VA | U.S. Department of Veterans Affairs

Clinical and Imaging Biomarker Trial of Uridine for Veterans with Suicidal Ideation

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Rocky Mountain Mental Illness, Research, Education and Clinical Center (MIRECC) for Suicide Prevention
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MHBB-012-16F | 5-Year Merit Review Study [CX-16-001]

ROCKY MOUNTAIN MIRECC

Disclosure Statement

- **Research Support**:
  - VA ORD Grants CX001611, CX00812 and BX002908.
  - NIDA Grants DA024070, DA043248 and DA041134.
  - NIMH Grant MH096858.
  - NARSAD Young Investigator Award.
  - U.S. Dept. of Veterans Affairs Mental Illness Research, Education and Clinical Center (MIRECC).
  - The Depressive and Bipolar Disorder Alternative Treatment Foundation (DBDAT).
  - University of Utah.
- **Drug Company Speaker's Bureau**: None.
- **Pharmaceutical Stock Shareholder**: None.
- **Consultant To Industry**: Dr. Renshaw receives consulting fees from Kyowa Hakko and Tal Medical.

Outline / Objectives

- Discuss VA research that supports the need for a “rapid acting” treatment for Veterans with suicidal ideation.
- Describe the rationale for studying oral Uridine as a “rapid” and hypothesis-driven treatment for suicidal ideation, through its shared mechanisms with two other “anti-suicidal” drugs: Lithium and Ketamine.
- Present the: **A)** Clinical (i.e. suicidal ideation) data; and **B)** Neuroimaging results, from 2 prior studies of Uridine for Bipolar Depression, conducted at the University of Utah.
- Discuss the translational integration of pre- and post-treatment brain imaging into clinical trials, i.e. “Target Engagement.”
- Q & A

Poll Question #1

- **Do You Currently Fulfill a Role in the VA Healthcare System, That Requires You to:**

  Work With, Create or Administer Policies Regarding, or Make Decisions That Potentially Affect – Veterans with Suicidal Ideation?

  - Yes.
  - No.

Veteran Suicide: The Scope of the Problem (2001-14)

- An average of **20** Veterans died by suicide each day.
- The rate of suicide among Veterans has increased by **31%**.
- Adjusting for age and gender, the risk for suicide is **22%** higher among Veterans vs. civilians.
- The increase has disproportionately affected Female Veterans:
  - Suicide risk is **2.5 times higher** in Female Veterans vs. civilians.
  - The suicide rate among Female Veterans has increased by **62%**.

Source: ***Facts About Veteran Suicide: August 2017 Fact Sheet*****. U.S. Department of Veterans Affairs, Office of Mental Health and Suicide Prevention (OMHSP).**

Recent Research May Point to a "Window of Opportunity"

- **23% of Veteran suicides occur within 7 days of the decedent's final VA visit, and 51% within 30 days of their final appointment.**
  (Smith et al. *Journal of Clinical Psychiatry* 2011; 72(5):622-9.)

- **A key 'warning sign' that increases the risk of death by suicide is documented Suicidal Ideation (Odds Ratio 3.46).**
  (Britton et al. *Psychiatry Research* 2012;200(2-3):395-9.)

- **"Lack of Access" to mental health services may be contributing to high suicide rate among Veterans.**
  (Hester RD. *International Journal of Mental Health Systems* 2017; 11(1):47-50.)

Current VA Research: Focus on Lithium and Ketamine

- **VA Cooperative Studies Program (CSP) #590: Lithium for Suicidal Behavior in Mood Disorders (Li+).**
  - Recruitment goal is n=1,862 Veterans at 30 VA sites.
  - Treatment with Lithium or Placebo for 1 year.

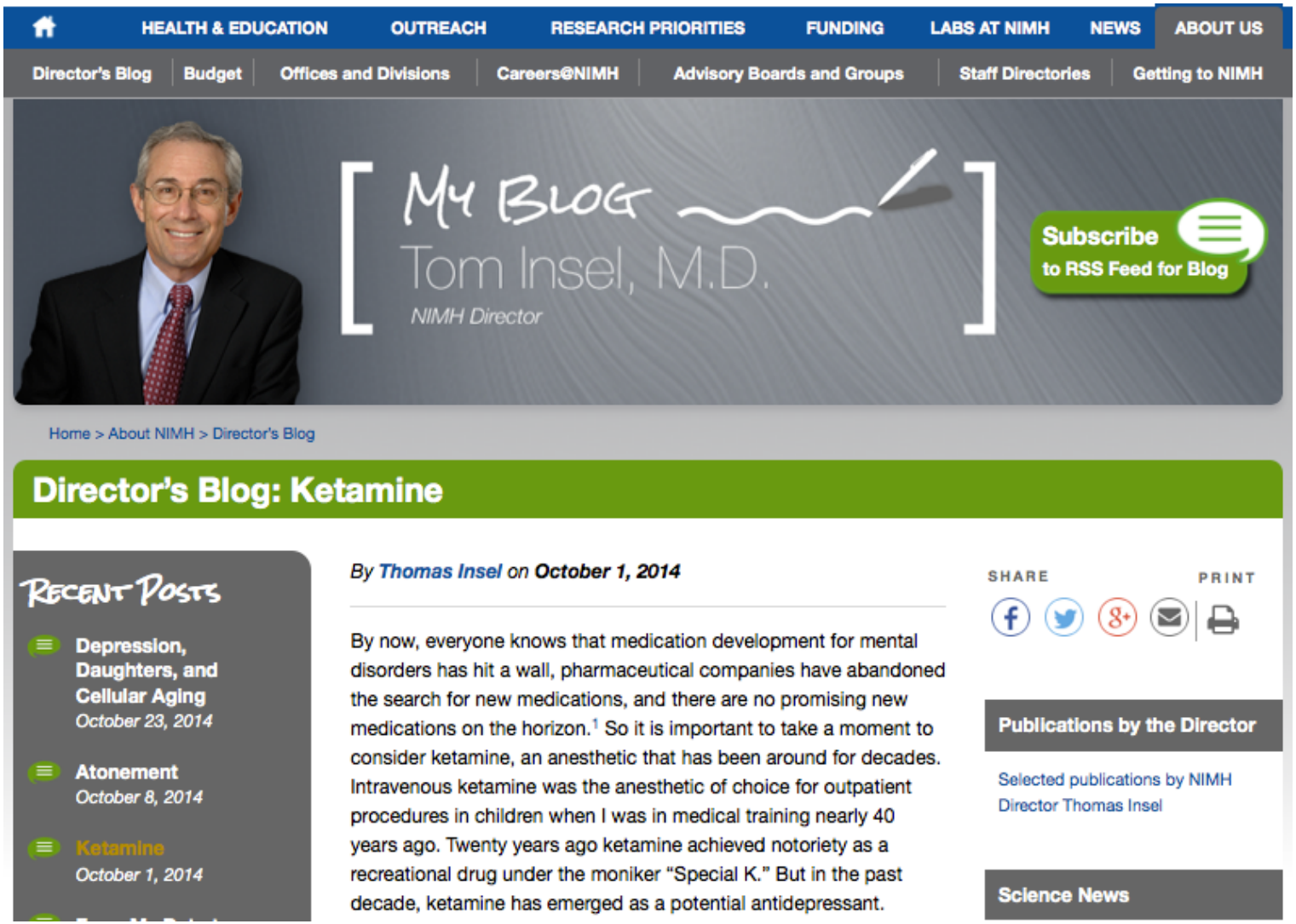
- **The ClinicalTrials.gov website shows six Ketamine Studies (5 for Mental Health Indications) Currently Recruiting:**

Row	Saved	Status	Study Title	Conditions	Locations
1	☐	Recruiting	**Ketamine** Infusion Therapy for PTSD in Combat **Veterans**	• Stress Disorders, Post-Traumatic	• Klarisana San Antonio, Texas, United States
2	☐	Recruiting	Open Label **Ketamine** Treatment for Major Depressive Disorder in **Veterans**	• Major Depressive Disorder	• VA Healthcare System West Haven, Connecticut, United States
3	☐	Recruiting	CAP-**Ketamine** for Antidepressant Resistant PTSD	• PTSD • Posttraumatic Stress Disorder	• VA Connecticut Healthcare System West Haven Campus, West Haven, CT West Haven, Connecticut, United States • Brooke Army Medical Center San Antonio, Texas, United States
4	☐	Recruiting	Efficacy of Repeated **Ketamine** Infusions for Treatment-resistant Depression	• Treatment-resistant Depression	• Minneapolis VA Health Care System, Minneapolis, MN Minneapolis, Minnesota, United States
5	☐	Recruiting	A Pilot Clinical Trial of Oral **Ketamine** for Acute Pain Management After Amputation Surgery	• Acute Pain Management • Analgesic, Nonopioid • Amputation of Lower Extremity, All Causes	• Rush University Medical Center Chicago, Illinois, United States
6	☐	Recruiting	**Ketamine** for Treatment Resistant Late-Life Depression	• Treatment Resistant Depressive Disorder	• Michael E. DeBakey VA Medical Cer Houston, Texas, United States

Poll Question #2

- **Have you Read and/or Heard About, the Excitement Surrounding Ketamine, as the New Rapid-Acting 'Wonder Drug' in Psychiatry?**
  - Yes.
  - No.
  - I'm not sure.

Ketamine: Intravenous (I.V.) Anesthesia Drug Has Generated Excitement



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Director's Blog: Ketamine

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- Atonement — October 8, 2014
- Ketamine — October 1, 2014

*By **Thomas Insel** on **October 1, 2014***

SHARE PRINT

By now, everyone knows that medication development for mental disorders has hit a wall, pharmaceutical companies have abandoned the search for new medications, and there are no promising new medications on the horizon.[1] So it is important to take a moment to consider ketamine, an anesthetic that has been around for decades. Intravenous ketamine was the anesthetic of choice for outpatient procedures in children when I was in medical training nearly 40 years ago. Twenty years ago ketamine achieved notoriety as a recreational drug under the moniker "Special K." But in the past decade, ketamine has emerged as a potential antidepressant.

Publications by the Director

Selected publications by NIMH Director Thomas Insel

Science News

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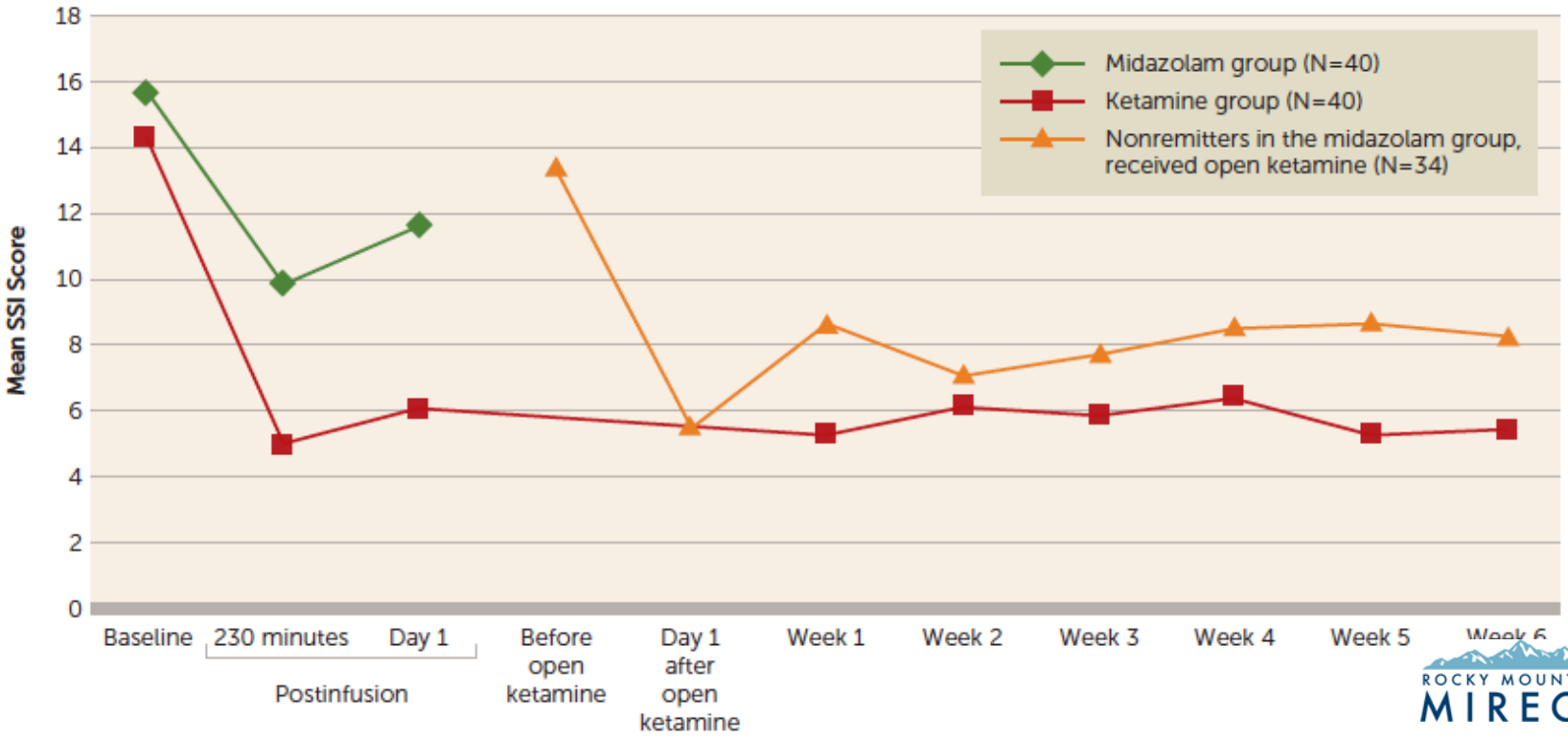
Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial

Michael F. Grunebaum, M.D., Hanga C. Galfalvy, Ph.D., Tse-Hwei Choo, M.P.H., John G. Keilp, Ph.D., Vivek K. Moitra, M.D., Michelle S. Parris, B.A., Julia E. Marver, B.A., Ainsley K. Burke, Ph.D., Matthew S. Milak, M.D., M. Elizabeth Sublette, M.D., Ph.D., Maria A. Oquendo, M.D., Ph.D., J. John Mann, M.D.

FIGURE 1. Change in Suicidal Ideation Over Time in Suicidal Patients With Major Depression Treated With a Subanesthetic Infusion of Ketamine or Midazolam[a]



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Neuroimaging Shows Ketamine Increases the Brain Levels of Two Amino Acid Neurotransmitters: GABA and Glutamine

Mol Psychiatry. 2016 Mar;21(3):320-7. doi: 10.1038/mp.2015.83. Epub 2015 Aug 18.

A pilot in vivo proton magnetic resonance spectroscopy study of amino acid neurotransmitter response to ketamine treatment of major depressive disorder.

Milak MS[1,2], Proper CJ[1], Mulhern ST[1], Parter AL[1], Kegeles LS[1,2], Ogden RT[1,2,3], Mao X[4], Rodriguez CI[1,2], Oquendo MA[1,2], Suckow RF[2,5], Cooper TB[2,5], Keilp JG[1,2], Shungu DC[2,4], Mann JJ[1,2,6].

Author information

Abstract

The N-methyl-D-aspartate receptor antagonist ketamine can improve major depressive disorder (MDD) within hours. To evaluate the putative role of glutamatergic and GABAergic systems in ketamine's antidepressant action, medial prefrontal cortical (mPFC) levels of glutamate+glutamine (Glx) and γ-aminobutyric acid (GABA) were measured before, during, and after ketamine administration using proton magnetic resonance spectroscopy. Ketamine (0.5 mg kg(-1) intravenously) was administered to 11 depressed patients with MDD. Glx and GABA mPFC responses were measured as ratios relative to unsuppressed voxel tissue water (W) successfully in 8/11 patients. Ten of 11 patients remitted (50% reduction in 24-item Hamilton Depression Rating Scale and total score ⩽10) within 230 min of commencing ketamine. mPFC Glx/W and GABA/W peaked at 37.8%±7.5% and 38.0%±9.1% above baseline in ~26 min. Mean areas under the curve for Glx/W (P=0.025) and GABA/W (P=0.005) increased and correlated (r=0.796; P=0.018). Clinical improvement

Neuropsychopharmacology. 2017 May;42(6):1201-1209. doi: 10.1038/npp.2016.184. Epub 2016 Sep 8.

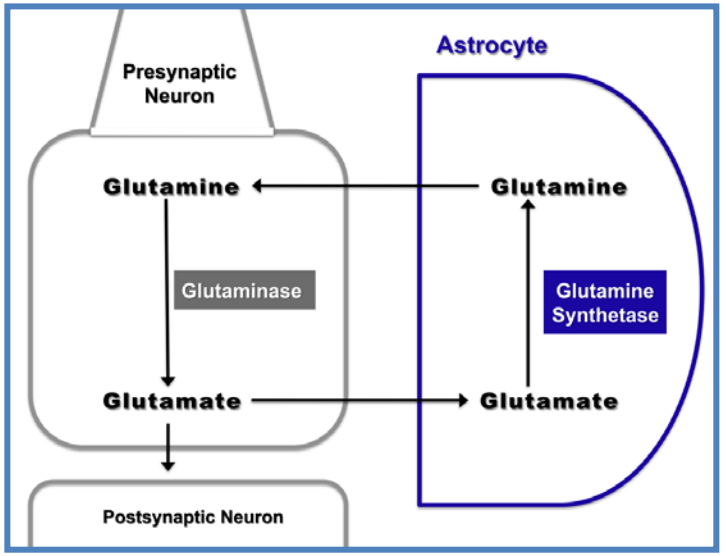
Temporal Dynamics of Antidepressant Ketamine Effects on Glutamine Cycling Follow Regional Fingerprints of AMPA and NMDA Receptor Densities.

Li M[1,2], Demenescu LR[1,2], Colic L[1,3], Metzger CD[4,5,6,7], Heinze HJ[2,3,6,7], Steiner J[6,7], Speck O[3,4,6,8], Fejtova A[3,6,9], Salvadore G[10], Walter M[1,3,6,7,11].

Author information

Abstract

The anterior cingulate cortex (ACC) has shown decreased glutamate levels in patients with major depressive disorder. Subanesthetic doses of ketamine were repeatedly shown to improve depressive symptoms within 24 h after infusion and this antidepressant effect was attributed to increased α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) throughput. To elucidate ketamine's mechanism of action, we tested whether the clinical time course of the improvement is mirrored by the change of glutamine/glutamate ratio and if such effects show a regional and temporal specificity in two distinct subdivisions of ACC with different AMPA/N-methyl-D-aspartate receptor profiles. In a double-blind, placebo-controlled intravenous infusion study of ketamine, we measured glutamate and glutamine in the pregenual ACC (pgACC) and the anterior midcingulate cortex at 1 and 24 h post infusion with magnetic resonance spectroscopy at 7 T. A significant interaction of time, region, and treatment was found for the glutamine/glutamate ratios (placebo, n=14; ketamine, n=12). Post-hoc analyses revealed that the glutamine/glutamate ratio increased significantly in the ketamine group, compared with placebo, specifically in the pgACC after 24 h. The glutamine/glutamate increase in the pgACC caused by ketamine at 24 h post infusion was reproduced in an enlarged sample (placebo, n=24; ketamine, n=20). Our results support a significant temporal and regional response in glutamine/glutamate ratios to a single subanesthetic dose of ketamine, which mirrors the time course of the antidepressant response and reversal of the molecular deficits in patients and which may be associated with the histoarchitectonical receptor fingerprints of the ACC subregions.



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Disruption of the Glutamate-Glutamine-GABA System is Implicated in Suicide and Depression

PLoS One. 2009 Aug 11;4(8):e6585. doi: 10.1371/journal.pone.0006585.

Global brain gene expression analysis links glutamatergic and GABAergic alterations to suicide and major depression.

Sequeira A[1], Mamdani F, Ernst C, Vawter MP, Bunney WE, Lebel V, Rehal S, Klempan T, Gratton A, Benkelfat C, Rouleau GA, Mechawar N, Turecki G.

Author information

1 McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Quebec, Canada.

Table 4. Differentially expressed genes directly implicated in synaptic transmission as determined using DAVID (2006).

Name	Symbol	Cytoband	Entrez Gene
gaba(a) receptor-associated protein like 1	GABARAPL1	12p13.2	23710
gamma-aminobutyric acid (gaba) a receptor, alpha 1	GABRA1	5q34–q35	2554
gamma-aminobutyric acid (gaba) a receptor, alpha 4	GABRA4	4p12	2557
gamma-aminobutyric acid (gaba) a receptor, alpha 5	GABRA5	15q11.2–q12	2558
gamma-aminobutyric acid (gaba) a receptor, beta 1	GABRB1	4p12	2560
gamma-aminobutyric acid (gaba) a receptor, delta	GABRD	1p|1p36.3	2563
gamma-aminobutyric acid (GABA) A receptor, gamma 1	GABRG1	4p12	2565
gamma-aminobutyric acid (gaba) a receptor, gamma 1	GRIA2	4q32–q33	2891
gamma-aminobutyric acid (gaba) a receptor, gamma 2	GABRG2	5q31.1–q33.1	2566
gamma-aminobutyric acid (gaba) b receptor, 2	GABBR2	9q22.1–q22.3	9568
gamma-aminobutyric acid (gaba) receptor, rho 1	GABRR1	6q14–q21|6q13–q16.3	2569
glutamate dehydrogenase 1	GLUD1	10q23.3	2746
glutamate receptor, ionotrophic, ampa 3	GRIA3	Xq25–q26	2892
glutamate receptor, ionotropic, ampa 1	GRIA1	5q33|5q31.1	2890
glutamate receptor, ionotropic, ampa 2	GRIA2	4q32–q33	2891
glutamate receptor, ionotropic, kainate 1	GRIK1	21q22.11	2897
glutamate receptor, ionotropic, n-methyl d-aspartate 2a	GRIN2A	16p13.2	2903
glutamate receptor, metabotropic 3	GRM3	7q21.1–q21.2	2913

In vivo measurement of Glutamate, Glutamine and GABA:

Two-dimensional J-Resolved Proton-1 MR Spectroscopy and Prior Knowledge Fitting *(ProFit)*

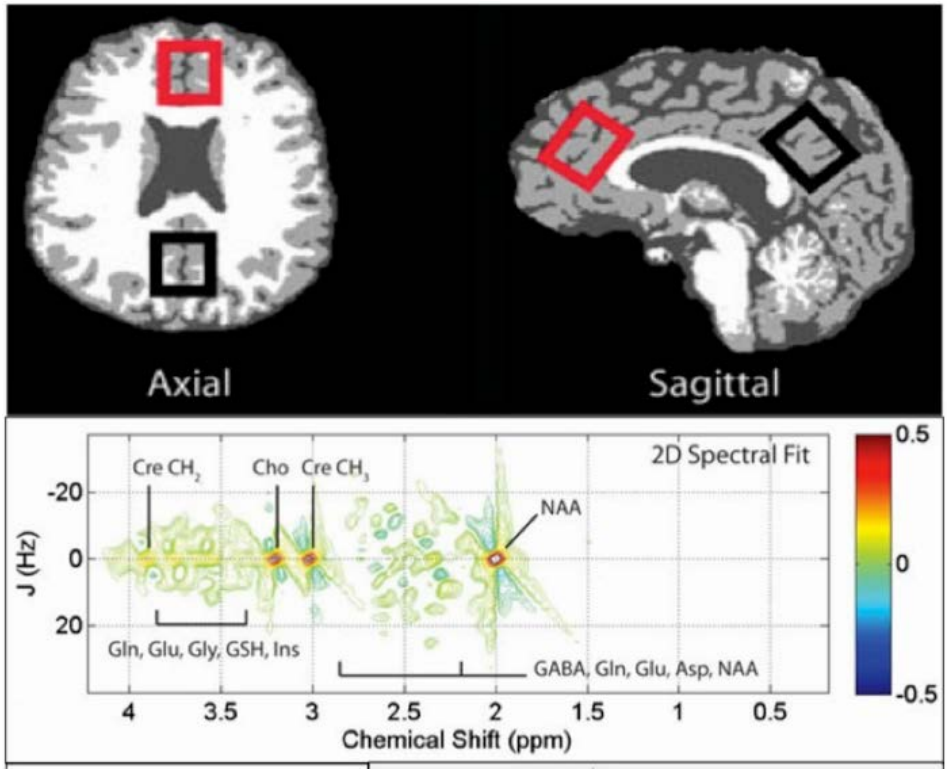
J Magn Reson Imaging. 2013 Mar;37(3):642-51. doi: 10.1002/jmri.23848. Epub 2012 Oct 10.

Two-dimensional J-resolved proton MR spectroscopy and prior knowledge fitting (ProFit) in the frontal and parietal lobes of healthy volunteers: assessment of metabolite discrimination and general reproducibility.

Prescot AP[1], Renshaw PF.

Author information

1 Brain Institute, Department of Radiology, University of Utah School of Medicine, Salt Lake City, Utah 84108, USA. andrew.prescot@utah.edu



Gln, Glutamine
Glu, Glutamate
Gly, Glycine
GSH, Glutathione
Ins, myo-Inositol
Asp, Aspartate
NAA, N-acetylaspartate

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Ketamine works through, and its antidepressant effect is dependent on, mTOR (aka mTORC1; the Mechanistic Target of Rapamycin)

Science. 2010 Aug 20;329(5994):959-64. doi: 10.1126/scien

mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists.

Li N[1], Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS.

Author information

Abstract

The rapid antidepressant response after ketamine administration in treatment-resistant depressed patients suggests a possible new approach for treating mood disorders compared to the weeks or months required for standard medications. However, the mechanisms underlying this action of ketamine [a glutamate N-methyl-D-aspartic acid (NMDA) receptor antagonist] have not been identified. We observed that ketamine rapidly activated the mammalian target of rapamycin (**mTOR**) pathway, leading to increased synaptic signaling proteins and increased number and function of new spine **synapses** in the prefrontal cortex of rats. Moreover, blockade of **mTOR** signaling completely blocked ketamine induction of synaptogenesis and behavioral responses in models of depression. Our results demonstrate that these effects of ketamine are opposite to the synaptic deficits that result from exposure to stress and could contribute to the fast antidepressant actions of ketamine.

The Function of mTOR is to Activate Pyrimidine Synthesis…

15 MARCH 2013 VOL 339 **SCIENCE** www.sciencemag.org

Quantitative Phosphoproteomics Reveal mTORC1 Activates de Novo Pyrimidine Synthesis

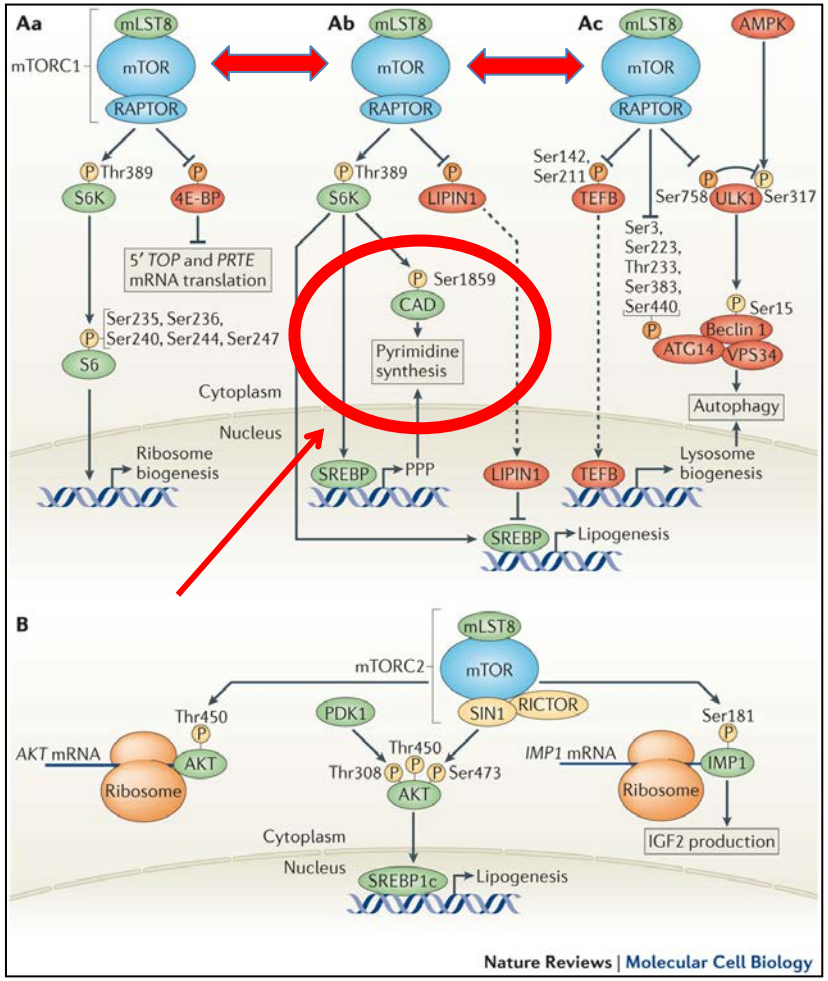
Aaron M. Robitaille,[1] Stefan Christen,[2] Mitsugu Shimobayashi,[1] Marion Cornu,[1] Luca L. Fava,[1]* Suzette Moes,[1] Cristina Prescianotto-Baschong,[1] Uwe Sauer,[2] Paul Jenoe,[1] Michael N. Hall[1]†

The Ser-Thr kinase mammalian target of rapamycin (mTOR) controls cell growth and metabolism by stimulating glycolysis and synthesis of proteins and lipids. To further understand the central role of mTOR in cell physiology, we used quantitative phosphoproteomics to identify substrates or downstream effectors of the two mTOR complexes. mTOR controlled the phosphorylation of 335 proteins, including CAD (carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase). CAD catalyzes the first three steps in de novo pyrimidine synthesis. mTORC1 indirectly phosphorylated CAD-S1859 through S6 kinase (S6K). CAD-S1859 phosphorylation promoted CAD oligomerization and thereby stimulated de novo synthesis of pyrimidines and progression through S phase of the cell cycle in mammalian cells. Thus, mTORC1 also stimulates the synthesis of nucleotides to control cell proliferation.

Stimulation of de Novo Pyrimidine Synthesis by Growth Signaling Through mTOR and S6K1

Issam Ben-Sahra,[1]* Jessica J. Howell,[1]* John M. Asara,[2] Brendan D. Manning[1]†

Cellular growth signals stimulate anabolic processes. The mechanistic target of rapamycin complex 1 (mTORC1) is a protein kinase that senses growth signals to regulate anabolic growth and proliferation. Activation of mTORC1 led to the acute stimulation of metabolic flux through the de novo pyrimidine synthesis pathway. mTORC1 signaling posttranslationally regulated this metabolic pathway via its downstream target ribosomal protein S6 kinase 1 (S6K1), which directly phosphorylates S1859 on CAD (carbamoyl-phosphate synthetase 2, aspartate transcarbamoylase, dihydroorotase), the enzyme that catalyzes the first three steps of de novo pyrimidine synthesis. Growth signaling through mTORC1 thus stimulates the production of new nucleotides to accommodate an increase in RNA and DNA synthesis needed for ribosome biogenesis and anabolic growth.



…and the Endogenous, Circulating Pyrimidine in Humans = Uridine

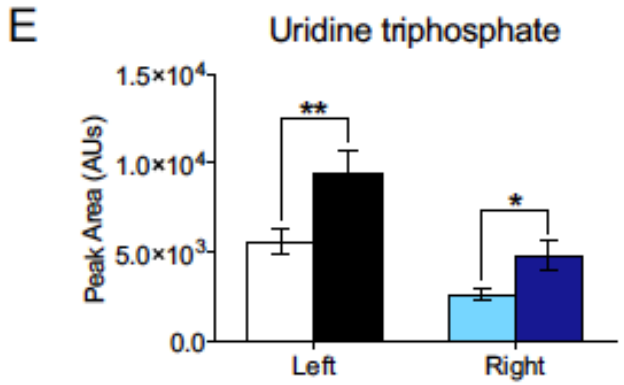
ARTICLE

Prophylactic ketamine alters nucleotide and neurotransmitter metabolism in brain and plasma following stress

Josephine C. McGowan[1], Collin Hill[2], Alessia Mastrodonato[3,4], Christina T. LaGamma[4], Alexander Kitayev[2], Rebecca A. Brachman[3], Niven R. Narain[2], Michael A. Kiebish[2] and Christine A. Denny[3,4]

Recently, we have shown that ketamine given prior to stress exposure protects against the development of depressive-like behavior in mice. These data suggest that it may be possible to prevent the induction of affective disorders before they develop by administering prophylactic pharmaceuticals, a relatively nascent and unexplored strategy for psychiatry. Here, we performed metabolomics analysis of brain and plasma following prophylactic ketamine treatment in order to identify markers of stress resilience enhancement. We administered prophylactic ketamine in mice to buffer against fear expression. Following behavioral analyses, untargeted metabolomic profiling was performed on both hemispheres of the prefrontal cortex (PFC) and the hippocampus (HPC), and plasma. We found that prophylactic ketamine attenuated learned fear. Eight metabolites were changed in the PFC and HPC upon ketamine treatment. Purine and pyrimidine metabolism were most significantly changed in the HPC, PFC, and, interestingly, plasma of mice two weeks after prophylactic administration. Moreover, most precursors to inhibitory neurotransmitters were increased whereas precursors to excitatory neurotransmitters were decreased. Strikingly, these long-term metabolomic changes were not observed when no stressor was administered. Our results suggest that prophylactic treatment differentially affects purine and pyrimidine metabolism and neurotransmission in brain and plasma following stress, which may underlie the long-lasting resilience to stress induced by a single injection of ketamine. These data may provide novel targets for prophylactic development, and indicate an interaction effect of prophylactic ketamine and stress. To our knowledge, this is the first study that identifies metabolomic alterations and biomarker candidates for prophylactic ketamine efficacy in mice.

Neuropsychopharmacology (2018) 0:1–9; https://doi.org/10.1038/s41386-018-0043-7



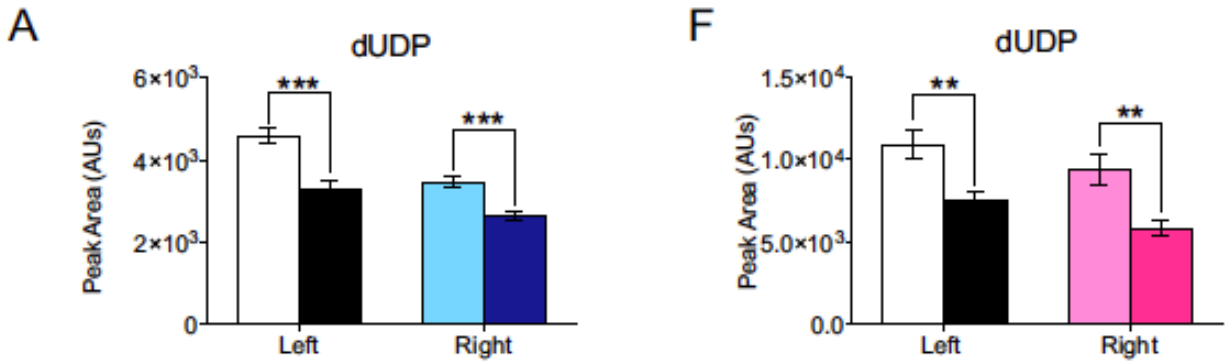


Fig. 4 Prophylactic ketamine significantly alters pyrimidine metabolism in the PFC and HPC following stress. **a–e** Pyrimidine metabolites are significantly altered in both hemispheres of the PFC following prophylactic ketamine administration. **f–h** Pyrimidine metabolites are significantly altered in both hemispheres of the HPC following prophylactic ketamine administration. **i, j** The amount of dUDP in both hemispheres of the PFC, but not the HPC, is positively correlated with freezing levels upon context re-exposure in CFC in mice administered prophylactic ketamine and stress. ($n = 9–10$ male mice per group). Error bars represent ± SEM. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Sal saline, Ket ketamine, PFC prefrontal cortex, HPC hippocampus, dUDP deoxyuridine-diphosphate

TABLE 1 Brain Mechanisms Common to Uridine*, Ketamine and Lithium

Relevant Disease	Effect	Uridine *	Ketamine	Lithium
Suicide	Engages Glutamate System (1H-MRS)	*Preliminary Data*	☑	☑
Suicide	↑ $GABA_A$ Receptor Activity	☑	☑	☑
Suicide	↑ Cortisol or Corticosterone	☑	☑	☑
Suicide	↑ BDNF	☑	☑	☑
Suicide	↓ IL-6	☑	☑	☑
Suicide	↓ GSK3β Function	☑	☑	☑
Suicide	↑ Synapse Formation	☑	☑	☑
Suicide	↑ Long-Term Potentiation	☑	☑	☑
Bipolar Disorder	↑ mTOR Activation	☑	☑	☑
Depression	↑ Forced Swim Test Performance	☑	☑	☑
Traumatic Brain Injury	↑ Outcomes	☑	☑	☑

* Includes Uridine Precursors, and Uridine Nucleotides such as Uridine Triphosphate (UTP)

** Ketamine's rapid antidepressant effect is dependent on mTOR activation (Li, 2010). mTOR activation leads to *de novo* pyrimidine synthesis (Ben-Sahra et al., 2013 Robitaille et al., 2013) and the endogenous, circulating pyrimidine in man = uridine.

Full-text PDF hard copies of all references are available from Dr. Kondo.

Uridine: Advantages Over Ketamine and Lithium

- **SAFETY:** Uridine is a constituent of human breast milk, and commercial infant formula (e.g. Enfamil, Similac).
(Thorell et al. *Pediatric Research* 1996;40(6):845-52; Alles et al. *Current Paediatrics* 2004;14(1):51-63.)

- **TOXICITY:** Ketamine is a derivative of Phencyclidine (a.k.a. PCP or "Angel Dust"). This makes Ketamine a psychotomimetic drug, gives it dissociative properties, and also means it has significant abuse potential.
(*NIDA Research Report Series: Hallucinogens and Dissociative Drugs*. U.S. National Institutes of Health; 2015.)

- **TOXICITY**: Lithium is fatal in overdose, and can cause permanent Brain Damage. If taken for several months or years, it often causes damage to the Kidneys and Thyroid.

- **COST:** Uridine is orally administered. However Ketamine is given I.V., and Lithium requires frequent lab studies/blood work.

- **ACCESS:** Primary Care Clinicians (i.e. Internal Medicine, Family Practice, OB-GYN, Nurse Practitioner, Physician Assistant, Urgent Care, CBOC, etc.) may not feel comfortable prescribing either Ketamine or Lithium.
Also – their VA privileges and credentialing may not allow them to.

Ketamine: Specific Concerns for Military Veterans

- A survey of Military Anesthesiologists revealed concerns regarding delirium, when Ketamine is administered to patients with a history of the following: combat veterans, soldiers with traumatic brain injury (TBI), and patients with post-traumatic stress disorder (PTSD).
(Wilson JT. *American Academy of Nurse Anesthetists Journal* 2014;82(5):355-62.)

- A Systematic Literature Review concluded the anti-suicidal effect of Ketamine is short-lived, lasting from 1-2 days up to a maximum of 10 days. Therefore Ketamine may require repeated administration, if given as a treatment for suicidal ideation; in addition, it is unknown if subsequent Ketamine treatments will have the same clinical effect.
(Reinstatler and Youssef. *Drugs in R&D* 2015;15(1):37-45.)

- There are multiple reports of Ketamine-associated bipolar manic episodes, tolerance and addiction, and dysphoric mood –
however, even more concerning are reports of **Delayed-Onset Suicidal Ideation** (Niciu et al. *Journal of Psychopharmacology* 2013;27(7):651-4) associated with Ketamine treatment, and **Completed Suicide** (Dinis-Oliveira et al. *Forensic Science International* 2010;202(1-3):e23-7) while under the influence of Ketamine.

Poll Question #3

- **Do you Believe it Could "Make a Difference" at Your VA Medical Center, if Non-Mental Health Clinicians Had Access to Prescribing a Safe and Effective Oral Medication, for Veterans with Suicidal Ideation?**
  - Yes.
  - No.
  - Maybe.
  - I don't know.

Prior Studies of Uridine (Pyrimidines) Conducted by Dr. Perry Renshaw

Clinical Trials of Uridine and Uridine Precursors for Bipolar Depression				
Year	**Treatment**	**Subjects**	**Outcomes**	**Reference**
2014	**Uridine**	n=24 adolescents	↓ Glx ↓ CDRS-R	clinicaltrials.gov/show/NCT01805440
2012	Citicoline	n=48 adults	↓ IDS-C	*J Affect Disord* 2012;143:257-60
2011	**Uridine**	n=7 adolescents (total n=24)	↓ CDRS-R	*J Child Adol Psychopharm* 2011;21; 171-5
2009	Cytidine	n=35 adults	↓ Glx; ↓ HAM-D	*Neuropsychopharmacology* 2009;3:1810-8
2008	Triacetyl-**Uridine**	n=11 adults	↓ pH; ↓ MADRS	*Exp Clin Psychopharm* 2008;16:199-206
2007	**Uridine**	n=84 adults	↓ MADRS	clinicaltrials.gov/show/NCT00322764

CDRS-R, Children's Depression Rating Scale-Revised; **Glx**, Glutamate+Glutamine; **HAM-D**, Hamilton Rating Scale for Depression; **IDS-C**, Inventory of Depressive Symptomatology-Clinician Version; **MADRS**, Montgomery-Asberg Depression Rating Scale

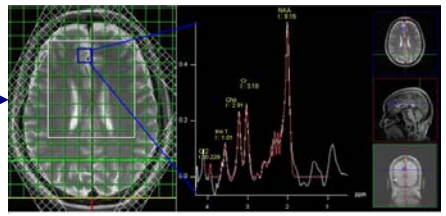
Translational Clinical Trial Design

Healthy Volunteers

Scan #1

Scan #2

GABA
GLUTAMINE/GLUTAMATE
(GLN/GLU RATIO)



Veterans With Suicidal Ideation

Pre-Treatment Scan

Treatment

Post-Treatment Scan

RESPONDERS

NON-RESPONDERS

Suicidal Ideation

Uridine or PBO
1000 mg
B.I.D.

Columbia–SSRS
Beck SSI

ROCKY MOUNTAIN MIRECC

Study #1: Open-Label Uridine for Adolescent Bipolar Depression

TABLE 1 Uridine Open-Label Study Results Including Columbia-Suicide Severity Rating Scale

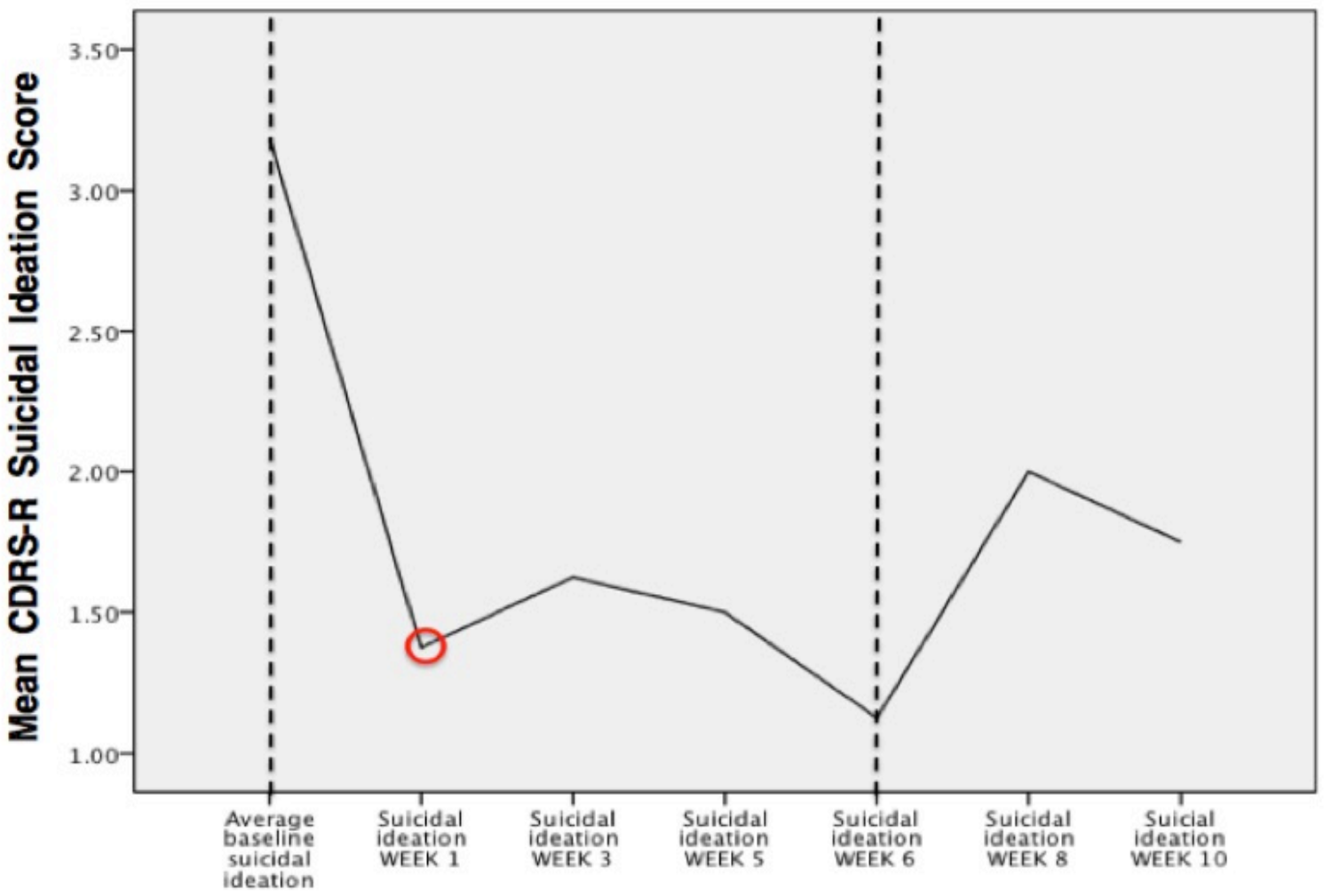
#	Age Sex	Diagnoses	CDRS-R Baseline	CDRS-R (Week)	CGI-S Baseline	CGI-I (Week)	Adverse Events	C-SSRS Baseline	C-SSRS During Treatment (Week 1-5)	C-SSRS Final (Week 6)	Concomitant Medications
1	14 F	Bipolar II ADHD ODD	71	20 (6)	5	2 (6)	None	Wish to be Dead Many Times Daily Unable to Control	None	None	None
2	15 F	Bipolar I ADHD	71	24 (6)	5	2 (6)	Suicidal Ideation†	Wish to be Dead 2-5 Times Weekly Unable to Control	Wish to be Dead 2-5 Times Weekly Unable to Control	None	None
3	17 F	Bipolar NOS ADHD Social Phobia	73	46 (1)	5	3 (1)	Insomnia†	Wish to be Dead Daily or Almost Daily Control With Difficulty	None	None	Aripiprazole 5mg
4	16 F	Bipolar I ADHD GAD	57	37 (6)	4	2 (6)	Vivid Dreams* Abdominal Cramp* Insomnia†	Wish to be Dead Many Times Daily Unable to Control	None	None	Aripiprazole 2mg
5	15 M	Bipolar II ADHD Social Phobia	61	28 (6)	4	2 (6)	Insomnia† Fatigue† Sinusitis† Hordeolum†	None	None	None	None
6	13 M	Bipolar II ADHD	61	27 (6)	4	2 (6)	Abdominal Cramp* Nausea* Diarrhea* Bronchitis†	None	None	None	None
7	17 F	Bipolar NOS	65	28 (2)	5	3 (2)	Dyspepsia* Back Pain†	None	None	None	Norethindrone acetate/ Ethinyl estradiol 1mg/20mg Ranitidine 100mg Calcium 1000mg
8	15M	Bipolar NOS Social Phobia ADHD Combined Encopresis	65	33 (5)	5	2 (5)	Headache Diarrhea Abdominal Cramp	None	None	None	None
9	17M	Bipolar I ADHD Combined Cannabis Dependence	44	30	4	2	Diarrhea Increased Appetite URI Fatigue	Active with Plan/Intent 2-5 Times/Week Control w/Lot of Difficulty	Self-Injurious Behavior	None	Aripiprazole 10mg Fluoxetine 40mg Trazodone 100mg Albuterol MDI prn
10	17M	Bipolar II ADHD Combined	61	29	5	2	Diarrhea Allergic Rhinitis Insomnia Headache	Active With Method (Had Knife in BR)/No Intent Daily or Almost Daily Control w/Lot of Difficulty	None	None	Aripiprazole 2mg Melatonin 3mg

CDRS-R Children's Depression Rating Scale-Revised Score
C-SSRS Columbia-Suicide Severity Rating Scale
CGI-S Clinical Global Impression-Severity Score
CGI-I Clinical Global Impression-Improvement Score
ADHD Attention-Deficit Hyperactivity Disorder
ODD Oppositional Defiant Disorder

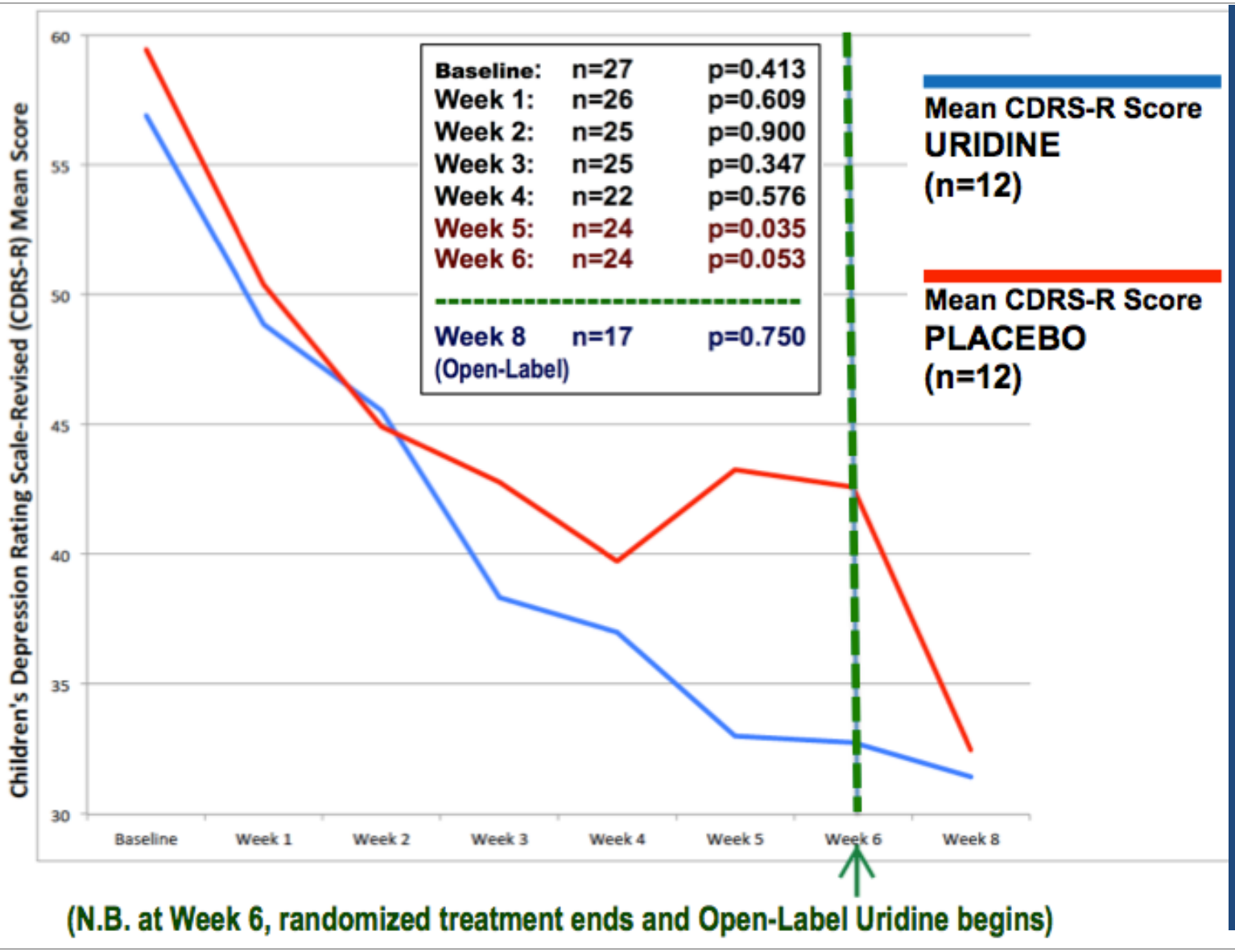
*Adverse Event Possibly Related to Study Drug
†Adverse Event Unrelated to Study Drug

ROCKY MOUNTAIN MIRECC

Study #1: Open-Label Uridine Clinical Trial – Children's Depression Rating Scale-Revised (CDRS-R), Suicidal Ideation Item



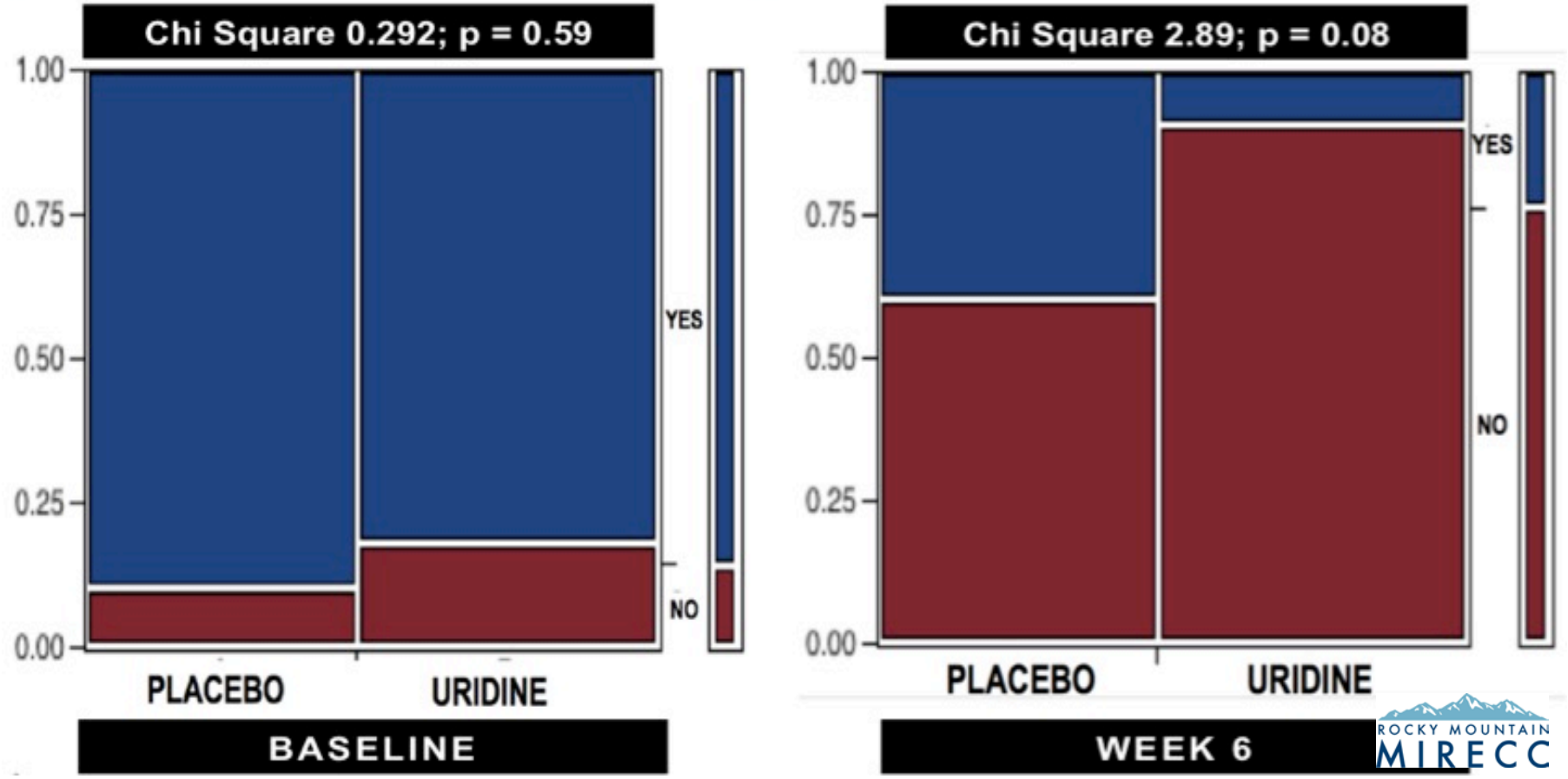
Study #2: Placebo-Controlled Uridine Clinical Trial



Depression Scores During 6 Weeks of Randomized Uridine vs. Placebo

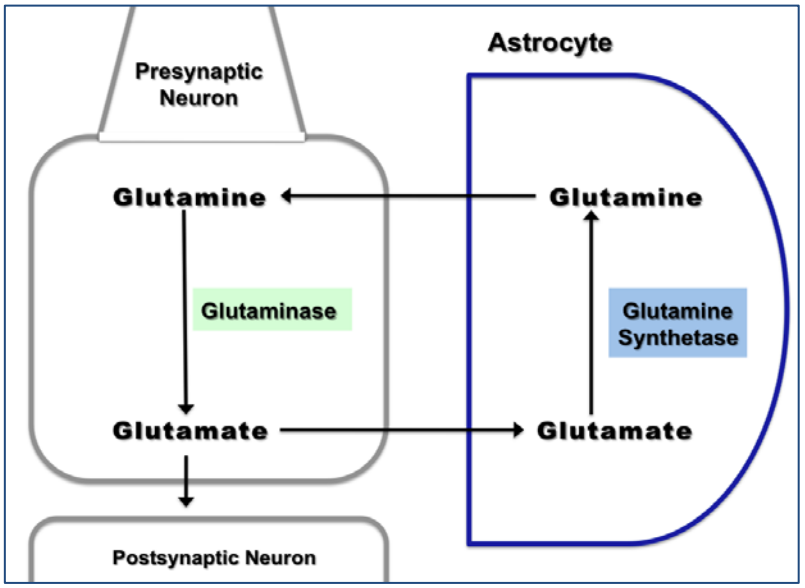
Study #2: Placebo-Controlled Uridine Clinical Trial Columbia-Suicide Severity Rating Scale (C-SSRS) Results

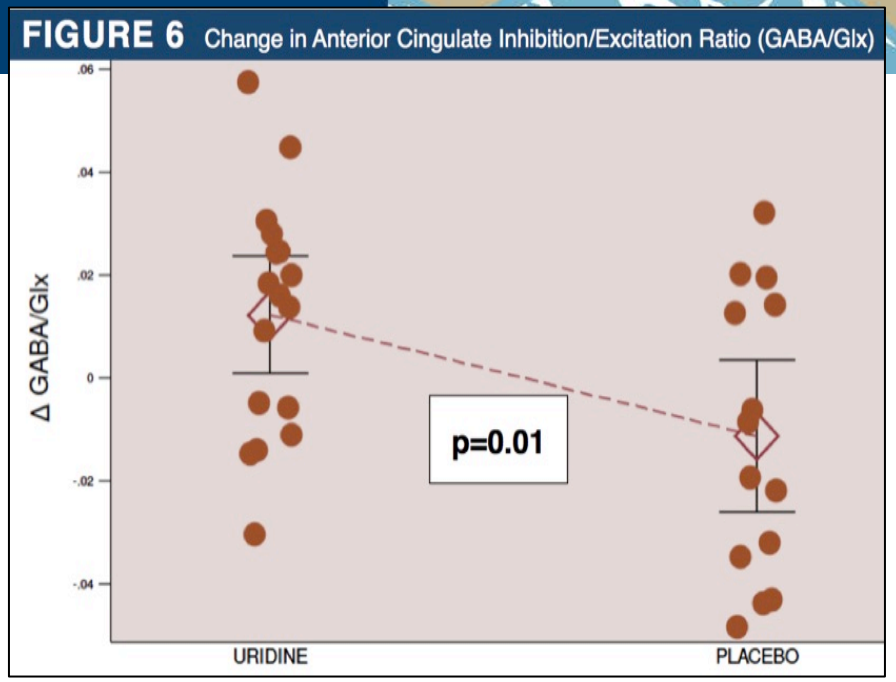
FIGURE 5 Suicidal Behavior (C-SSRS): Uridine vs. Placebo

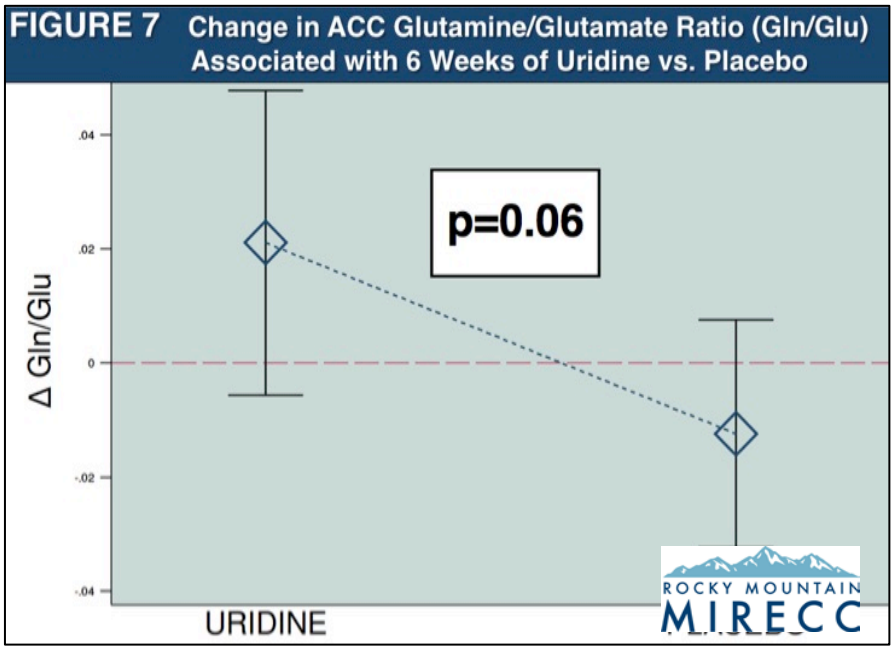


ROCKY MOUNTAIN MIRECC

Study #2: Brain GABA, and the Glutamine/Glutamate Ratio (Gln/Glu) in the Uridine vs. Placebo Groups







Imaging Studies of Ketamine: Impact on Glutamine and GABA

Int J Neuropsychopharmacol. 2012 Sep;15(8):1063-72. doi:

OXFORD ACADEMIC | PMC FREE Full text | Find It

An investigation of amino-acid neurotransmitters as potential predictors of clinical improvement to ketamine in depression.

Salvadore G[1], van der Veen JW, Zhang Y, Marenco S, Machado-Vieira R, Baumann J, Ibrahim LA, Luckenbaugh DA, Shen J, Drevets WC, Zarate CA Jr.

Author information

Abstract

Amino-acid neurotransmitter system dysfunction plays a major role in the pathophysiology of major depressive disorder (MDD). We used proton magnetic resonance spectroscopy (^{1}H-MRS) to investigate whether prefrontal levels of amino-acid neurotransmitters predict antidepressant response to a single intravenous infusion of the N-methyl-D-aspartate (NMDA) antagonist **ketamine** in MDD patients. Fourteen drug-free patients with MDD were scanned 1-3 d before receiving a single intravenous infusion of **ketamine** (0.5 mg/kg). We measured gamma aminobutyric acid (GABA), glutamate, and Glx/glutamate ratio (a surrogate marker of **glutamine**) in the ventromedial prefrontal cortex (VM-PFC) and the dorsomedial/dorsal anterolateral prefrontal cortex (DM/DA-PFC). Correlation analyses were conducted to determine whether pretreatment GABA, glutamate, or Glx/glutamate ratio predicted change in depressive and anxiety symptoms 230 min after **ketamine** administration. Pretreatment GABA or glutamate did not correlate with improved depressive symptoms in either of the two regions of interest ($p>0.1$); pretreatment Glx/glutamate ratio in the DM/DA-PFC was negatively correlated with improvement in depressive symptoms [$r\ s(11)=-0.57$, $p<0.05$]. Pretreatment glutamate levels in the VM-PFC were positively correlated with improvement in anxiety symptoms [$r\ s(11)=0.57$, $p<0.05$]. The findings suggest an association between lower Glx/glutamate ratio and greater improvement in response to **ketamine** treatment. Because **glutamine** is mainly contained in glia, the decreased Glx/glutamate ratio observed in this study may reflect the reduction in glial cells found in the same regions in post-mortem studies of individuals with MDD, and suggests that the presence of this neuropathological construct may be associated with antidepressant responsiveness to **ketamine**.

Am J Psychiatry. 2005 Feb;162(2):394-6.

psychiatryonline full-text article | Find It

Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: a 4-T proton MRS study.

Rowland LM[1], Bustillo JR, Mullins PG, Jung RE, Lenroot R, Landgraf E, Barrow R, Yeo R, Lauriello J, Brooks WM.

Author information

Abstract

OBJECTIVE: The authors' goal was to test in humans the hypothesis that N-methyl-d-aspartate receptor (NMDAR) antagonism results in increased cortical glutamate activity, as proposed by the NMDAR hypofunction model of schizophrenia.

METHOD: 4-T 1H proton magnetic resonance spectroscopy (1H-MRS) was used to acquire in vivo spectra from the bilateral anterior cingulate of 10 healthy subjects while they received a subanesthetic dose of either placebo or **ketamine**, an NMDAR antagonist. Assessments given before and after **ketamine** or placebo administration included the Brief Rating Psychiatric Rating Scale, the Scale for the Assessment of Negative Symptoms, the Clinician-Administered Dissociative States Scale, and the Stroop task.

RESULTS: As predicted, there was a significant increase in anterior cingulate **glutamine**, a putative marker of glutamate neurotransmitter release, with **ketamine** administration. This increase was not related to schizophrenia-like positive or negative symptoms but was marginally related to Stroop performance.

CONCLUSIONS: In humans as in animals, an acute hypofunctional NMDAR state is associated with increased glutamatergic activity in the anterior cingulate.

Mol Psychiatry. 2016 Mar;21(3):320-7. doi: 10.1038/mp.201

PMC Full text | Find It

A pilot in vivo proton magnetic resonance spectroscopy study of amino acid neurotransmitter response to ketamine treatment of major depressive disorder.

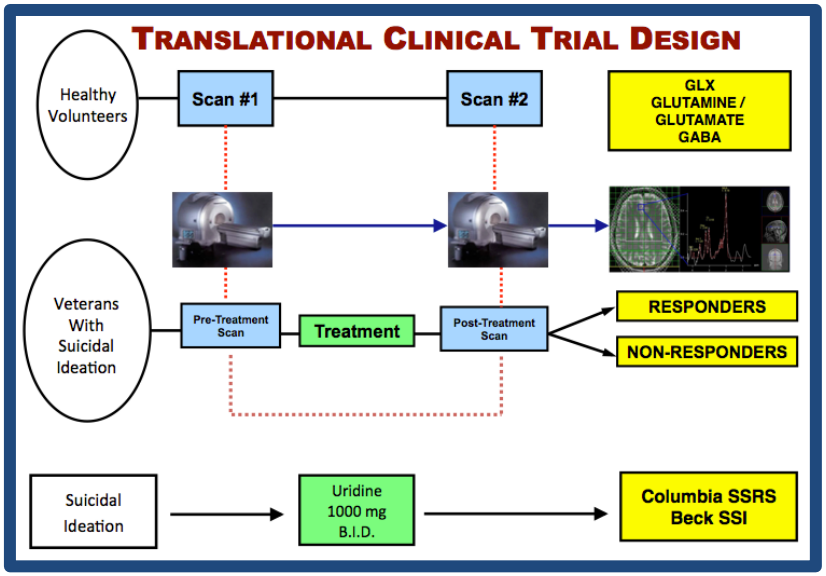
Milak MS[1,2], Proper CJ[1], Mulhern ST[1], Parter AL[1], Kegeles LS[1,2], Ogden RT[1,2,3], Mao X[4], Rodriguez CI[1,2], Oquendo MA[1,2], Suckow RF[2,5], Cooper TB[2,5], Keilp JG[1,2], Shungu DC[2,4], Mann JJ[1,2,6].

Author information

Abstract

The N-methyl-D-aspartate receptor antagonist **ketamine** can improve major depressive disorder (MDD) within hours. To evaluate the putative role of glutamatergic and GABAergic systems in **ketamine**'s antidepressant action, medial prefrontal cortical (mPFC) levels of glutamate+glutamine (Glx) and **γ-aminobutyric acid** (GABA) were measured before, during, and after **ketamine** administration using proton magnetic resonance spectroscopy. **Ketamine** (0.5 mg kg(-1) intravenously) was administered to 11 depressed patients with MDD. Glx and GABA mPFC responses were measured as ratios relative to unsuppressed voxel tissue water (W) successfully in 8/11 patients. Ten of 11 patients remitted (50% reduction in 24-item Hamilton Depression Rating Scale and total score ⩽10) within 230 min of commencing **ketamine**. mPFC Glx/W and GABA/W peaked at 37.8%±7.5% and 38.0%±9.1% above baseline in ~26 min. Mean areas under the curve for Glx/W ($P=0.025$) and GABA/W ($P=0.005$) [illegible]ed ($r=0.796$; $P=0.018$). Clinical improvement correlated with 90-min norketamine [illegible]0.78, $P=0.023$), but no other measures.

ROCKY MOUNTAIN MIRECC



Uridine Placebo-Controlled Randomized Phase (4 Weeks): Schedule of Procedures

WEEK #	- 1	0	1	2	3	4
Informed Consent	☑					
SCID-5-RV Diagnostic Interview	☑					
PhenX Demographic Common Data Elements	☑					
Medical History; Physical Examination	☑					
Laboratory Testing; Urine Drug Screen	☑					☑
Pregnancy Test (females)	☑	☑				☑
Magnetic Resonance Spectroscopy Brain Scan		☑	☑			
Adverse Events; Concomitant Medications	☑	☑	☑	☑	☑	☑
C-SSRS, SSI, SBQ-R, INQ, ACSS, FNRS, BPAQ, RFLI, CAPS, MADRS	☑	☑	☑	☑	☑	☑
Patient Satisfaction; Patient Engagement	☑	☑	☑	☑	☑	☑
Safety Planning Intervention	☑	☑	☑	☑	☑	☑

Progress-to-Date

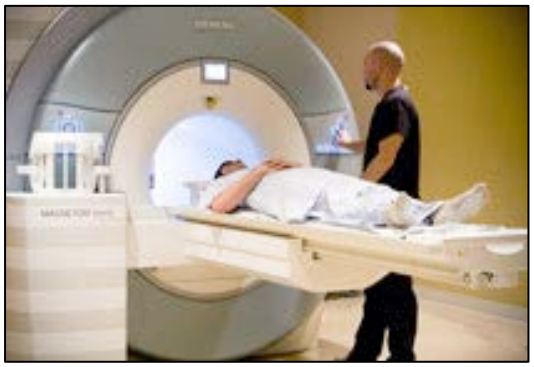
- The U.S. Food and Drug Administration (FDA) has sanctioned the study, after much discussion and debate.
- The University of Utah Institutional Review Board (IRB) application has been approved.
- We have received a Certificate of Confidentiality for the study.
- Year 1 funds arrived on-station in at the Salt Lake City VA on 27 February 2018.
- The study recruitment materials have been created and approved.
- The Salt Lake City R&D office is working with the University of Utah, and VA VISN 19, on the contracts required to allow us to perform our neurochemistry brain scans.
- Two Veteran participants enrolled last week!

Anticipated Outcomes

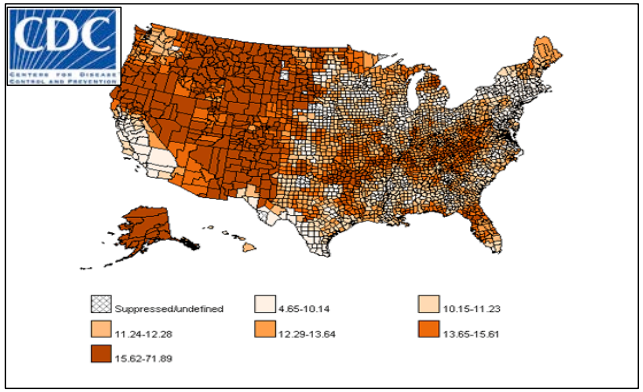
Short Term: Our immediate goal is to examine the feasibility of conducting a VA clinical trial where the inclusion criterion, treatment target, and primary outcome measure is "Suicidal Ideation" (SI) itself – as opposed to an DSM-5/ICD-10 diagnosis such as depression, bipolar disorder, PTSD or TBI. Cross-sectional neuroimaging studies of SI have been conducted, but rarely has a prospective, placebo-controlled clinical trial of SI been attempted; on the contrary, treatment studies inside and outside of VA traditionally 'exclude' individuals who present with suicidal risk.

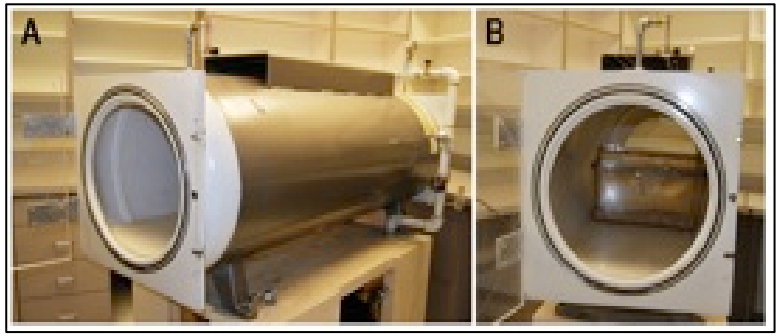
Long Term: The long-term goal of this research is to develop Uridine and related treatments for use in Veterans who are at-risk for suicide, while using non-invasive Magnetic Resonance Spectroscopy brain imaging to elucidate the neural substrates of suicidal behavior in the VA patient population.

ROCKY MOUNTAIN MIRECC FOR SUICIDE PREVENTION



Brain
Energy
Metabolism





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