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- **Online:** https://dhswi.zoomgov.com/j/1606358142
- **Phone:** 669-254-5252
- Enter the Webinar ID: 160 635 8142#.
  - Press # again to join. (There is no participant ID)

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From Love Medicine to Antidepressant: Sub Anesthetic Intravenous Ketamine in Treatment of Depression

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Director Interventional Psychiatry Service

Disclosures

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Board of Directors or officer	None	N/A
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Industry funds to UW or Emory for my research	Consultant Janssen on s-ketamine Investigator s-ketamine trial LivaNova RECOVER trial	Consultant Investigator Investigator
Other	Interventional Psychiatry Service Emory University Hospital Interventional Psychiatry Service UW Healthcare Transcend Pharmaceutical	Physician/ Director Physician/ Director Consultant

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Ketamine “Off Label” Disclosure

- Racemic Ketamine is NOT approved by FDA for treatment of Major Depressive Disorder or any other psychiatric disorder

INDICATIONS AND USAGE

Ketalar is indicated as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best

suited for short procedures but it can be used, with additional doses, for longer procedures.

Ketalar is indicated for the induction of anesthesia prior to the administration of other general anesthetic agents.

Ketalar is indicated to supplement low-potency agents, such as nitrous oxide.

S-Ketamine FDA Indication

----------INDICATIONS AND USAGE----------

SPRAVATO® is a non-competitive *N*-methyl *D*-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of:

•Treatment-resistant depression (TRD) in adults. (1)

•Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. (1)

•Limitations of Use:

•The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO. (1)

•SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established. (1)

Objectives

- Ketamine: A Quick Tutorial
  - FDA Indications
  - Pharmacology
- History
  - Discovery and early human use
  - The Psychonauts and cultural relevance
- Ketamine in Mood Disorders
  - Clinical studies in depression
- Ketamine in the “Real World” and the future

Ketamine: A Quick Tutorial

History – Medical Use

- 1962 – PCP derivative, Calvin Stevens (Parke-Davis)
  - CL-369
  - CI-581
- First in human use
  - 8/3/1964
  - a person fully awake but “not there”
  - Dissociative anesthesia
  - Domino, E.F., Chodoff, P., Corssen, G. (1965) “Pharmacologic effects of CI-581, a new dissociative anesthetic, in man,” *Clinical and Pharmacological Therapeutics* 6: 279–291.
  - McCarthy, D.A., Chen, G., Kaump, D.H., Ensor, C.J. (1965) “General anesthetic and other pharmacological properties of CI-581,” *Journal of New Drugs* 5: 21– 33.
- Favorable over PCP for anesthesia (↓psychotomimetic, ↓ duration, no need for circulatory support)
- FDA approval 1970
  - Field surgery Vietnam War
- WHO list of essential medications

Legal Classifications

- US – Schedule III
- **Schedule III:** Drugs with low to moderate potential for abuse and/or addiction, but less dangerous than Schedule I or II. These drugs are obtained through prescription.
  - Codeine< 90 mg, buprenorphine/ Suboxone, anabolic steroids
- Schedule II
  - Methadone, Vicodin, Demerol, oxycontin
- Schedule IV
  - Xanax, Soma, Klonopin

Central nervous system

- Non-competitive NMDA receptor antagonist
- Dissociative anesthesia
  - Interferes with spinal cord pain transmission
  - Inhibits nitric oxide synthase
- Blocks voltage-sensitive Ca2+ channels & depresses Na+ channels (inhibitory, anti-pain)
- Noradrenergic and serotonergic uptake inhibitor (anti-pain)

Pharmacodynamics: Peripheral systems

- Inhibits catecholamine reuptake → stimulates sympathetic nervous system → Cardiovascular effects
  - Increased heart rate, blood pressure, temperature
- Increased serotonergic activity → GI effects
  - Nausea and vomiting
- Induced catecholamine release, stimulation of beta-2-adrenergic R → Pulmonary effects
  - Broncho dilation

Physical Effects to Monitor

- Horizontal gaze nystagmus
- Vertical gaze nystagmus
- Lack of convergence
- Elevated pulse
- Elevated blood pressure
- Elevated body temperature
- Rigid muscles, cyclic behavior, and lack of response to painful stimuli
- General lack of coordination

Pharmacokinetics

TABLE 1. Pharmacokinetics of Ketamine for Different Routes of Administration[38,91]

Route of Administration	Typical Dosing	Bioavailability, %	Time of Onset	Duration of Action After Dosing
Intravenous	1–4.5 mg/kg for general anesthesia induction; 1–6 mg/kg per hour for anesthesia maintenance; 0.5–2 mg/kg for 1-d outpatient or 3- to 5-d inpatient awake ketamine infusions in chronic pain (higher dosages titrated to effect from lower doses); 0.2–0.75 mg/kg for procedural analgesia, can be repeated; 0.1 mg/kg for IV infusion test; 5- to 35-mg/h continuous infusion for acute traumatic or postoperative pain, 1–7 mg/demand dose mixed with opioids in patient-controlled analgesia	N/A	30 s	5–10 min for bolus doses
Intramuscular	2–4 times IV dosing; 5–10 mg/ kg for surgical anesthesia; 0.4–2 mg/kg for procedural analgesia; bolus and treatment dosing 0.10–0.5 mg/kg for chronic pain	75–95	2–5 min	30–75 min
Intranasal	0.2–1 mg/kg for chronic pain and sedation; 3–6 mg/kg for procedural analgesia and anesthetic premedication	25–50	5–10 min	45–120 min
Subcutaneous	0.1–1.2 mg/kg per hour for chronic pain; bolus and treatment dosing 0.10–0.6 mg/kg	75–95	10–30 min	45–120 min
Oral	0.3–1.25 mg/kg for chronic pain; up to 3 mg/kg for procedural analgesia and anesthetic premedication	10–20	5–20 min	2–4 h
Rectal	5–10 mg/kg for anesthesia premedication and procedural analgesia	25–30	5–15 min	2–3 h
Topical	1%–10% cream for chronic pain	<5	<2 d	NA

Ketamine Reinvented as an Antidepressant

Antidepressant Effects of Ketamine in Depressed Patients

Robert M. Berman, Angela Cappiello, Amit Anand, Dan A. Oren, George R. Heninger, Dennis S. Charney, and John H. Krystal

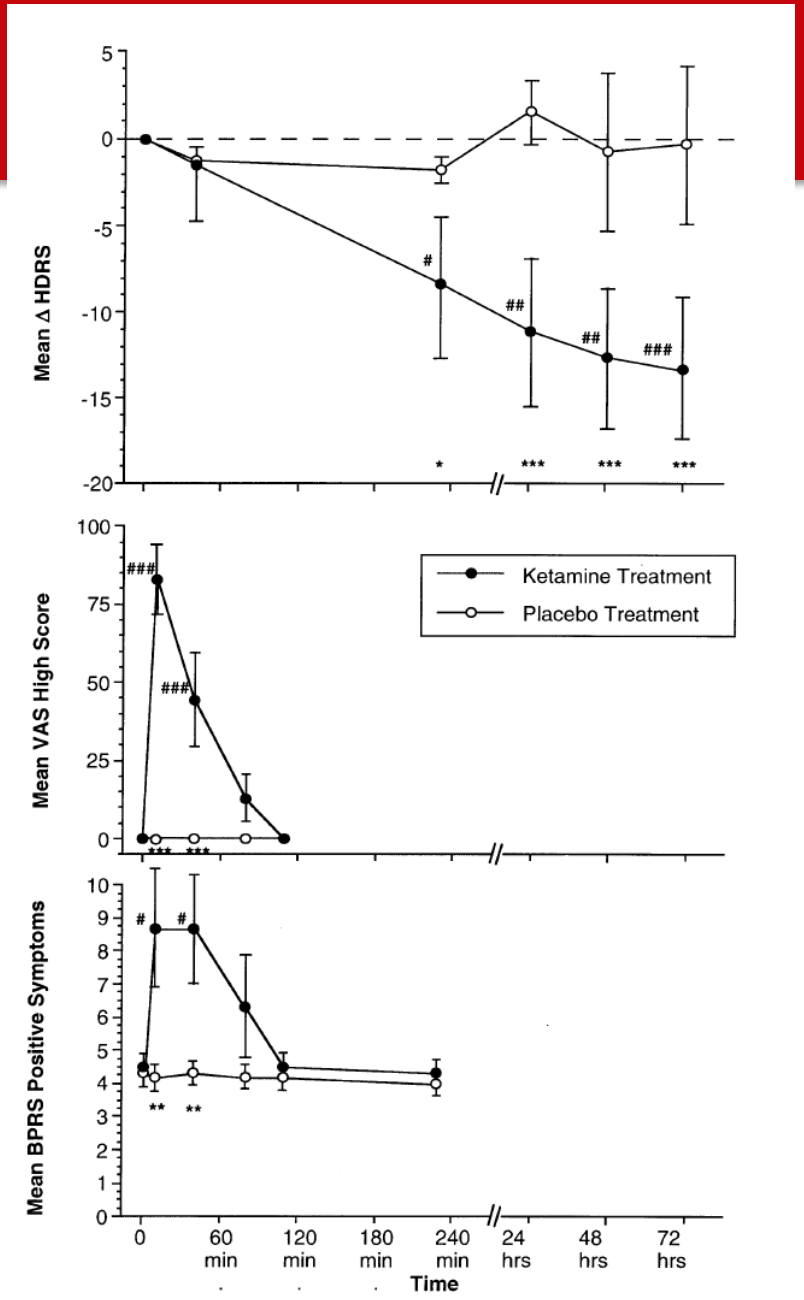
- Glutamate is important
- 7 subjects with MDD
- Intravenous infusion
  - Placebo
  - Ketamine 0.5 mg/ kg; 40 min infusion
- HDRS-25 reduction

BIOL PSYCHIATRY
2000;47:351–354

Antidepressant Effects of Ketamine in Depressed Patients

- 50% response status over 3 days
- 1-2 week duration of benefit
  - 1 patient with prolonged benefit
- Specific symptoms items
  - Depressed mood
  - Suicide ideation
  - Helplessness
  - Worthlessness

BIOL PSYCHIATRY
2000;47:351–354



BIOL PSYCHIATRY
2000;47:351–354

Terapia antidepresiva con CI 581

A. E. FONTANA *
J. A. LOSCHI

While the analysis of dreams makes it possible to re-structure unconscious contents through transference, CI 581 allows the therapist not only to witness the dream but also to introduce himself into it and to correct, in situ, the primitive experience through the bi-personal relationship, by means of contacts, attitudes, rhythms and words which, by increasing the symbolization process, will gradually restore to language its real sense and meaning.

In other words, transference is endowed with the surgical possibility of reestablishing a new imprinting, modifying the past and altering the hitherto unchangeable course of time.

Acta Psiquiat. Psicol. America Latina; 1974 (20.32)

Ketamine Clinical Trials in Psychiatric Conditions

Ketamine Publications in Psychiatry

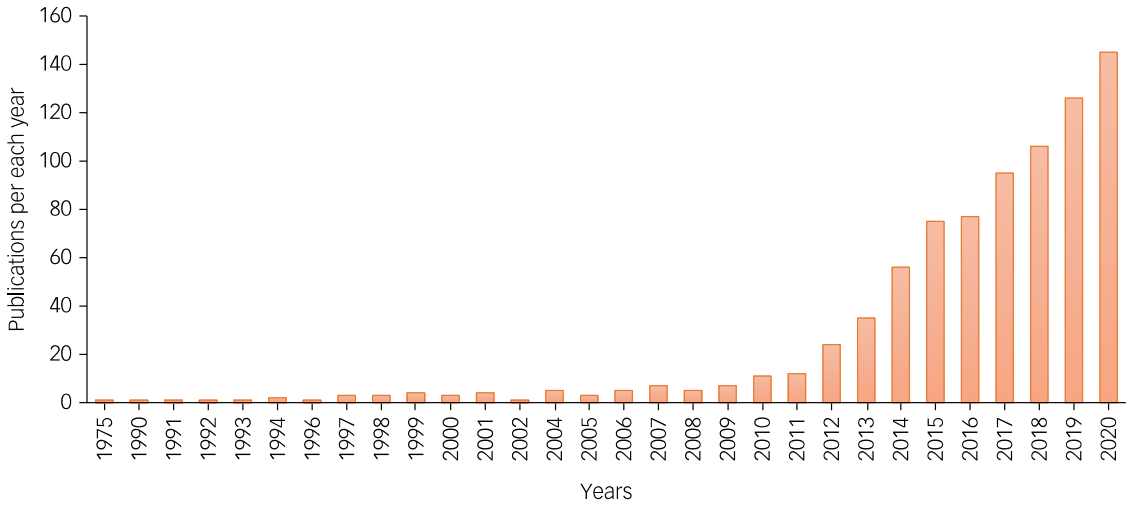
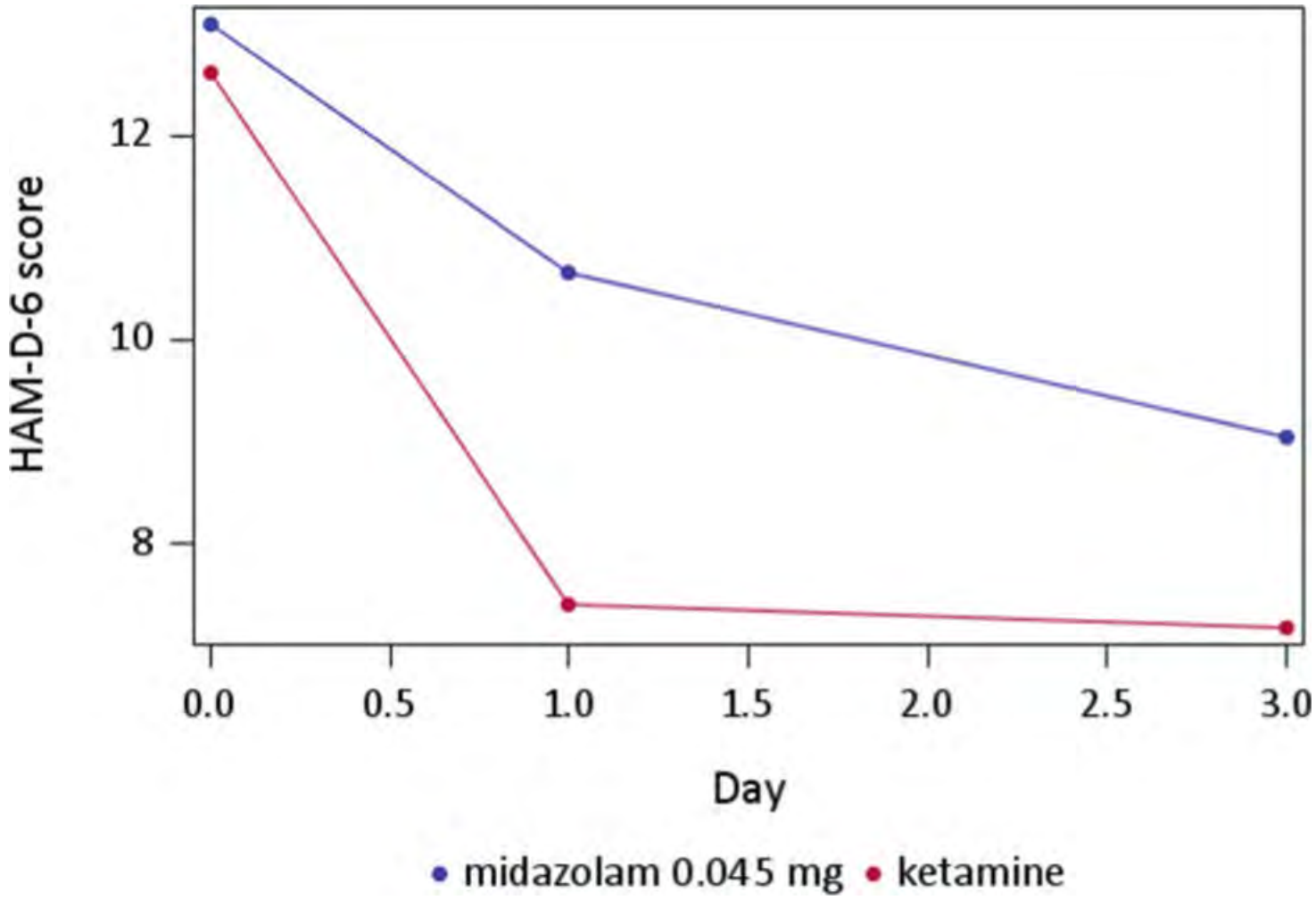


Fig. 2 Number of publications with search terms ketamine and mental health in PubMed per year, from 1975 till December 2020.

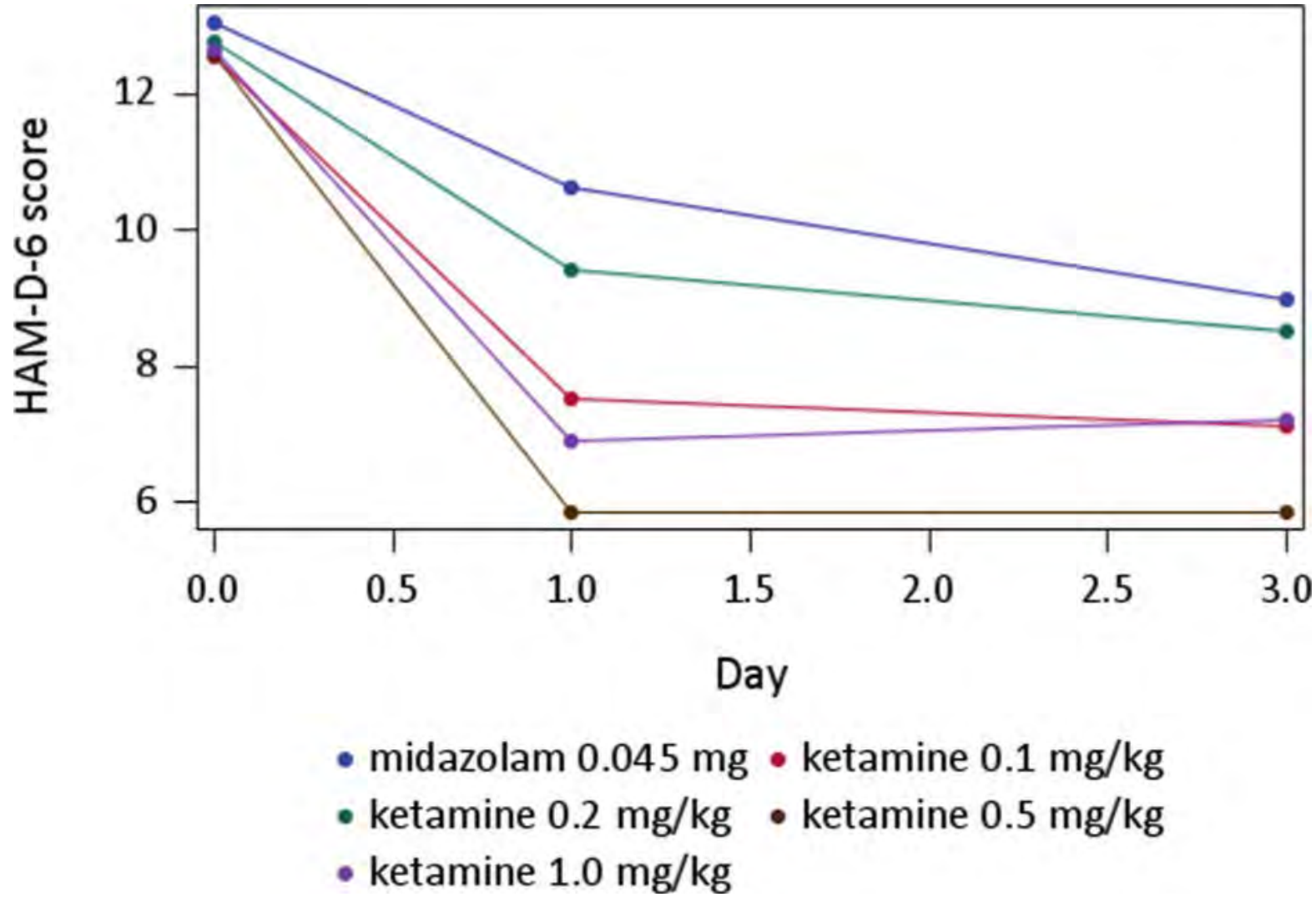
IV ketamine vs Active Placebo in Major Depressive Disorder

- Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD)
  - Molecular Psychiatry (2020) 25:1592–1603
- Double blind placebo-controlled trial
  - 99 subjects
  - Single dose
  - Ketamine dose 0.1 mg/kg, 0.2 mg/ kg, 0.5 mg/ kg, 1.0 mg/ kg
  - Midazolam 0.045 mg/kg “active placebo”
  - HAM-D 6 outcome
- Continued conventional antidepressants
- All dose combined and 0.5 mg/ kg and 1 mg/kg superior to “placebo”

IV Ketamine vs IV Midazolam



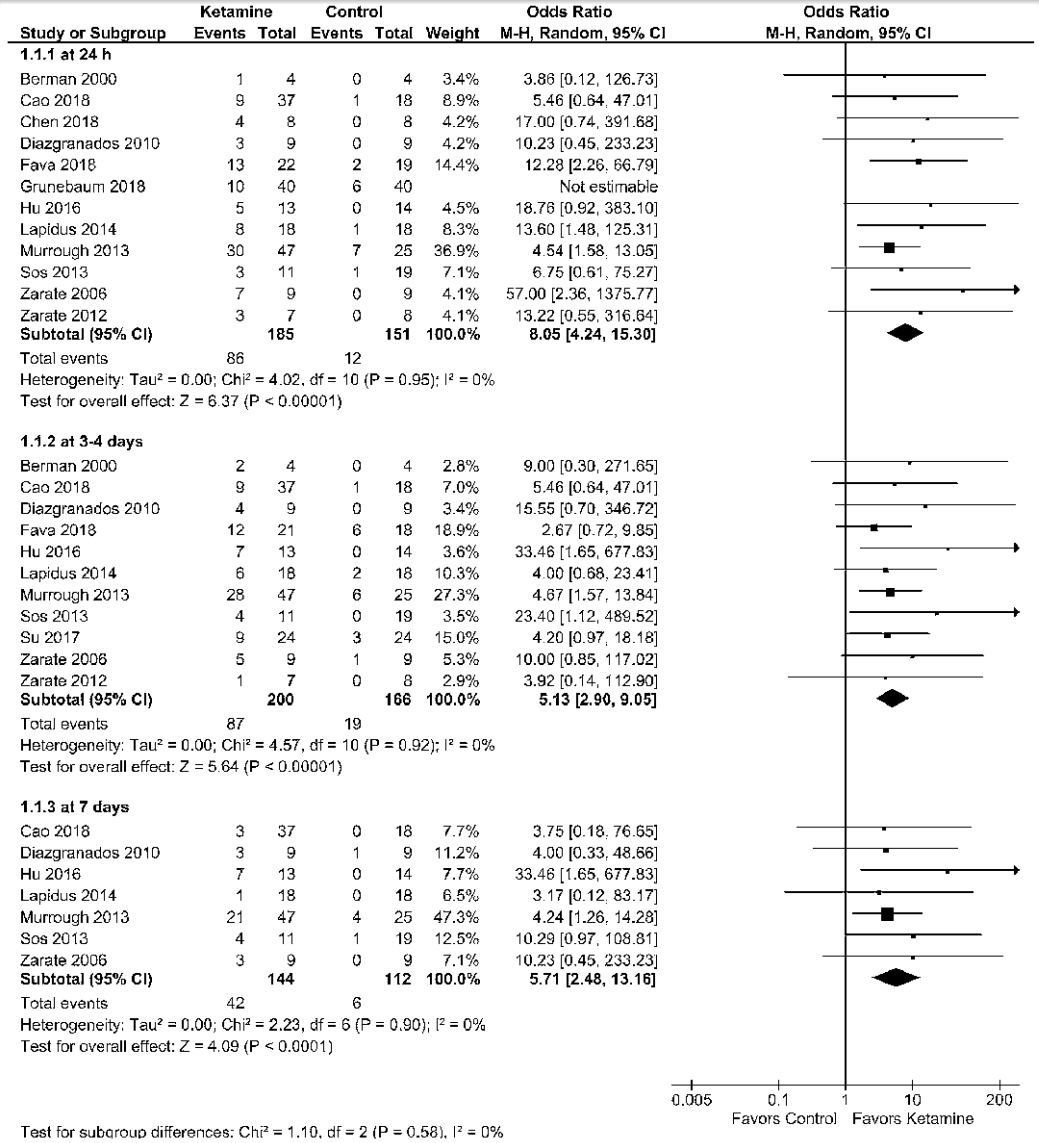
Dose Response IV Ketamine



Meta Analysis of IV Ketamine Trials

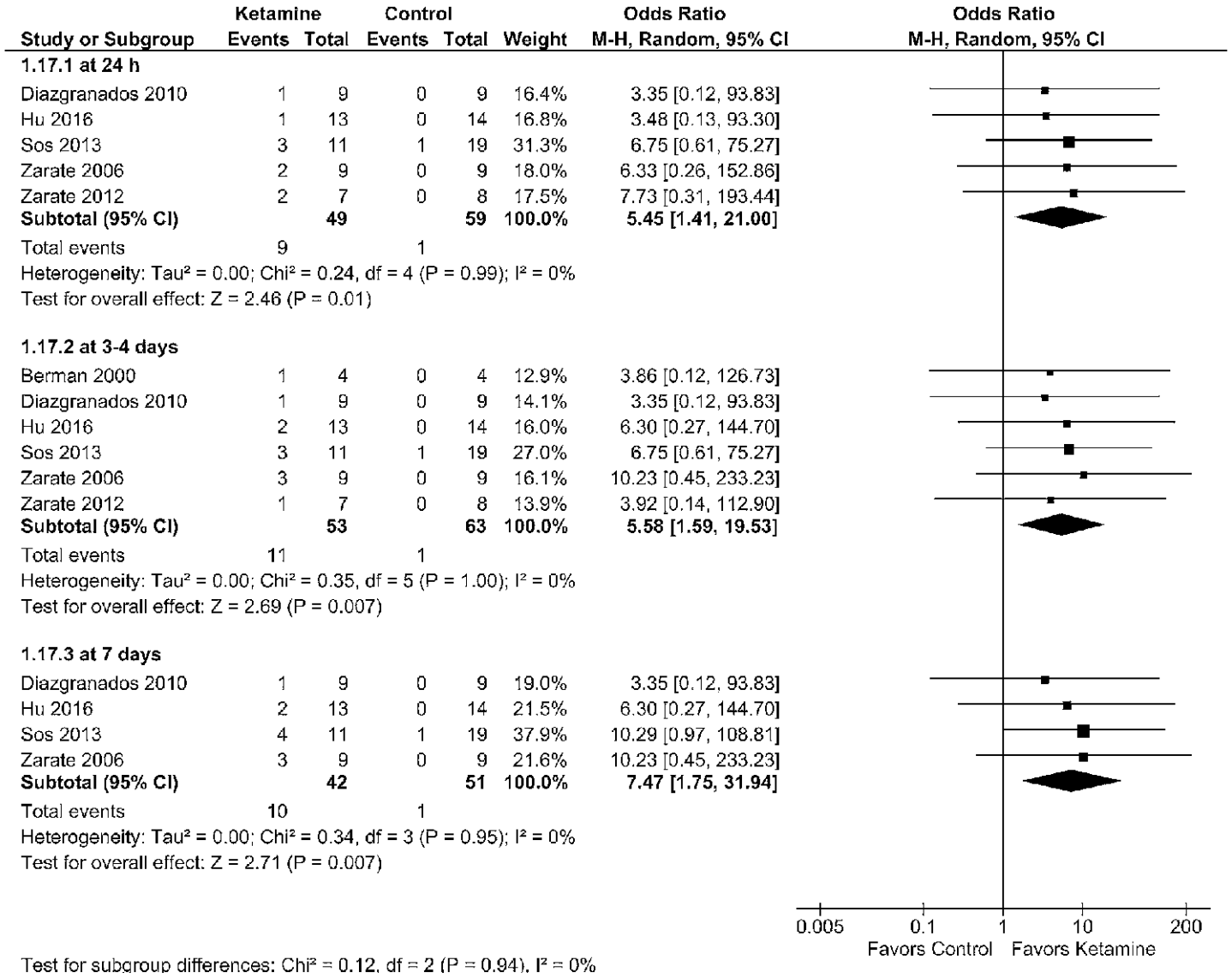
- **Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: a meta-analysis of randomized clinical trials**
  - **Pharmacological Reports (2020) 72:543–562**
  - **“Ketamine” and Depression” initial search terms**
    - **1418 citations returned**
    - **20 met inclusion criteria for meta-analysis**
      - **16 single dose**
      - **4 multiple dose**
  - **Depression severity scores, response and remission analyzed**
  - **Outcome at 1, 3-4 and 7 days for single dose**
  - **Outcome at 2-3 weeks for repeated dose treatment**

Single Dose IV Ketamine and Response at 1, 4, 7 Days



Study or Subgroup	Ketamine Events	Ketamine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 at 24 h						
Berman 2000	1	4	0	4	3.4%	3.86 [0.12, 126.73]
Cao 2018	9	37	1	18	8.9%	5.46 [0.64, 47.01]
Chen 2018	4	8	0	8	4.2%	17.00 [0.74, 391.68]
Diazgranados 2010	3	9	0	9	4.2%	10.23 [0.45, 233.23]
Fava 2018	13	22	2	19	14.4%	12.28 [2.26, 66.79]
Grunebaum 2018	10	40	6	40		Not estimable
Hu 2016	5	13	0	14	4.5%	18.76 [0.92, 383.10]
Lapidus 2014	8	18	1	18	8.3%	13.60 [1.48, 125.31]
Murrough 2013	30	47	7	25	36.9%	4.54 [1.58, 13.05]
Sos 2013	3	11	1	19	7.1%	6.75 [0.61, 75.27]
Zarate 2006	7	9	0	9	4.1%	57.00 [2.36, 1375.77]
Zarate 2012	3	7	0	8	4.1%	13.22 [0.55, 316.64]
Subtotal (95% CI)		**185**		**151**	**100.0%**	**8.05 [4.24, 15.30]**
Total events	86		12			
Heterogeneity: Tau² = 0.00; Chi² = 4.02, df = 10 (P = 0.95); I² = 0%						
Test for overall effect: Z = 6.37 (P < 0.00001)						
1.1.2 at 3-4 days						
Berman 2000	2	4	0	4	2.8%	9.00 [0.30, 271.65]
Cao 2018	9	37	1	18	7.0%	5.46 [0.64, 47.01]
Diazgranados 2010	4	9	0	9	3.4%	15.55 [0.70, 346.72]
Fava 2018	12	21	6	18	18.9%	2.67 [0.72, 9.85]
Hu 2016	7	13	0	14	3.6%	33.46 [1.65, 677.83]
Lapidus 2014	6	18	2	18	10.3%	4.00 [0.68, 23.41]
Murrough 2013	28	47	6	25	27.3%	4.67 [1.57, 13.84]
Sos 2013	4	11	0	19	3.5%	23.40 [1.12, 489.52]
Su 2017	9	24	3	24	15.0%	4.20 [0.97, 18.18]
Zarate 2006	5	9	1	9	5.3%	10.00 [0.85, 117.02]
Zarate 2012	1	7	0	8	2.9%	3.92 [0.14, 112.90]
Subtotal (95% CI)		**200**		**166**	**100.0%**	**5.13 [2.90, 9.05]**
Total events	87		19			
Heterogeneity: Tau² = 0.00; Chi² = 4.57, df = 10 (P = 0.92); I² = 0%						
Test for overall effect: Z = 5.64 (P < 0.00001)						
1.1.3 at 7 days						
Cao 2018	3	37	0	18	7.7%	3.75 [0.18, 76.65]
Diazgranados 2010	3	9	1	9	11.2%	4.00 [0.33, 48.66]
Hu 2016	7	13	0	14	7.7%	33.46 [1.65, 677.83]
Lapidus 2014	1	18	0	18	6.5%	3.17 [0.12, 83.17]
Murrough 2013	21	47	4	25	47.3%	4.24 [1.26, 14.28]
Sos 2013	4	11	1	19	12.5%	10.29 [0.97, 108.81]
Zarate 2006	3	9	0	9	7.1%	10.23 [0.45, 233.23]
Subtotal (95% CI)		**144**		**112**	**100.0%**	**5.71 [2.48, 13.16]**
Total events	42		6			
Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 6 (P = 0.90); I² = 0%						
Test for overall effect: Z = 4.09 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.10, df = 2 (P = 0.58), I² = 0%						

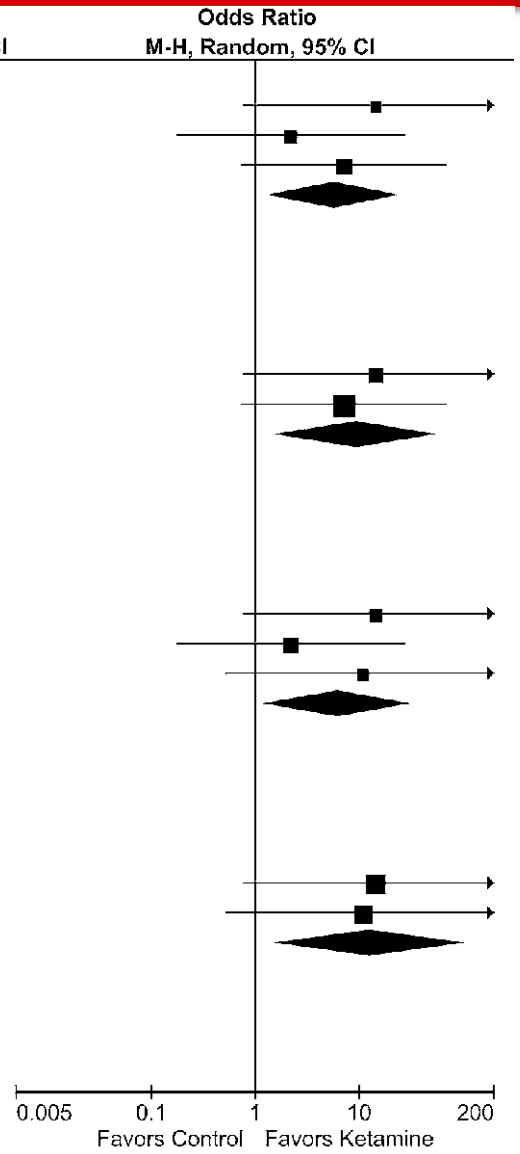
Single Dose IV Ketamine and Remission at 1,4, 7 days



Repeated IV Dose Ketamine and Remission at 2-3 Weeks

Study or Subgroup	Ketamine Events	Ketamine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.5.1 All studies						
Domany 2019	6	22	0	18	24.9%	14.58 [0.76, 279.04]
Ionescu 2019	2	12	1	12	33.4%	2.20 [0.17, 28.14]
Singh 2016	6	16	1	13	41.8%	7.20 [0.74, 70.20]
Subtotal (95% CI)		**50**		**43**	**100.0%**	**5.78 [1.33, 25.18]**
Total events	14		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 2 (P = 0.61); I² = 0%						
Test for overall effect: Z = 2.34 (P = 0.02)						
1.5.2 Sensitivity analysis						
Domany 2019	6	22	0	18	37.3%	14.58 [0.76, 279.04]
Singh 2016	6	16	1	13	62.7%	7.20 [0.74, 70.20]
Subtotal (95% CI)		**38**		**31**	**100.0%**	**9.37 [1.54, 56.84]**
Total events	12		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.43 (P = 0.02)						
1.5.3 All studies						
Domany 2019	6	22	0	18	30.6%	14.58 [0.76, 279.04]
Ionescu 2019	2	12	1	12	41.0%	2.20 [0.17, 28.14]
Singh 2016	3	13	0	16	28.4%	11.00 [0.51, 235.20]
Subtotal (95% CI)		**47**		**46**	**100.0%**	**6.20 [1.21, 31.69]**
Total events	11		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 2 (P = 0.57); I² = 0%						
Test for overall effect: Z = 2.19 (P = 0.03)						
1.5.4 Sensitivity analysis						
Domany 2019	6	22	0	18	51.8%	14.58 [0.76, 279.04]
Singh 2016	3	13	0	16	48.2%	11.00 [0.51, 235.20]
Subtotal (95% CI)		**35**		**34**	**100.0%**	**12.73 [1.52, 106.61]**
Total events	9		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 2.35 (P = 0.02)						

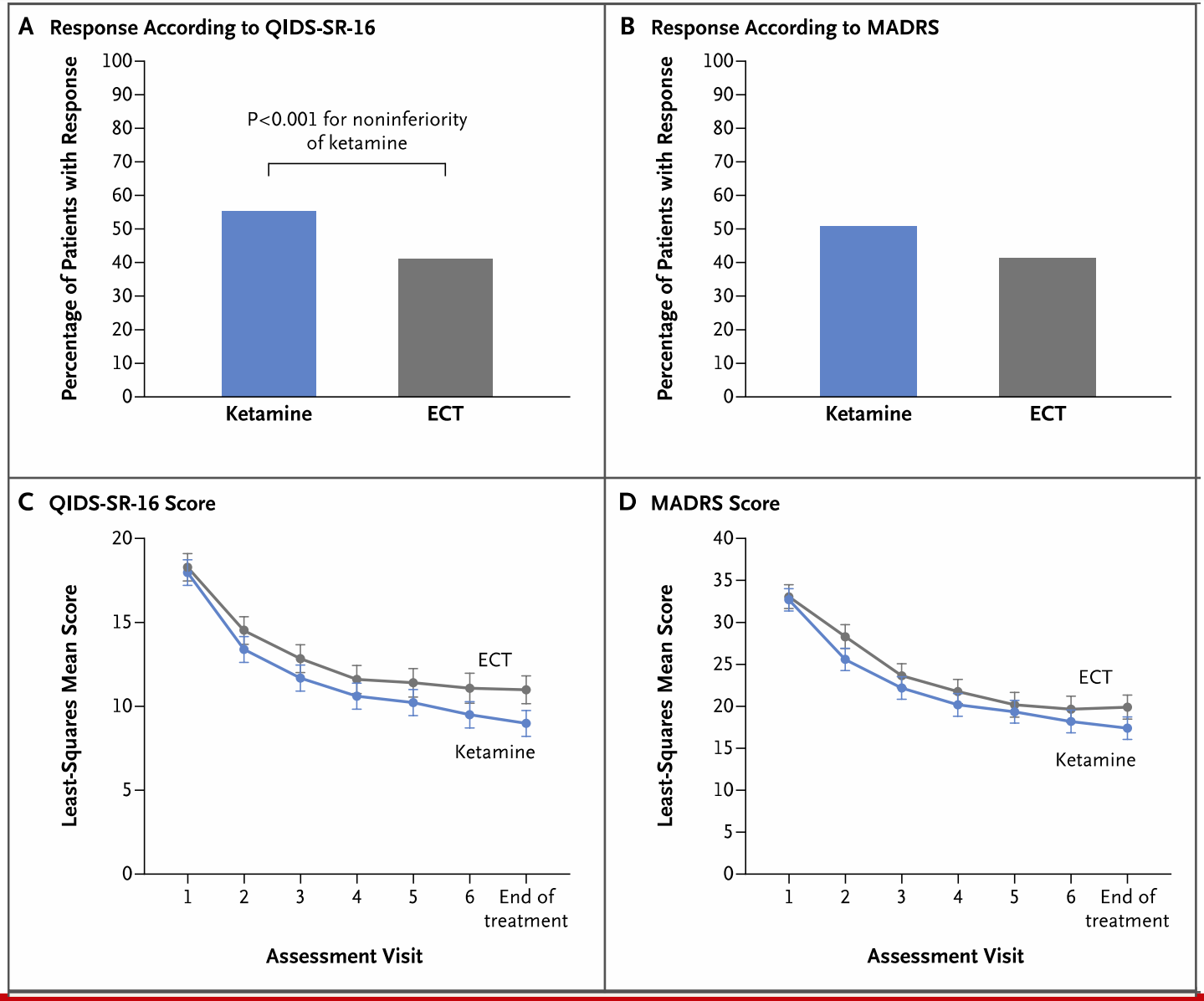
Test for subgroup differences: Chi² = 0.47, df = 3 (P = 0.93), I² = 0%



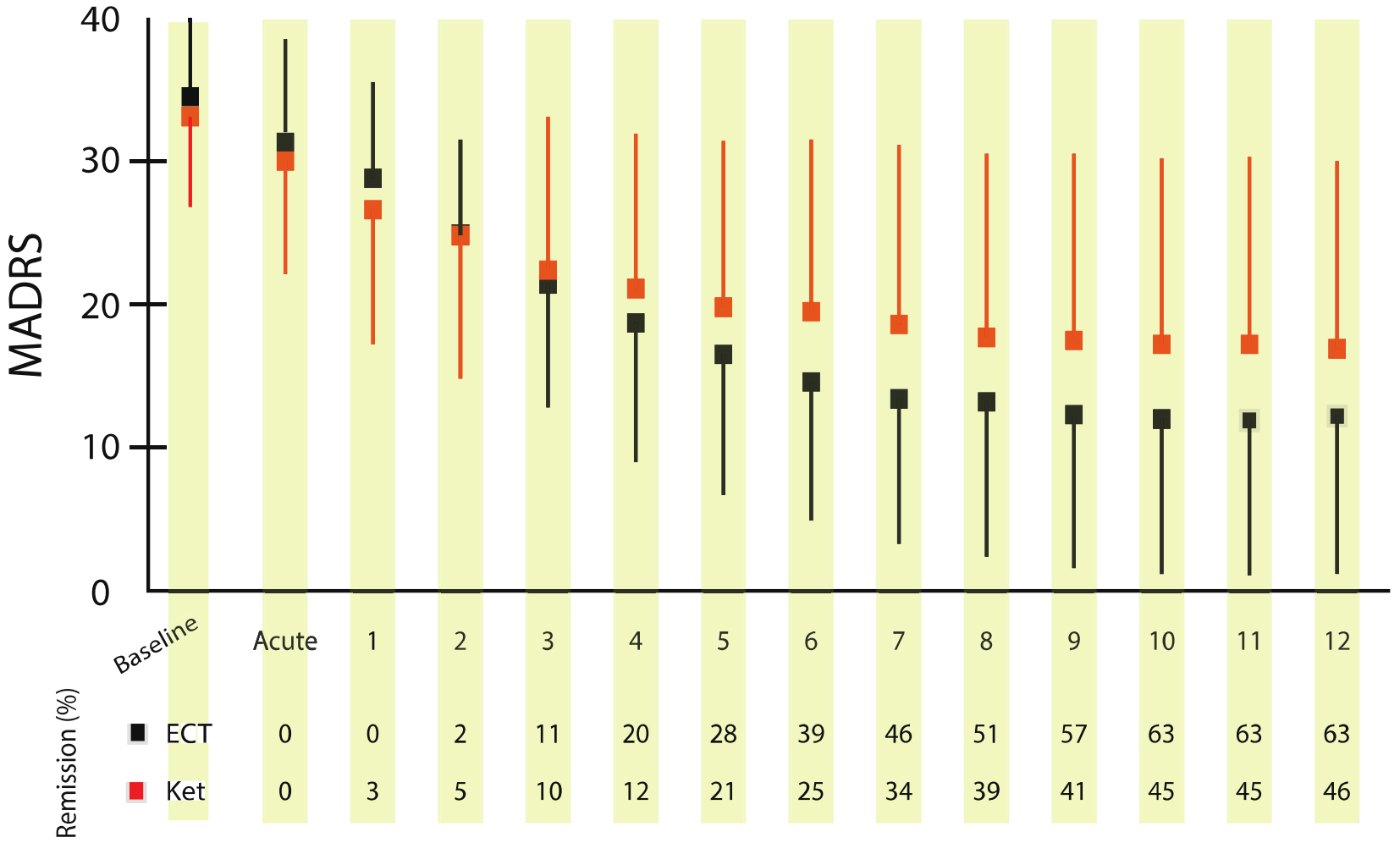
IV Ketamine vs ECT in USA and Europe

- Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression
  - n engl j med 388;25 nejm.org June 22, 2023
  - Open Label, randomized non inferiority design
  - Multi center trial
    - 5 clinical sites
  - 403 patients randomized
    - 195 ketamine
    - 170 ECT
- Racemic Ketamine as an Alternative to Electroconvulsive Therapy for Unipolar Depression: A Randomized, Open-Label, Non-Inferiority Trial (KetECT)
  - *International Journal of Neuropsychopharmacology* (2022) 25(5): 339–349
  - Open Label, randomized non inferiority design
  - Multi center trial
    - 6 clinical sites
  - 186 patients randomized
    - 95 ketamine
    - 91 ECT

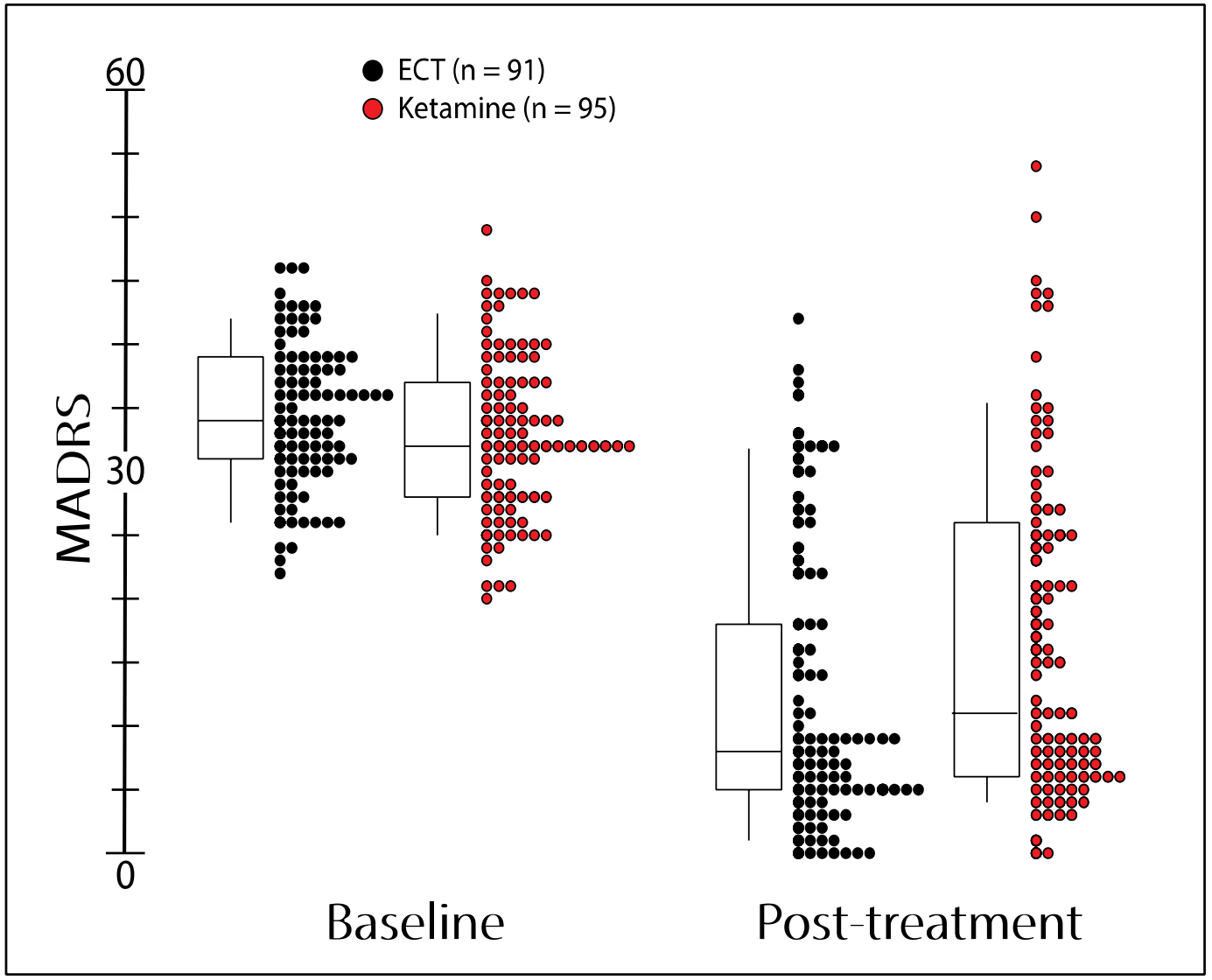
IV Ketamine vs ECT USA Trial



IV Ketamine vs ECT European Trial



IV Ketamine vs ECT European Trial Score Distribution



IV Ketamine in Major Depressive Disorder

- Considerable peer reviewed data on efficacy
  - Single dose
  - Multi dose
- Efficacy comparable to ECT
- Lack of long-term trials
- Lack of long-term maintenance trials
- Favorable safety profile

Blood Pressure Safety of Subanesthetic Ketamine for Depression: A Report on 684 Infusions

Riva-Posse, Patricio; Reiff, Collin R.; Edwards, Johnathan A.; Job, Gregory P.; Galendez, Gail C.; Garlow, Steven J.; Saah, Tammy C.; Dunlop, Boadie W.; McDonald, William M.

Journal Affective Disorders *in press*

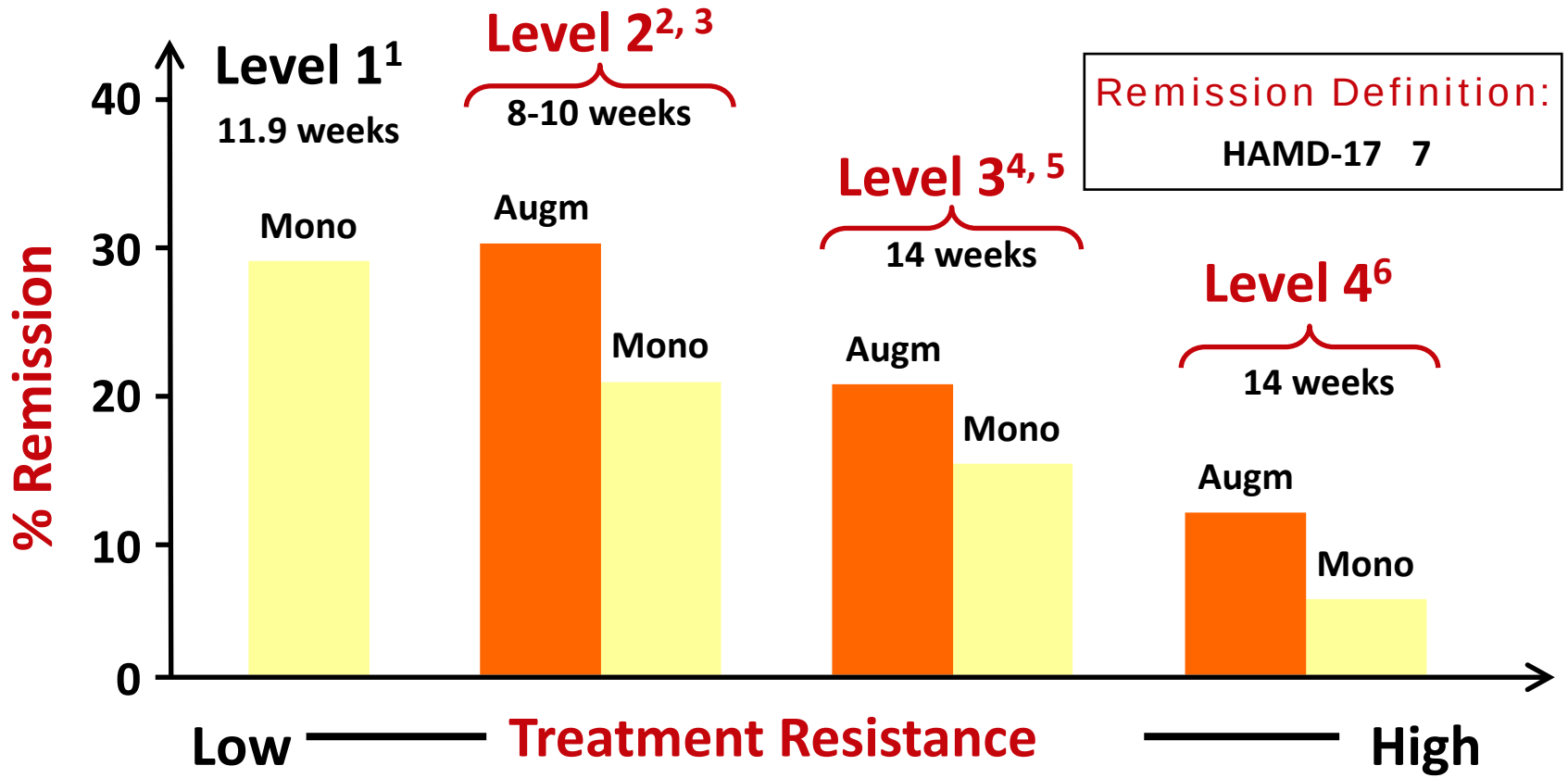
- 66 patients average 10.4 infusions per patient
  - 36% essential hypertension/ antihypertensive
  - NPO EXCEPT antihypertensive
- At 30 minutes
  - systolic 3.28 mmHg
    - Normotensive 2.26 mmHg
    - Hypertensive 6.31 mmHg
  - diastolic 3.17 mmHg
- Resolved by 30 min post infusion
- No tolerance or habituation
- No adverse cardiovascular events/ interventions
- No discontinuations for other adverse events

A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders

Gerard Sanacora, MD, PhD; Mark A. Frye, MD; William McDonald, MD; Sanjay J. Mathew, MD; Mason S. Turner, MD; Alan F. Schatzberg, MD; Paul Summergrad, MD; Charles B. Nemeroff, MD, PhD; for the American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments

- Clinician training
  - Credentialed procedure
  - Moderate sedation
  - ACLS
- Patient selection and assessment
  - Informed consent
  - Medical evaluation
  - Outcome measures
  - Stopping rules
- Monitoring
  - Cardiovascular during procedure
  - Cognitive
  - Genitourinary
  - Addiction

STAR-D Remission Rates Across All 4 Levels



Mono = single medication regimen; Augm = combination medication treatment; [1]Trivedi MH et al. (2006), Am J Psychiatry 163:28-40; [2]Trivedi MH et al. (2006), N Engl J Med 354:1243-1252; [3]Rush AJ et al. (2006), N Engl J Med 354:1231-1242; [4]Nierenberg AA et al. (2006), Am J Psychiatry 163:1519-1530; [5]Fava M et al. (2006), Am J Psychiatry 163:1161-1172; [6]McGrath PJ et al. (2006), Am J Psychiatry 163(9):1531-1541

My Journey into the Bright World: A Skeptic No More……

Ketamine Responsive Patient: Long Term Maintenance

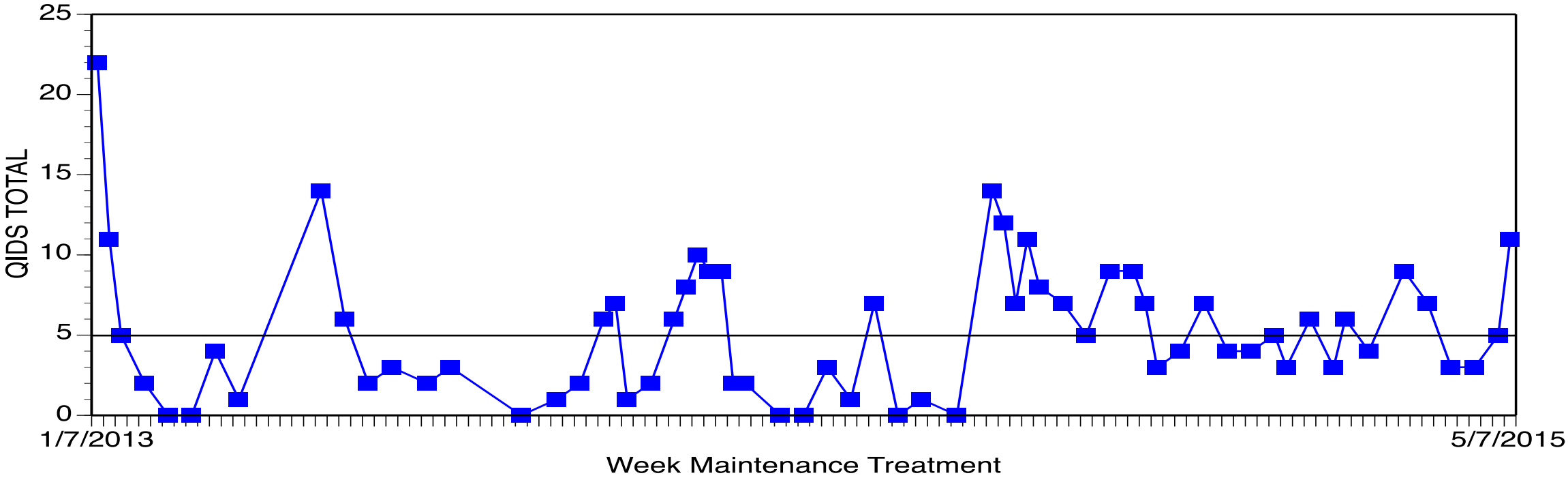
- 50s female
- Initial treatment depression age 18
- 3 life-time psych hospitalizations for suicidal behavior
  - Most recent more than 10 years ago
- Extensive treatment history
  - TCA, MAOI, SSRI
  - Appropriate Psychotherapy

Ketamine Responsive Patient: Long Term Maintenance

- Current treatment
  - Effexor 375 mg
  - Bi frontal ECT
    - 30+ total ECT over 15 month
    - 20+ Bi frontal
  - Long term psychotherapist
- Referral to ketamine
  - Lack of efficacy of ECT
  - Cognitive issues ECT
  - Ketamine added to ECT anesthesia last 3 treatments
  - 16 days between last ECT and first ketamine

That morning I went into the the infusion feeling miserable, discouraged and very frightened for my life. I tried to be hopeful but didn't want to have a lot of expectations either. After the infusion I felt OK, not really bad but not good either. I had no problems with the infusion itself. The next morning I woke up in the hospital having had a good night sleep. I knew within 15 seconds of waking up that things were different. I felt so much better and would say that I was even happy. I was much, much better. Unbelievably better. I felt no depression at all……

Ketamine Responsive Patient: Maintenance Course



Hey Dr. G.

Yesterday was the 3rd anniversary of my starting Ketamine. It was a day that I reflected on my long journey with TRD and how different the past 3 years have been. I consider myself to be extremely fortunate to be able to receive this particular drug. There's no doubt that I would have died if I didn't start it when I did. I want to say thank you for going out on that shaky limb without "permission" to help save my life. I'm so happy you were totally wrong about the ketamine and it worked!

Maintenance of Ketamine Response

- Length of benefit unique to each patient
  - patients in long term maintenance (6 month to 5 years)
- No apparent interaction or maintenance effect
  - Conventional antidepressants do NOT maintain ketamine benefit
- No interaction with DBS in limited experience
  - 4 patients with DBS and ketamine
- Unclear interaction with ECT
- No adverse outcomes
  - Neurocognitive
  - Genitourinary
  - Addiction or diversion
  - Psychotic breaks

Where Do We Go From Here

- Ketamine is an efficacious antidepressant
  - IV ketamine > intranasal s-ketamine
  - ECT= IV ketamine but different
  - Ketamine as anti suicide agent
- In some select cases, it has provided sustained antidepressant effects
  - “Miracle cure”
- IV is burdensome but so is intranasal
  - Time and cost but consider vs. ECT or other biological infusions
  - IV greater level of control vs. Intranasal or other “self” modality
- Long term use consequences are not known
  - chronic drug users significant SE
  - animal studies
- Next steps:
  - Ketamine-like compounds?

Ketamine Cannot

- Put money in patient’s bank account
- Find job; find better job
- Change spouse, parents, children
- Bring back the dead
- Facilitate time travel
  - To correct past deeds/misdeeds/ wrongs/ losses
- Bring Happiness/ Satisfaction/ Joy