratio.

## References:

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AVOVA determined significance in metabolite level differences between scans.

**Figure 1** – Left: Single-voxel and whole-slab spectra. Voxel size is 27cc, scan-time was 23 minutes.



**B) PCr/B-NTP for 8 subjects pre / post treatment: right frontal cortex**

