HOPE FOR DEPRESSION
RESEARCH FOUNDATION

- Lecture: "*Developing Novel Treatments for Major Depression: Focus on Ketamine*"

- Event: HDRF Inaugural Seminar & Luncheon
  New York - October 22nd, 2008

- Speaker: Dennis S. Charney, M.D.
  Anne and Joel Ehrenkranz Dean,
  Mount Sinai School of Medicine
  Executive Vice President for Academic Affairs,
  The Mount Sinai Medical Center
  Interim Chairman, Department of Psychiatry
  Professor, Departments of Psychiatry,
  Nueroscience, and Pharmacology &
  Systems Therapeutics

Developing Novel Treatments for Major Depression: Focus on Ketamine

Dennis S. Charney, M.D.

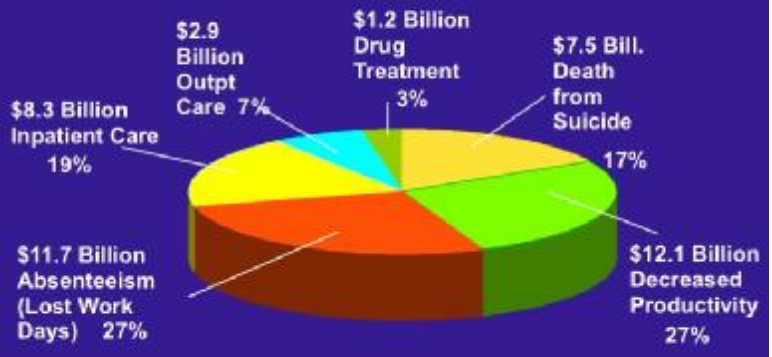
Dean
Mount Sinai School of Medicine

Major Depression-Prevalence

- 18 million people in the U.S (17% of population)
- 340 million people worldwide
- Twice as common in women
- Third most costly disease
- 2/3 of depressed people never treated

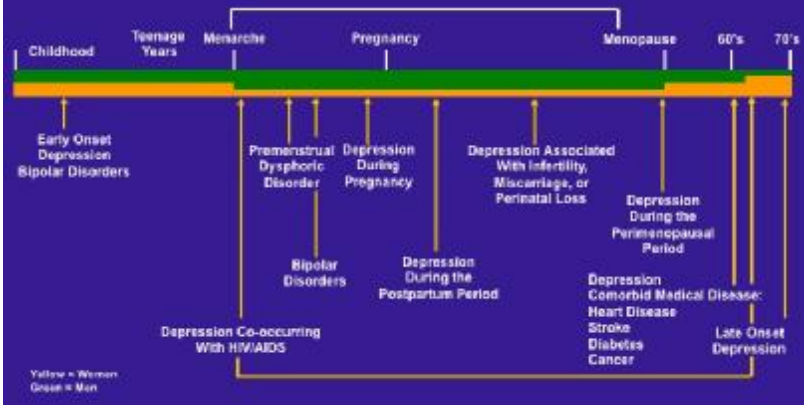
Financial Impact of Depression

Estimated Annual Cost of Depression in U.S.: $43.7 Billion



Depression Guideline Panel. Depression in Primary Care: Vol 1. Detection and Diagnosis. Clinical Practice Guideline No. 5. 1993; Hirschfeld RMA et al. JAMA. 1997;(Jan);277(4):333-340; Finkelstein SN et al. Psychopharmacol Bull. 1996;32(1):13-40; Consensus Conference on Undertreatment of Depression. 1996

Mood Disorders Across the Lifecycle

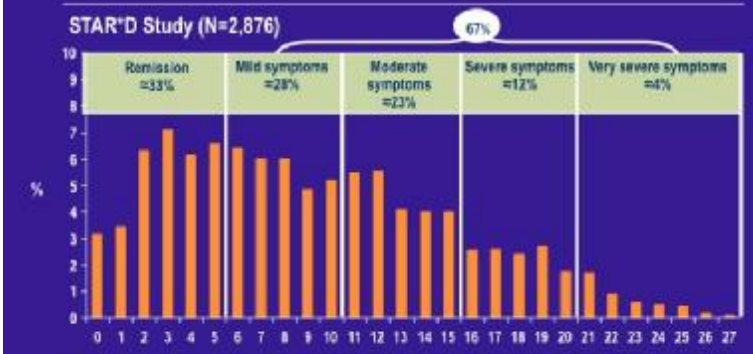


Treatments for Mood Disorders

- Medication
- Psychotherapy
  - Cognitive Behavioral Therapy
  - Interpersonal Therapy (IPT)
- Phototherapy
- Electroconvulsive therapy (ECT)
- Brain Stimulation
  - rTMS
  - Vagus Nerve Stimulation
  - Deep Brain Stimulation

First-line antidepressants include…

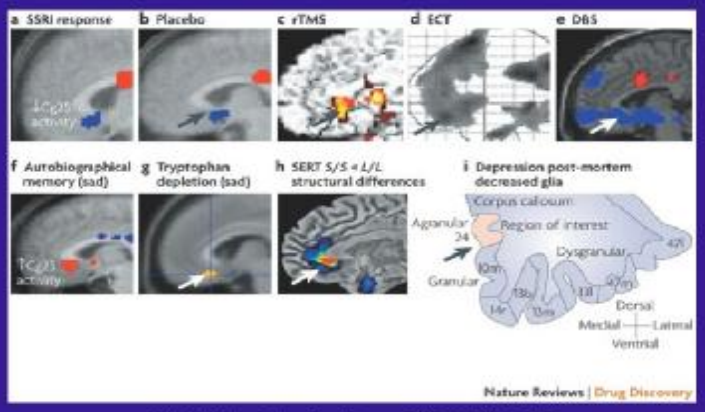
67% of patients still have symptoms after SSRI treatment



Depressive symptoms (QIDS-SR score) after up to 12 wk antidepressant treatment

Adapted from Trivedi MH, et al. *Am J Psychiatry*. 2006;163:28-40.

Area 25: Key Brain Region Associated with Treatment Response



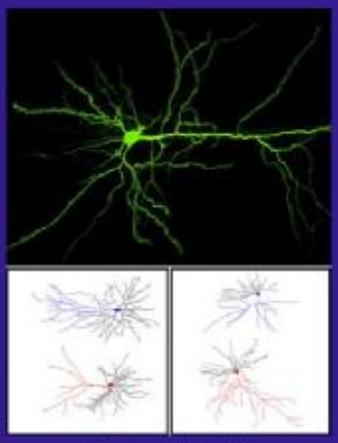
Aqid et al. *Nature Reviews Drug Discovery* 6, 189–201 (March 2007)

Overview: Glutamate Modulation in Treatment Resistant Depression

- Patients with severe depression who do not respond to conventional monoaminergic drugs may be characterized by impairments in amino acid neurotransmitter function
- Evidence from clinical and preclinical studies suggests that directly targeting the NMDA / glutamate receptor may offer a rapid method of treating acute depressive episodes

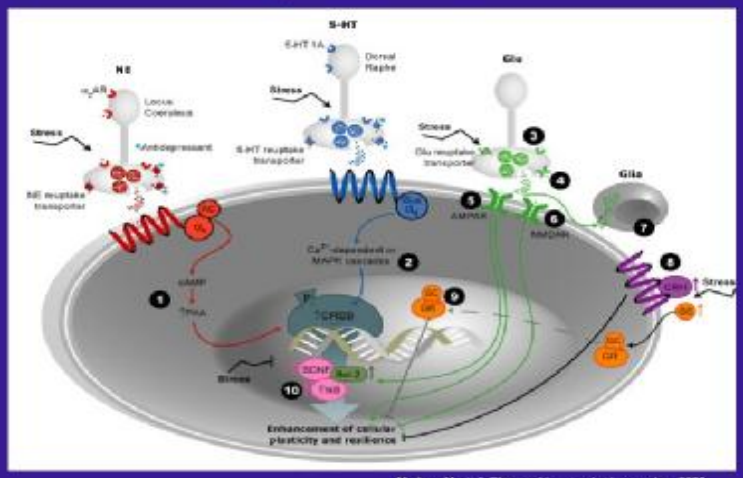
The Glutamate System may Mediate Between Stress and Depression

- Stress increases extracellular glutamate in the hippocampus
- NMDA receptor antagonists attenuate stress-induced atrophy of CA-3 pyramidal neurons
- Over-activity of ionotropic glutamate receptors leads to neurotoxic effects



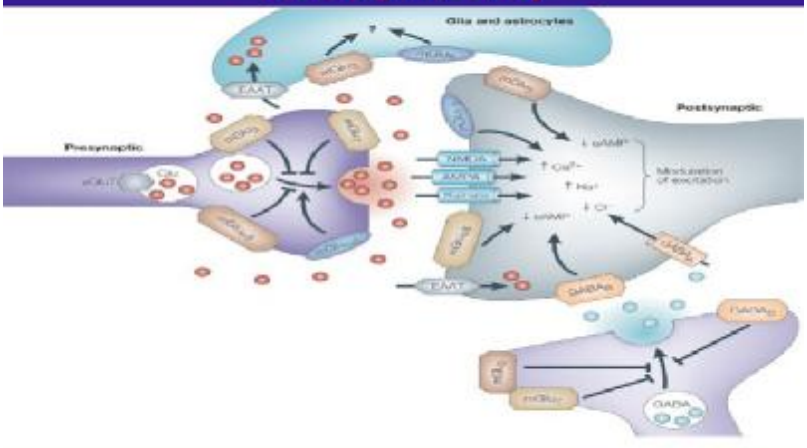
McEwen et al. J of Neurosci. 2006.

Enhancement of Cellular Plasticity is Final Common Pathway for Antidepressant Treatments



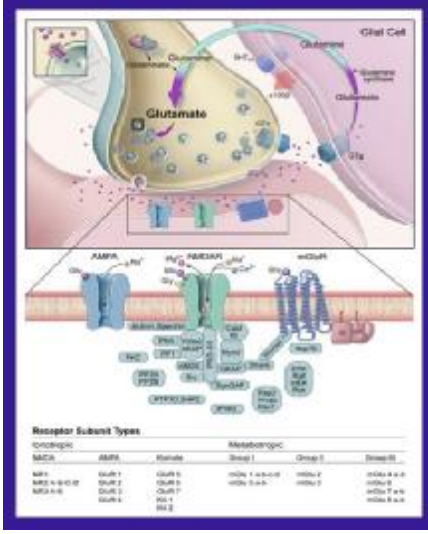
Mathew, Manji & Charney. Neuropsychopharmacology. 2008

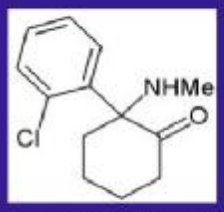
Glutamate System Offers Novel Potential Targets For Drug Discovery



Swanson et al. 2005

Ketamine: Pharmacology





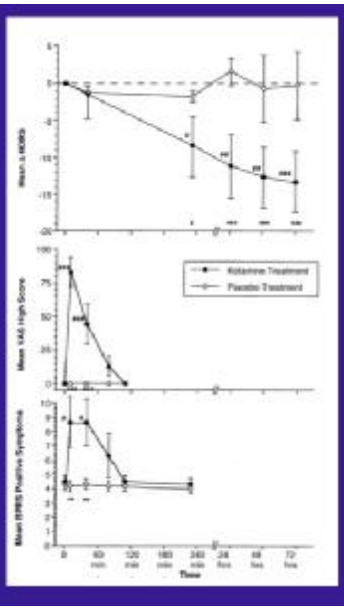
- High-affinity NMDA R antagonist
- FDA-approved as an anesthetic at induction doses of 1-3 mg/kg
- Peak plasma concentrations occur within 1 min following IV administration
- Distribution $t_{1/2}$= 10-15 min
- Elimination $t_{1/2}$= 2 hr; norket $t_{1/2}$ = 4 hr
- CYP-2B6 important for N-methylation

Antidepressant Effects of IV Ketamine Reported in Hospitalized Patients with Major Depression

- Rapid (within 2 hours) and robust antidepressant effects lasting up to 2 weeks reported following a single subanesthetic infusion of 0.5 mg/kg over 40 minutes
- No studies have investigated IV ketamine as a continuation treatment to determine whether initial response can be maintained over a longer period

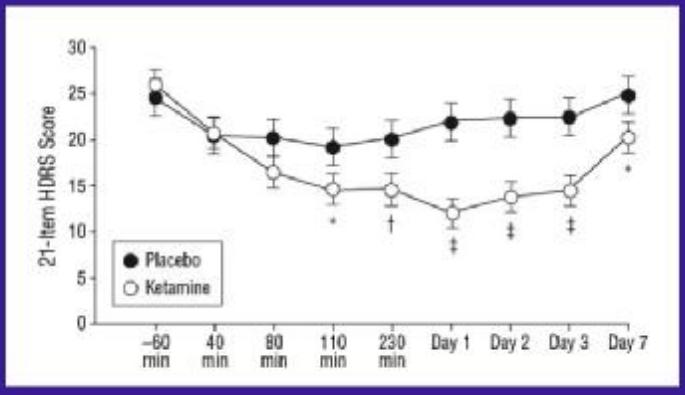
Study #1

- Inpatient sample with major depressive disorder (n=9)
- Within-subject cross-over design ketamine vs saline infusion
- 0.5 mg/kg infusion over 40 minutes
- 4 of 8 patients receiving IV ketamine had > 50% improvements in HDRS score



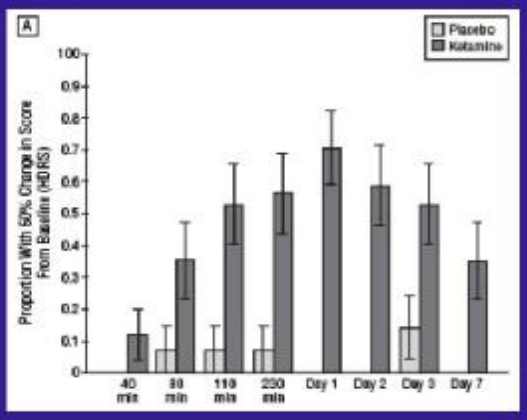
Berman, RM, et al. *Biol Psychiatry*. 2000.

Study #2: Replication of a Rapid Antidepressant Effect of Ketamine



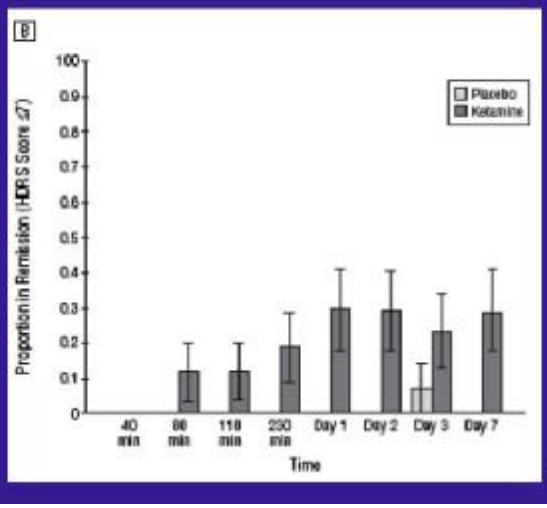
Zarate CA, et al. *Arch Gen Psychiatry*. 2006.

Ketamine-induced Reduction in Depressive Symptoms over 1 Week: Response Rates



Zarate et al 2006

Remission Rates over 1 Week



Zarate et al 2006

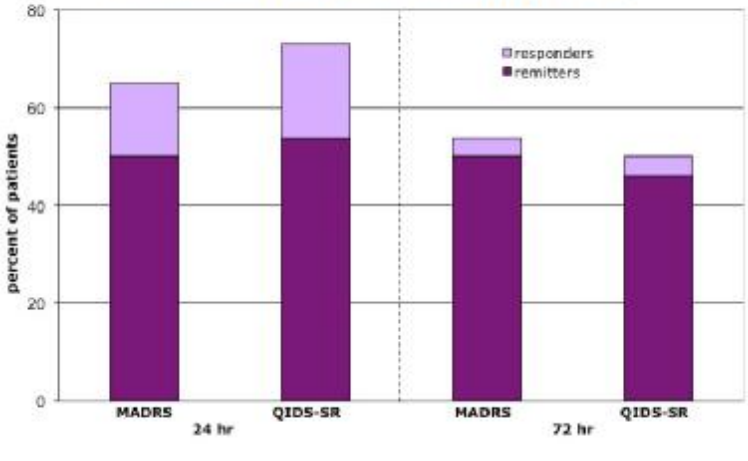
Study 3 at Mount Sinai

1. Does IV ketamine possess acute antidepressant properties?
2. What is the tolerability and safety of IV ketamine in patients with treatment-resistant depression?
3. Can we prevent relapse post IV ketamine with continuation pharmacotherapy?

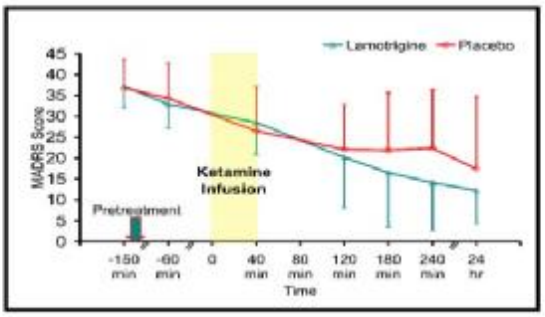
Characteristics of TRD Patients Receiving IV Ketamine Infusion (n=26)

Feature	Mean
Age (yr)	48.2 ± 11.8
Sex (*n*, % female)	10 (38.5)
Received psychiatric disability (*n*, % yes)	12 (46.2)
Number of adequate antidepressants trials	6.0 ± 4.1
Age at first major depressive episode (yr)	18.5 ± 12.2
Ultrachronic (*n*, %)	24 (92.3)
Comorbid anxiety disorder (*n*, % yes)	20 (76.9)
Family history of major depression (*n*, % yes)	13 (50)
Baseline Montgomery-Asberg Depression Rating Scale	36.9 ± 5.4
Quick Inventory of Depressive Symptomatology-Self-Report.	18.6 ± 3.9

Efficacy of IV ketamine in treatment-resistant depression (n=26)

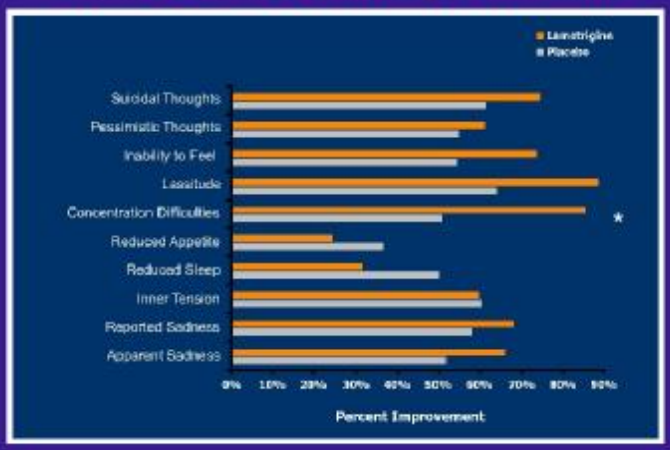


Change in MADRS in 24 Hours



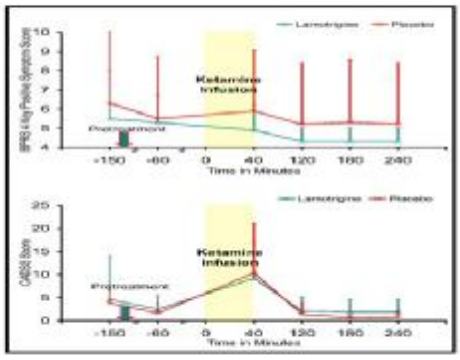
Ketamine infusion: 0.5 mg/kg over 40 min

Improvement Across Individual MADRS Items 24 Hours Following IV Ketamine



* p< .05

Transient Acute Psychotomimetic Effects Following IV Ketamine



Study 3 Conclusions

- The largest sample of treatment-resistant depression studied to date demonstrated:
  - A single infusion of IV ketamine has rapid antidepressant properties
  - Benefit was durable in outpatients
  - IV ketamine was safe and well-tolerated

Mathew et. al., 2008

Study 4: Repeated Dose Ketamine Study

Aims

- To test a pharmacological strategy for maintaining the acute antidepressant effects of IV ketamine over longer time periods.
- To individualize dosing for continuation IV ketamine administration based on initial dose tolerability.

Hypotheses

- Patients who respond to a single IV ketamine dose will maintain response and tolerate continuation IV ketamine (5 additional doses over a 2-week period).
- A majority of patients receiving continuation IV ketamine will continue to do well for at least 2 weeks following the last infusion.

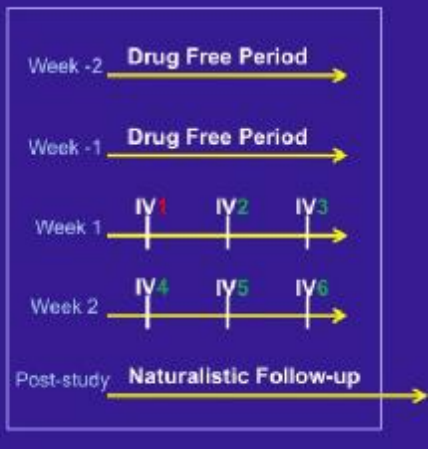
Evidence for Feasibility of Repeated Intravenous Ketamine Infusions

Diagnosis	N	Ketamine	Results	Reference
Treatment-resistant eating disorder	15	Average of 4 (range 2-9) infusions of 10 h, 20 mg/h each	Decrease in compulsive behaviors and **improved mood** which lasted on average >1 year	Mills et al 1998
Refractory pain	40	Infusions of 4 h, 10-20 mg/h each for 10 consecutive weekdays	Reduced pain, increased pain relief, improved movement initiation and **decreased need of tricyclic antidepressant use** which lasted 1.5-15 months	Goldberg et al 2005
Severe treatment-resistant depression	2	Continuous infusion of 0.27-0.30 mg/kg/h for 5 days	**Remission** that lasted >1 year in one patient and ~2.5 months in the other patient (and >1 year when repeated)	Correll and Futter 2006

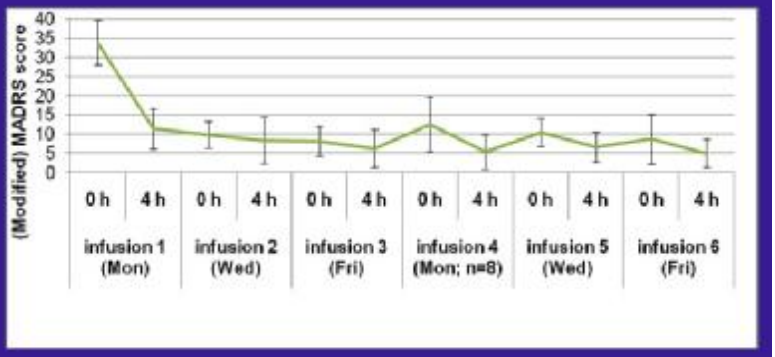
Repeated IV Ketamine Administration for Relapse Prevention

Inclusion criteria

- Men and women (n=5-10)
- 21 to 70 years
- DSM-IV diagnosis of major depression, chronic or recurrent, without psychotic features
- At least moderate severity [IDS-C score ≥ 37]
- Treatment-resistant [failed ≥ 3 antidepressant trials]
- No history of (hypo)mania
- No substance use disorder for at least 3 months

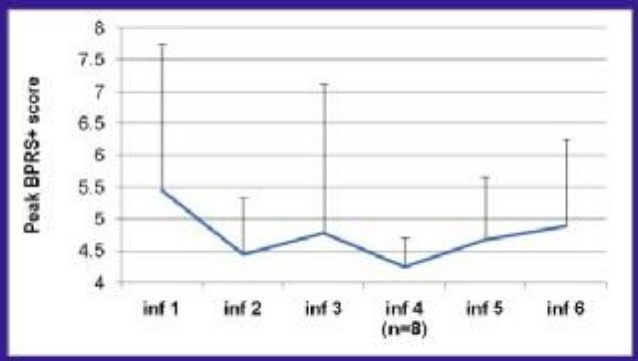


Improvement in Depression Ratings with Repeated IV Ketamine Infusions (n=9)



aan het Rot et. al., 2008

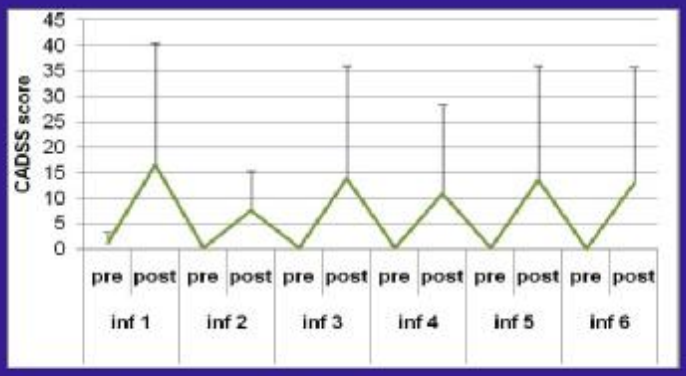
Minimal BPRS Positive Symptoms Observed Over 6 Treatment Sessions (n=9)



BPRS (Brief Psychiatric Rating Scale) Positive Symptom subscale scores range= 4-24

BPRS + items= suspiciousness, hallucinations, unusual thought content, conceptual disorganization

Few Dissociative Side Effects Observed Over 6 Treatment Sessions, n=9



CADSS=Clinician Administered Dissociative States Scale
CADSS measures altered sense of time, derealization, depersonalization
0-2= low 3-10= medium 11-25= high ≥ 26= very high

Side Effects after Repeated IV Ketamine Infusions in TRD (n=9)

Symptom	Moderate		Severe	
	Week 1	*Week 2*	*Week 1*	*Week 2*
Abnormal sensations	0	2	0	0
Blurred vision	0	0	1	1
Diminished mental	1	**2**	1	**2**
Dizziness or faintness	1	0	0	0
Feeling drowsy or sleepy	2	0	0	0
Feeling strange or unreal	1	1	1	1
Headache	0	0	1	1
Hearing or seeing things	2	0	1	1
Numbness or tingling	1	0	0	0
Poor coordination or unsteadiness	1	1	0	0
Poor memory	1	0	0	0
Rapid or pounding heartbeat	1	0	0	0
Weakness or fatigue	0	1	0	0

Durability of Response to Repeated IV Ketamine Infusions in TRD (n=9)

Patient	Response duration after a single dose of intravenous ketamine, counted from baseline (Study 3) [1]	Response duration after first dose of intravenous ketamine, counted from baseline (Study 4) [2]
1	10 days	29 days
2	2 days	22 days
3	2 days	33 days
4	1 day	23 days
5	2 days	0 days [4]
6	31 days	50 days
7	7 days	23 days
8	0 days [3]	> 40 days [5]
9	20 days	> 33 days [5]
10	8 days	22 days

[1]Patients who responded 3 days were randomized to continuation riluzole or placebo. [2]First 14 days included five additional ketamine doses. [3]Patient was a non-responder as per 24-h MADRS, even though a responder as per 24-h QIDS-SR. [4]Patient was a non-responder after the first ketamine dose and did not receive the five additional doses. [5]Patients have not yet been exited from study due to continued response.

Patient Perspective: Ms. S (1)

Ms. S, a single white 51 y.o. F who works as a high school special education teacher, became depressed in 1992 when she experienced a number of stressors including the sudden death of her brother and the hospitalization of both of her parents. She has endured multiple courses of treatment with antidepressants, psychotherapy, experimental tx with rTMS, and been hospitalized 3 times without experiencing any relief.

Before receiving ketamine, Ms. S reported being depressed "98% of the time", having no interest in the activities she used to enjoy, and no mental or physical energy. Even daily chores such as opening mail or going to the ATM for cash were burdensome and difficult to initiate. She felt hopeless and thought about suicide daily, though she never went so far as to plan to harm or kill herself. She felt a need to stay alive for the sake of her family (her elderly father who lives close by).

Patient Perspective: Ms. S (2)

24 hr following infusion #1, Ms. S experienced relief from nearly all of her depressive symptoms, reporting significant improvements in her mood, energy level, and capacity and desire to experience pleasure.

She remained well for the entire 2-wk infusion period and is currently in her 6th week in follow-up post-ketamine.

The following is an excerpt from an email she sent to our research team this week, approximately 6 weeks following her last ketamine infusion (she remains off all antidepressant medications).

Patient Perspective: Ms. S (3)

"...my "take" on how ketamine has transformed my life and how it has literally "turned light and sound and the positive back on" for me where for so long i have barely survived in pain and darkness and without hope. i guess maybe that is the greatest difference, i can feel hope and joy again after so very long without it. and the ever present suicidality has become part of my past, not my present. and i am aware of a future where, before, all the future i could see was more pain and despair. the most amazing thing to me is that it is as if i were never depressed; that the areas of my brain that seemed shut off are now functioning on all cylinders and the buttons that depression kept pressing are getting a long deserved break from stimulation. what has happened is as miraculous as a person who emerges fully conscious and speaking from a coma or vegetative state, or if a burn victim were to awaken pain and scar-free..."

Patient Perspective: Ms. S (4)

"I know all predictors are that I will fully relapse. But, I am hopeful that ketamine will emerge from study and will be available as a treatment. I truly believe it will help other people, who like me, have been impervious to treatment. I know, it has, for these six plus weeks' time, "cured" me. (I don't use that word lightly.) I pray (again, not a word I use lightly) that ketamine is available to me, if and when, I should need it again."

Video Patient Perspective: Ms. K

Ms. K, a 50 y.o. Hispanic, thrice-married woman with one son, lives with her husband, supporting herself by working as an internet technology consultant for a brokerage firm. She remembers first feeling depressed and having suicidal thoughts at age 9 and reports a chronic low mood since adolescence. She remitted for several years in her 20s. Ms. K's current episode began at age 28, with post-partum onset, and is characterized by persistent anxious rumination, insomnia, anhedonia ("my feelings- they ran away"), and chronic suicidal ideation. At screening, Ms. K indicated that she had formulated multiple suicide plans but that her concern for her family prevented her from acting on these thoughts.

Following the 1st of 6 IV ketamine infusions, her MADRS score declined from 31 to 14 in 24 hours. This level of response (about 50% reduction in depressive symptoms) was maintained through the sixth infusion and for 33 days total.

Video Patient Perspective: Ms. A

Ms. A, a 53 y.o. white, divorced woman lives with her fiancé, 17 y.o. daughter, and 2 y.o. granddaughter. She receives psychiatric disability and last worked 5 years ago as a cashier. She can't recall a time when she felt well, and reports chronic symptoms of low mood, anhedonia, social anxiety, and PTSD symptoms (was sexually abused by her older brother from ages 4-15) since childhood. She went on to develop both cocaine and alcohol dependence, from which she has been in sustained full remission for 7 years.

At the time of her IV ketamine infusion, her delusional guilt (holding herself responsible for her own molestation and seeing her depression as punishment), inability to feel love for her daughter and granddaughter, and chronic passive suicidal ideation were the most salient symptoms.

Mood & Anxiety Disorders Program at Mount Sinai School of Medicine

DENNIS CHARNEY

Marije aan het Rot
Gizley Andrade
James Blair
Karina Blair
Doug Brodman
Kate Collins
Jin Fan
Heidi Fitterling
Adriana Feder
Chris Kelly
Heather Lawson
Sanjay Mathew
Jazmin Moral
James Murrough
Antonia New
Fatih Ozbay
Rebecca Price

Key Collaborators:

GCRC Nursing and Administrative Staff

Anesthesiology
Andrew Perez
David Reich

Support: M01-RR-0071 (GCRC); NIMH
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Contact Information

- Director, Sanjay Mathew,MD
  Phone: 212-241-4480
  Email: sanjay.mathew@mssm.edu
- MAP Administrator, Heidi Fitterling, MPH
  Phone: 212-241-7906
  Email: map@mssm.edu