Ketamine therapy for TRD: Current evidence and real world applications

Tobias Marton MD PhD

Asst Clinical Professor, UCSF

Staff Psychiatrist, SFVA

Overview

- Review existing evidence for use of ketamine in the treatment of treatment-refractory depression (TRD)
- Discuss current knowns , unknowns,potential mechanisms and controversies of ketamine therapy for TRD
- Overview of IV ketamine therapy clinical and research program at SFVAHCS

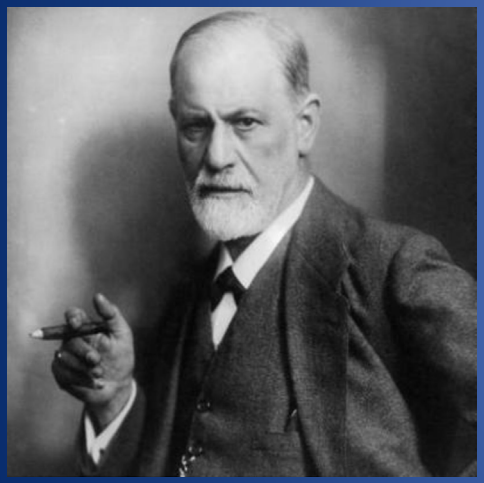
Treatment Refractory Depression (and PTSD):

We have alot of patients who are not getting better

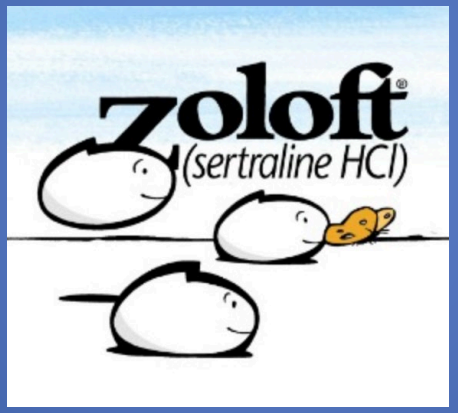
- Treatment Refractory Depression (TRD)
  - Monoamine based antidepressant therapy limited by:
    - Time to effect – 4-8 weeks of treatment
    - Limited efficacy – 30-40% non-response rate
  - Need for new drug targets and more rapid-acting treatments
  - TRD: >2 failed AD trials

- Veterans:
  - Suicide crisis in veteran population
  - Large population of veterans with co-morbid depression and PTSD.
    - High risk for suicide in this population
    - Often difficult to treat
    - Problem of addressing just depression or PTSD leading to symptom relapse (ECT)
  - *We have a lot of veterans getting intensive treatment currently (psychotherapy, medication support, case management, inpatient treatment etc.) who are not really getting better*

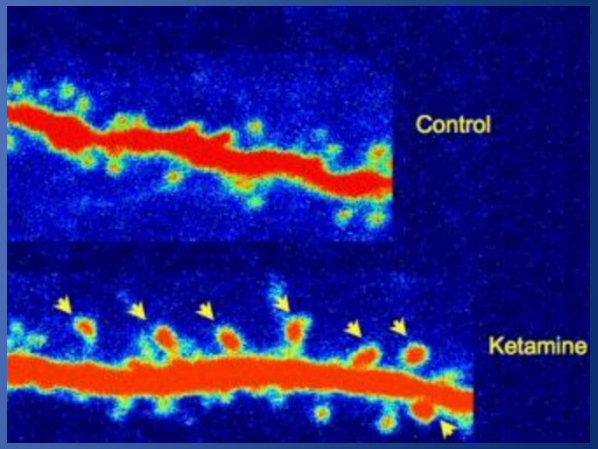
How will rapid acting antidepressants change psychiatric care?



Months to Years

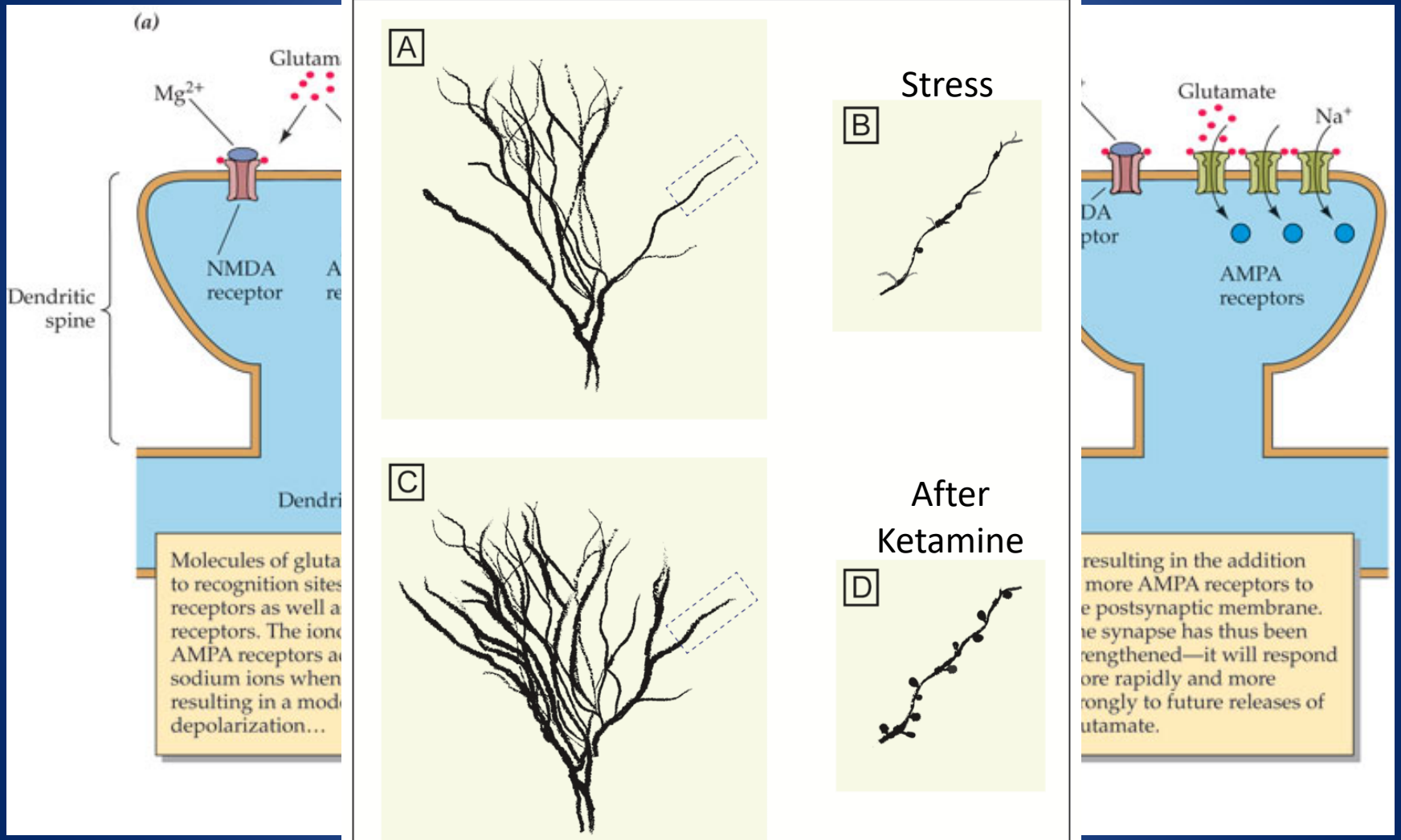


Weeks to Months

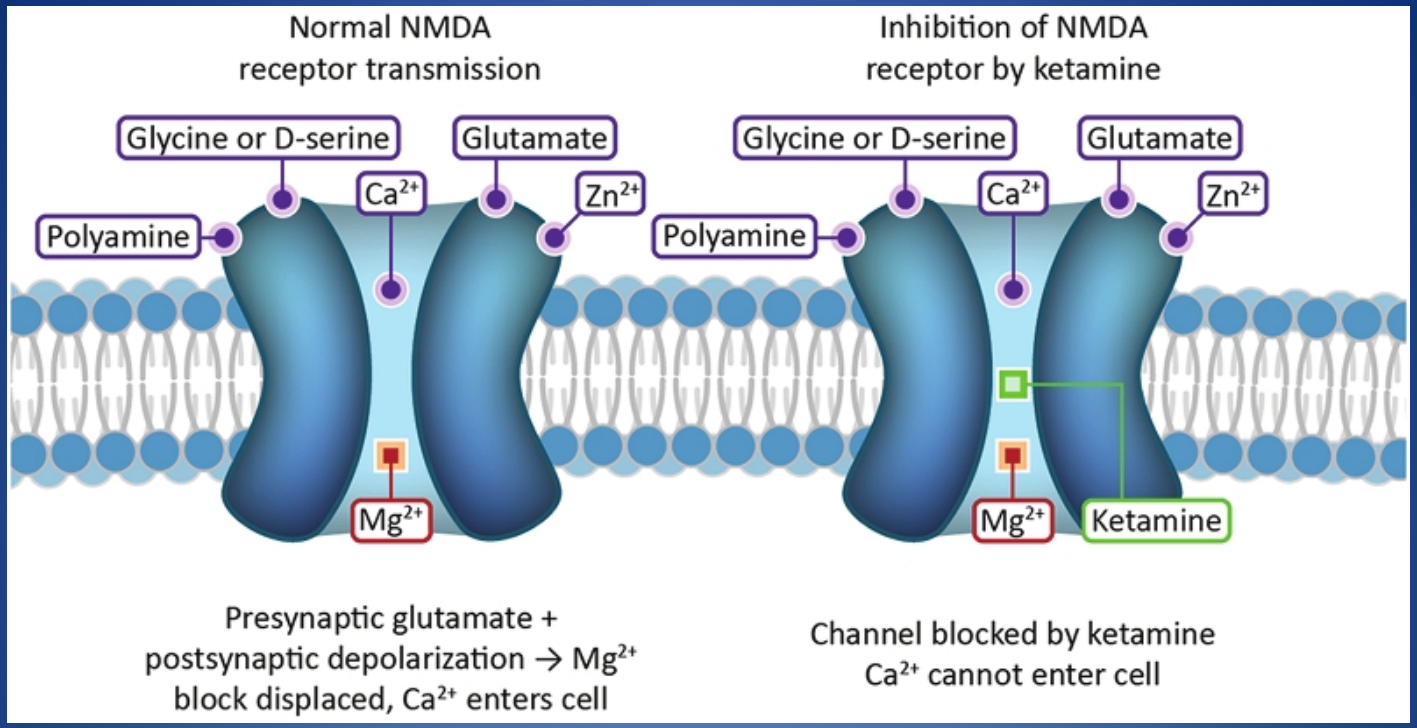


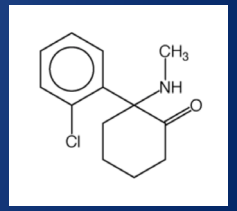
Hours to Days

Glutamate signaling & Synaptic Plasticity



Ketamine Pharmacology





- Ketamine is an arylcycloalkylamine related to PCP
- Non-competitive, voltage dependent NMDAR antagonist - binds the PCP binding site in the ion channel, preventing Ca influx
- Also agonist at opioid receptors and adrenergic receptors

Ketamine – "dissociative anesthetic"

- **Anesthesia:** "Dissociation" – interruption of thalamo-cortical networks.
  - General anesthesia at 2 mg/kg
  - Use in humans limited 2/2 sensory side effects

- **Recreation:** "Dissociation" – psychological effects at 0.1 – 1mg/kg
  - Schedule III
  - Large abuse problem in Asia – movement for international ban

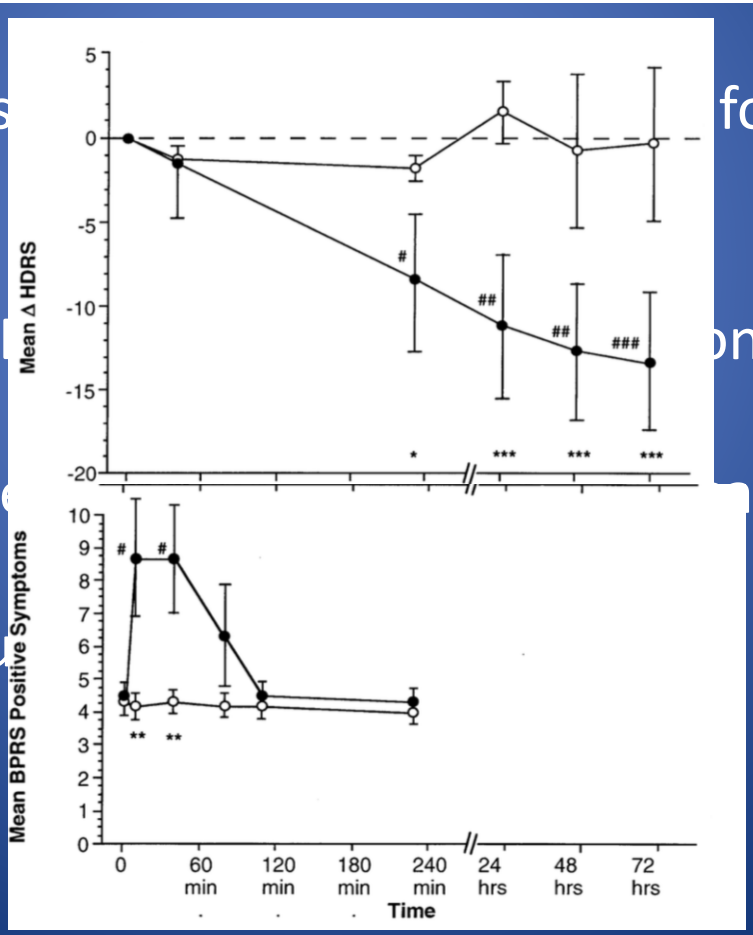
Ketamine: Clinical Trials for TRD

BRIEF REPORTS

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

- Krystal's group firs for depression – 2000
- 7 patients with M ons x 2 weeks
- Double-blind plac line infusion)
- Ketamine 40 minu



Ketamine Efficacy in TRD – Zarate 2006

- Zarate at NIH hospital 2005-2006
- 18 subjects with TRD (failed >2 AD trials)
- Double blind placebo controlled cross over study
- Received ketamine or saline infusion on 2 separate days/1 week apart

Ketamine Efficacy in TRD – Zarate 2006

Patient treatment histories

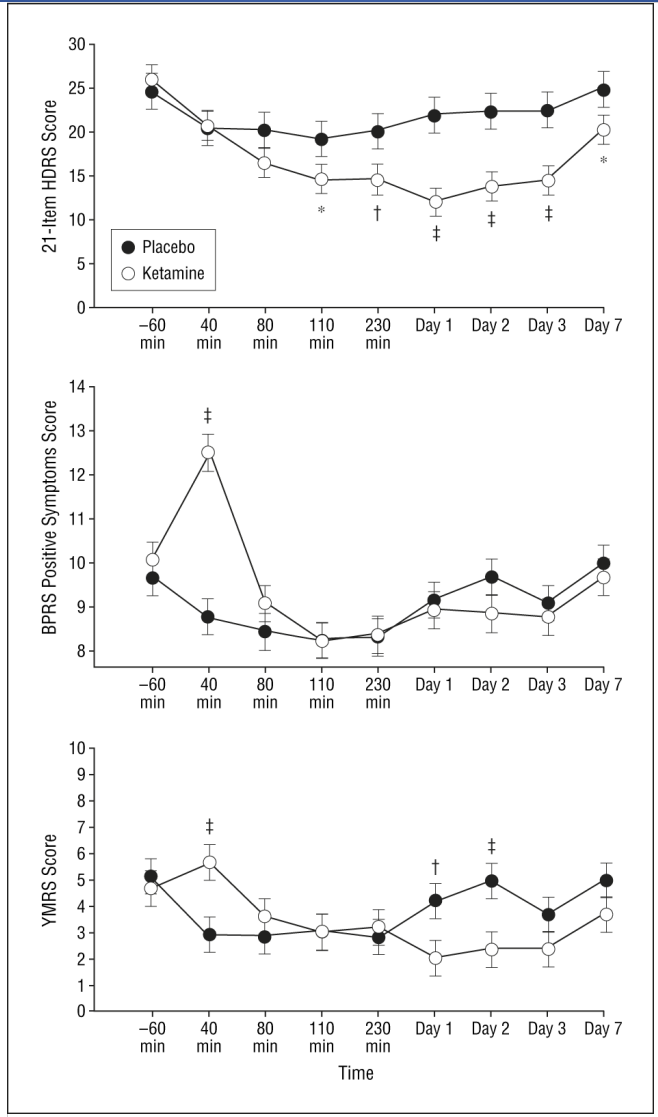
Table. Demographic and Clinical Characteristics

Participant/ Sex/Age, y	Length of Illness, y	Current Episode, mo	No. of Previous Episodes	Failed Medication and Somatic Treatments*	Lifetime Diagnosis of Any Substance Abuse or Dependence†	Lifetime Diagnosis of Alcohol Abuse or Dependence	Peak Change in BPRS[31] Positive Symptoms Subscale Score While Taking Ketamine Hydrochloride	% Change in HDRS Score (Day 1)‡	
								Ketamine	Placebo
1/F/43	24	4	10	SSRI (2); MAOI; AAP (2); BZD (3)	No	No	+9	–90	NA
2/M/46	29	144	2	SSRI (3); SNRI; BUP; OAD (4); AAP; LAM; stimulant; BZD	No	No	+2	–85	–15
3/F/35	20	11	20	SSRI; BUP; TCA; OAD (2); AAP; LAM; BZD (3)	Yes	No	+5	–78	NA
4/F/43	24	24	4	SSRI (3); SNRI; BUP; OAD (2); lithium; LAM; stimulant (2)	No	No	+7	–78	+11
5/F/45	27	9	1	SSRI (3); BZD	Yes	Yes	–1	–74	+14
6/F/56	38	24	10	SSRI (3); BUP; TCA (2); VPA; BZD (2)	Yes	Yes	+7	–64	–18
7/F/57	44	60	9	SSRI (3); BUP; MAOI; OAD (2); AAP (3); lithium; LAM; stimulant; BZD (3); ECT	Yes	Yes	+3	–61	0
8/F/19	3	8	4	SSRI (3); BUP; stimulant	No	No	0	–57	–27
9/F/48	33	60	9	SSRI (4); BUP; OAD; VPA; stimulant; BZD	Yes	No	+8	–55	NA
10/M/45	14	1	6	SSRI (4); TCA; OAD (3); stimulant; BZD (3); ECT	Yes	Yes	+2	–54	+25
11/M/28	16	17	4	SSRI (2); SNRI; TCA; OAD; AAP (2); lithium; LAM; BZD (3)	No	No	–1	–50	–41
12/F/46	13	4	9	SSRI (2); BUP; TCA (2)	No	No	+6	–50	0
13/M/55	22	4	9	SSRI (2); BUP; AAP; lithium; BZD (2)	No	No	–2	–39	NA
14/F/62	6	12	4	SSRI (3); OAD (2); BZD	No	No	+3	–39	–10
15/F/60	47	55	3	SSRI (2); TCA; BZD (2)	No	No	+1	–36	–26

(*continued*)

Ketamine Efficacy in TRD – Zarate 2006

- Day 1: 71% response rate, 29% remission rate
- Day 7: 35% response rate
- Greater change in BPRS during infusion predicted response



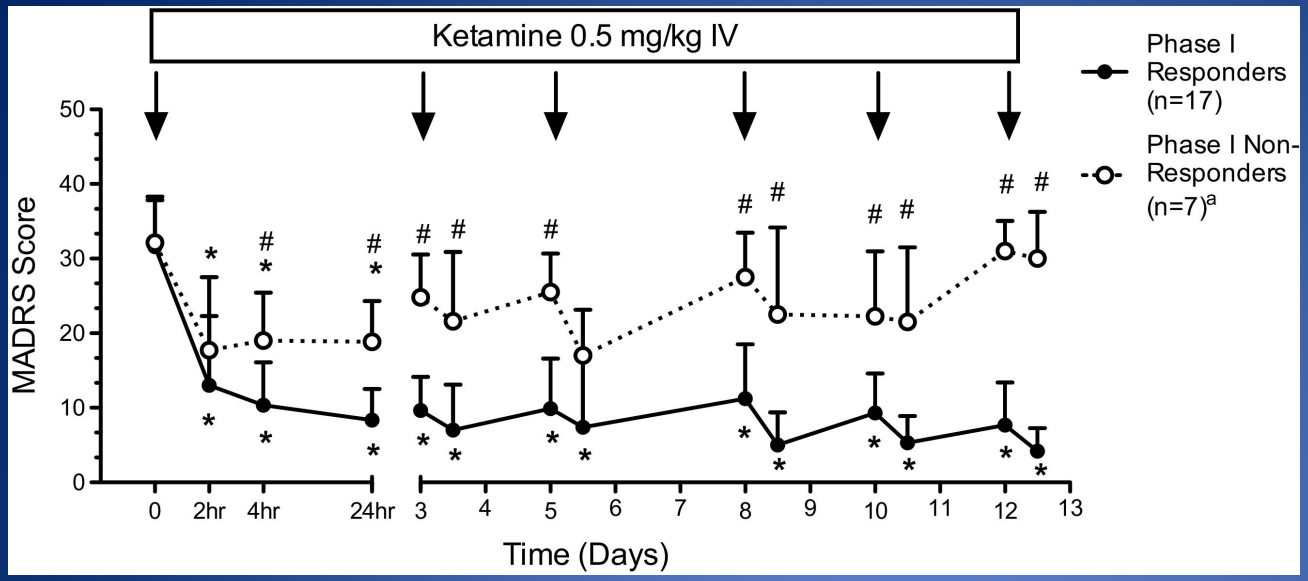
Copyright ©2015 American Medical Association

HDRS

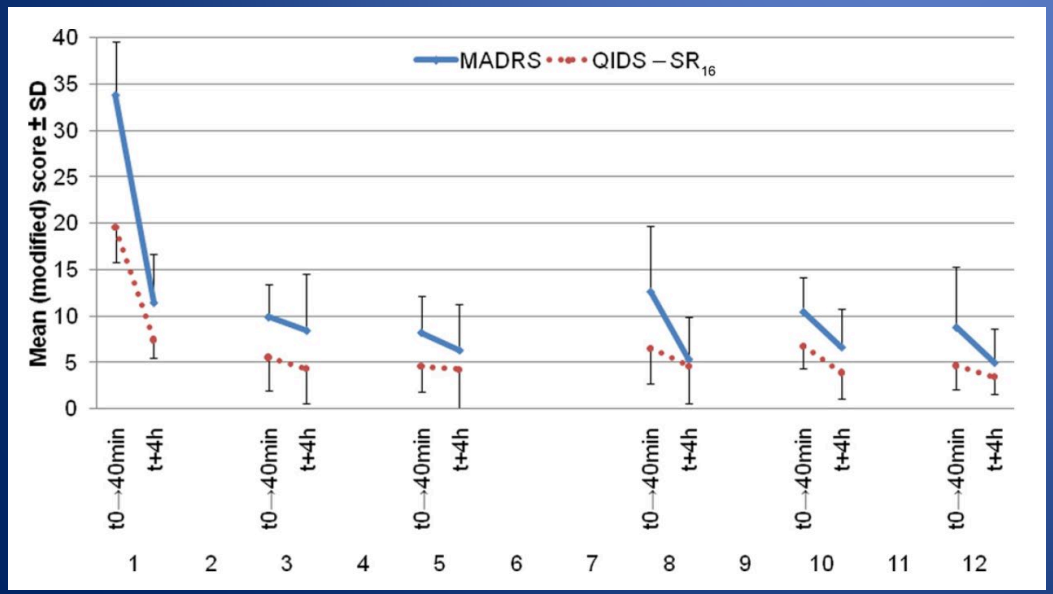
BPRS

YMRS

Ketamine maintenance?



- Murrough et al.
- 5 follow up infusions 3x weekly
- Response to infusion #1 predicted treatment response to repeat infusions

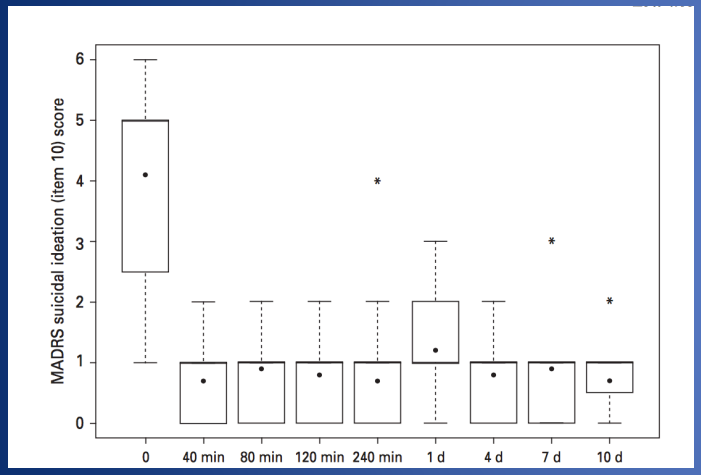


- 9/10 patient showed initial response and continued with 3x weekly treatment
- 8/9 patients relapsed within 3 weeks of last infusion – one sx free at 3 months
- No acute safety or tolerability issues reported

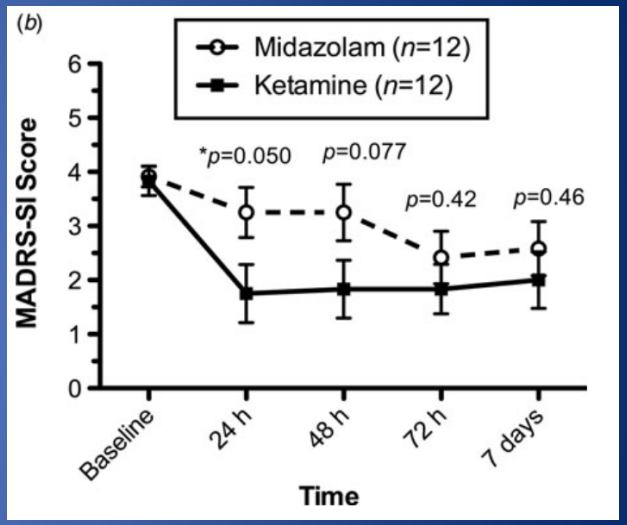
Marije aan het Rot 2010

Ketamine for acute suicidality

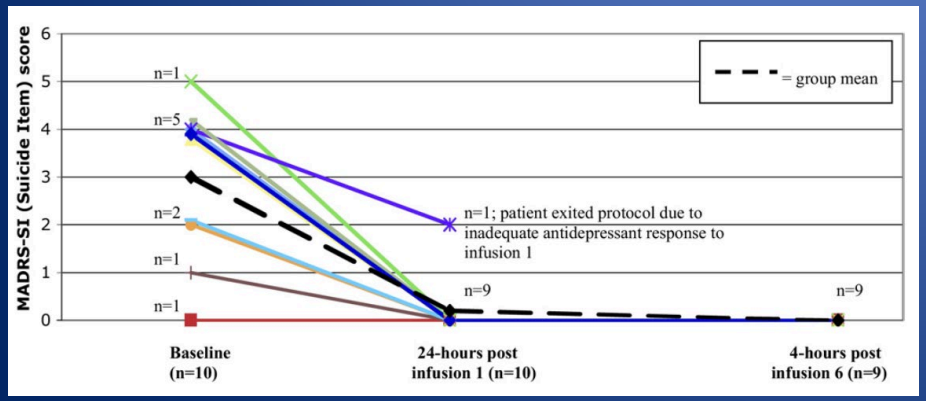
- 9 studies to date examining ketamine for SI – multiple settings and trial types (open label ER setting, RCTs, case reports)
- Mostly positive results with open label trials



Larkin and Beautrais 2011 – open label study in ER setting
- 0.2mg/kg IV Bolus
- all 14 patients with SI resolution at 10 days



Murrough 2015 – no difference from midazolam control at 7 days
-Not restricted to TRD



Price 2009 – repeat infusion, open label

Ketamine for PTS

- N=41, ketamine vs. midazolam,
- Significant and rapid reduction i
  IES-R), remained significant afte
- At two weeks sxs remained redu
  responded to ketamine, vs. 1 w

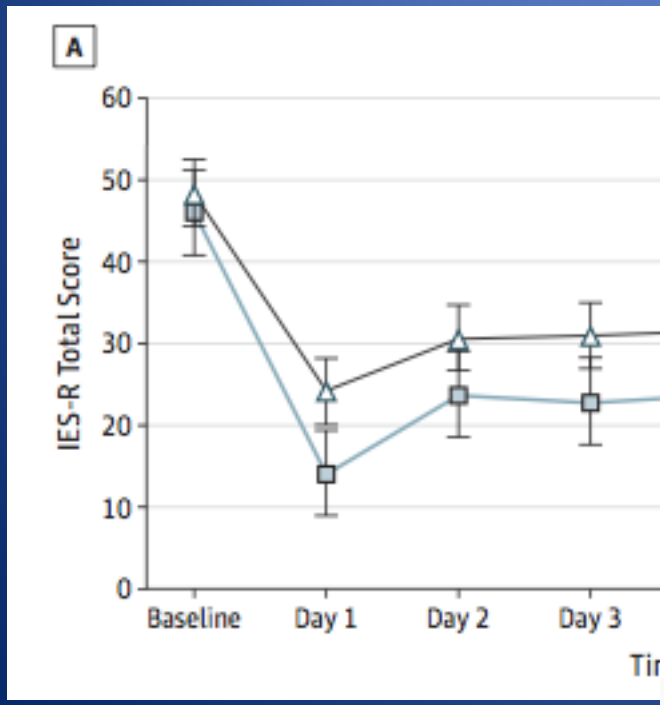
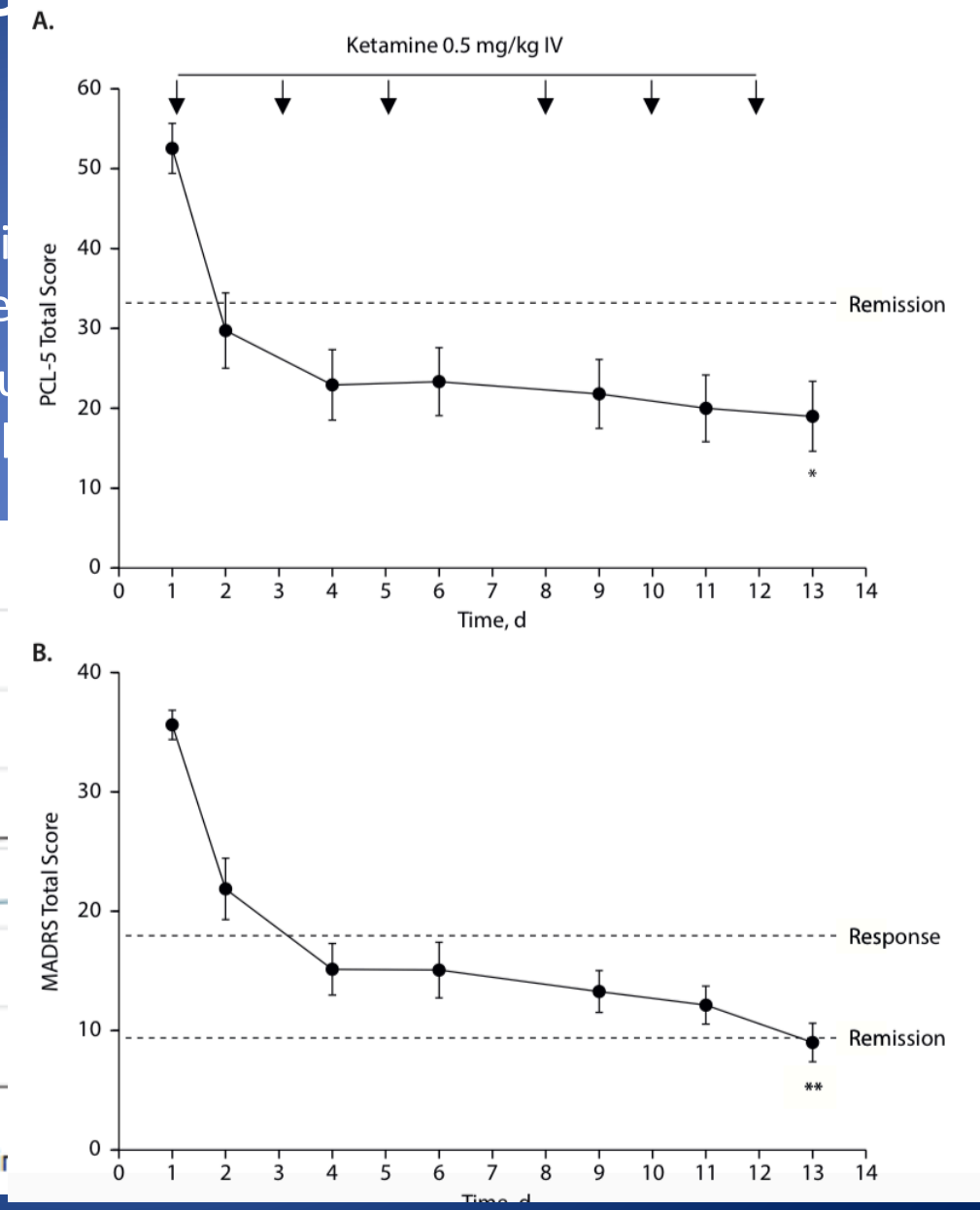


Figure 1. Change in Mean (A) PTSD Symptom and (B) Depressive Symptom Levels After Repeated Ketamine Infusions in a Sample of Individuals (N = 15) With Comorbid Chronic PTSD and TRD[a]



Albott et al 2018

Don’t pop the champagne just yet…

Special Communication

April 2017

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

Gerard Sanacora, MD, PhD[1]; Mark A. Frye, MD[2]; William McDonald, MD[3]; et al

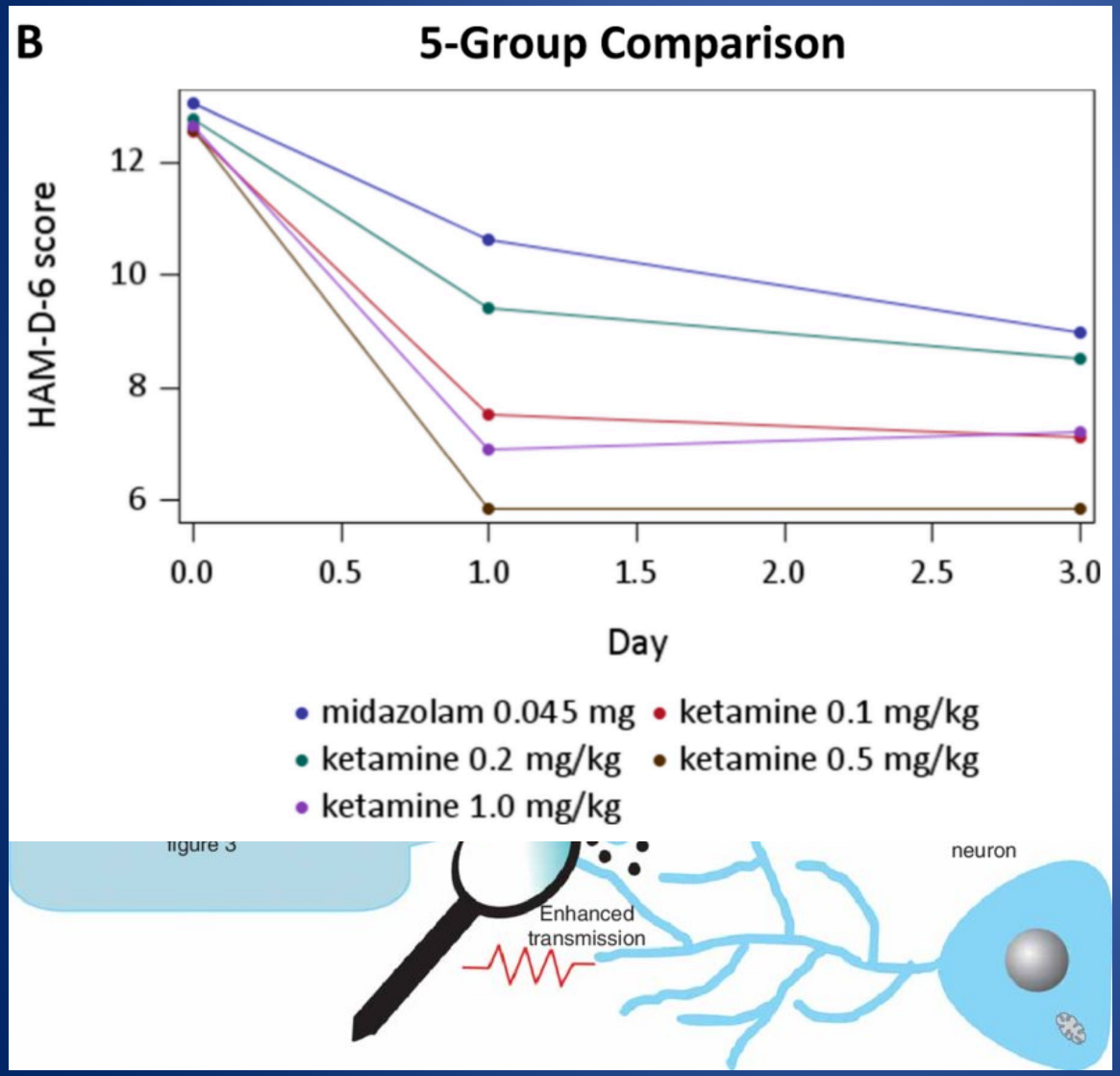
» Author Affiliations

JAMA Psychiatry. 2017;74(4):399-405. doi:10.1001/jamapsychiatry.2017.0080

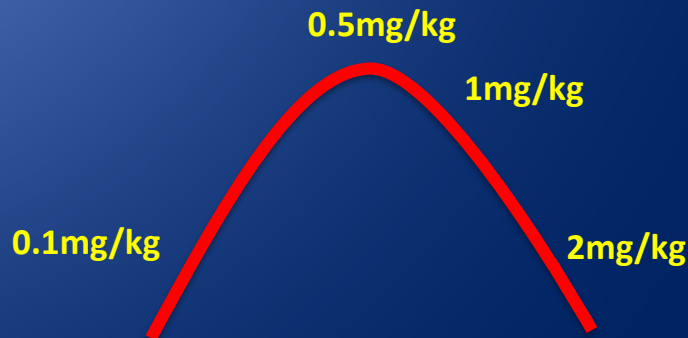
- Lots of unknowns:
  - Safety -> neurotoxicity, cystitis, dependence/abuse
  - Unexplored parameter space – dose response curve, maintenance! etc
  - Concern for profit driven clinics in the community - substandard care

Ketamine: mechanisms and controversies

Ketamine: putative molecular mechanism

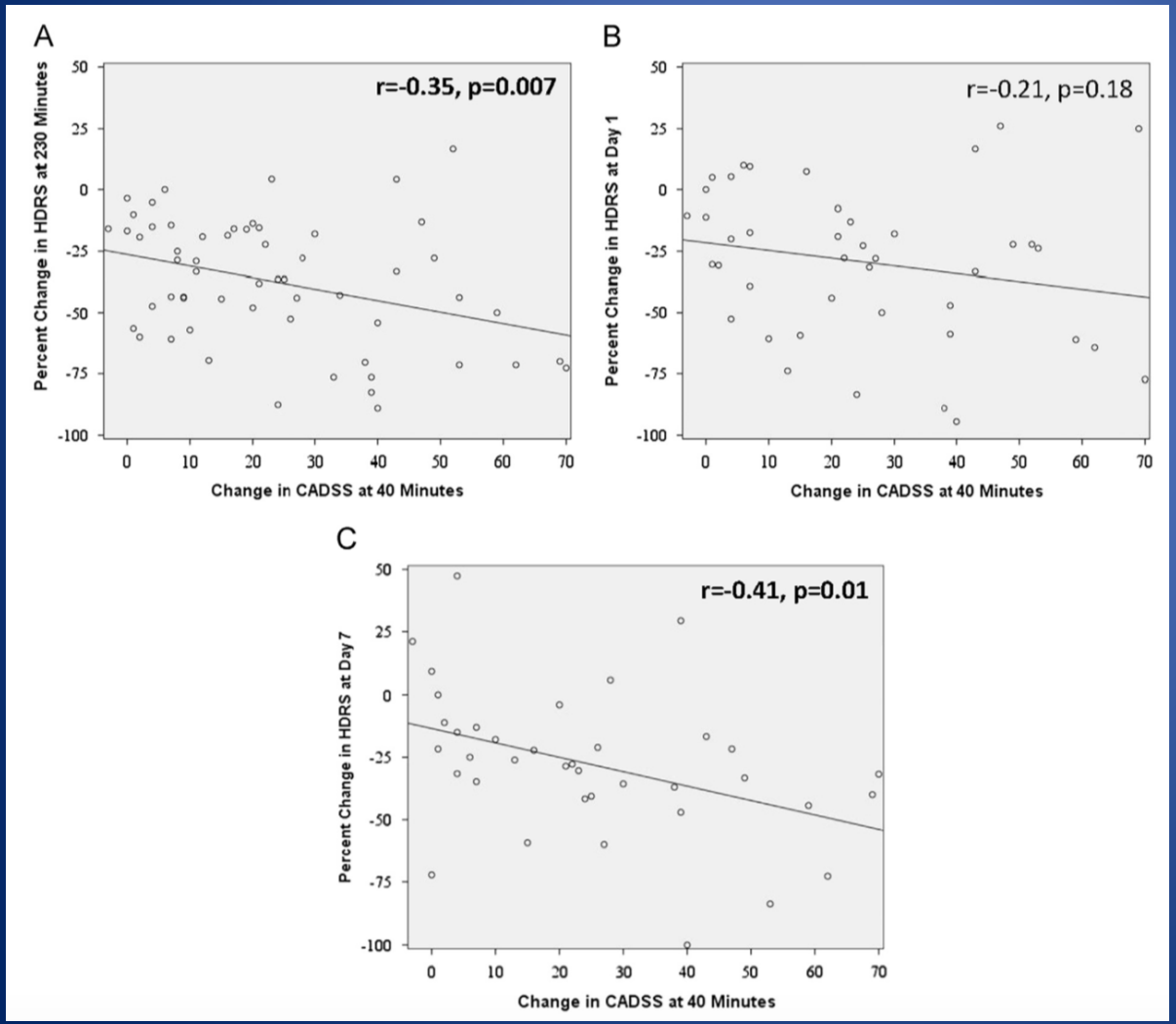


- Ketamine antagonist at NMDA Receptors
- At therapeutic dosing – preferentially blocks NMDARs on pre-synaptic GABA INs -> disinhibition of pyramidal neurons -> glutamate surge -> LTP
- Inverted U-shaped pharmacodynamics consistent with this mechanism



What about "psychological" mechanisms?

- Does the "dissociative" experience matter?



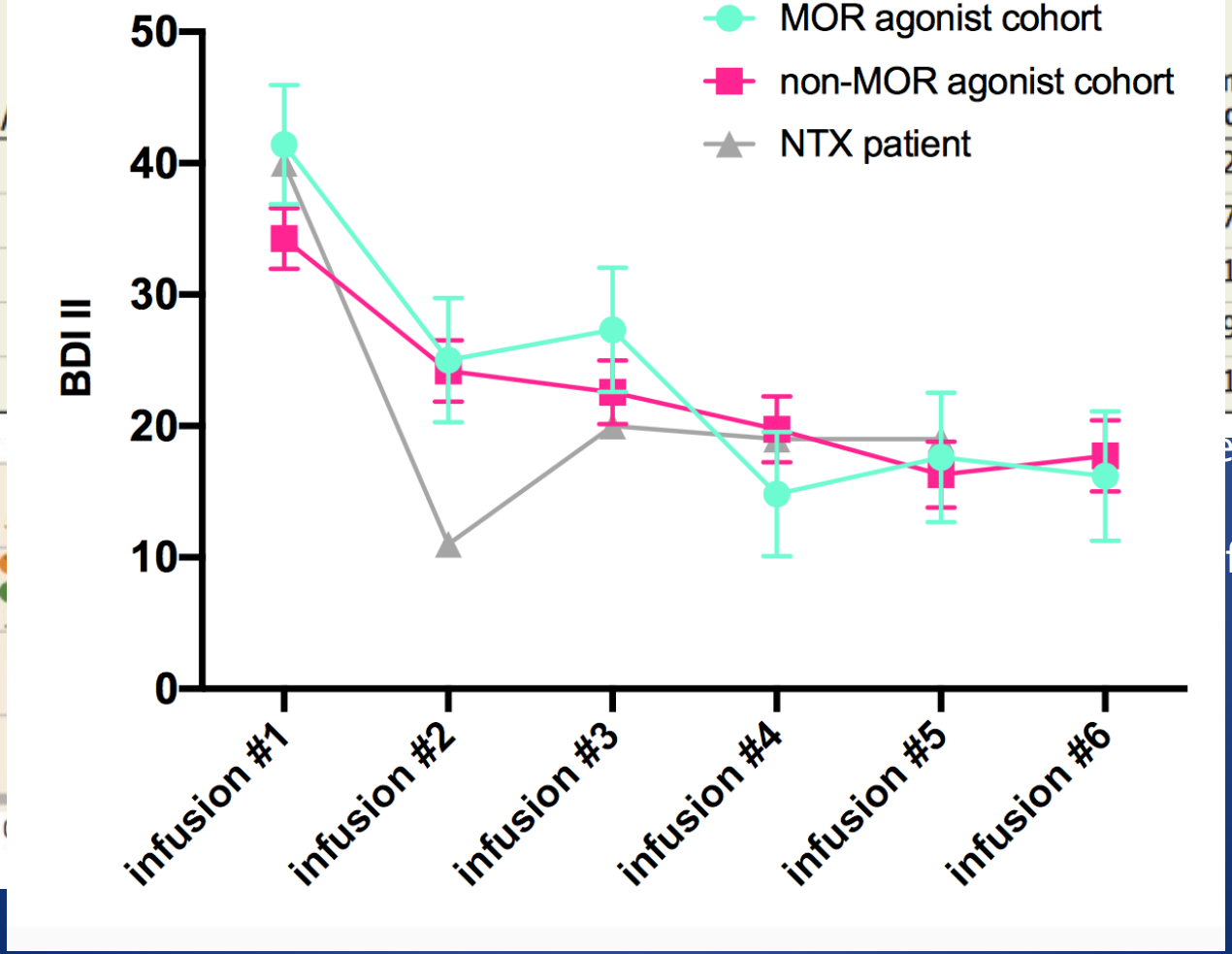
- Current use of ketamine as a "legal" psychedelic assisted psychotherapy drug in the community
  - *No evidence for this use of ketamine*
- Study of 108 TRD patients getting ketamine at 0.5mg/kg
- More dissociation correlated with efficacy at day 3 hours and day 7. Modest r-value

Luckenbaugh et al 2014

Ketamine's antidepressant activity: Really just an opioid?

Table. Depr

Patient No./	tment nprovement, o. (%)
1/M/60	2 (92)
2/M/45	7 (57)
3/F/61	1 (78)
4/M/48	9 (59)
5/M/32	1 (89)



u

d

ession

as well as

ffects

Ketamine: mechanisms and controversies

SFVAMC Ketamine Infusion Program

SFVAHCS Ketamine Infusion Outcomes

- First veteran treated 2/17
  - Treated ~50 veterans since starting clinic 2 years ago
  - Starting ~2 new veterans/month, mostly inpatients
  - Over 800 individual infusions

  - Patient Demographics
    - 10/35 women
    - 35/35TRD (>3 AD trials). ***Average 8 failed med trials*** (range 3 to 15)
    - 21/35 prior ECT – either non-responder, partial responder (PTSD) or cognitive side effects
    - 13/35 co-morbid PTSD
    - 4/31 bipolar (3 BADI, 1 BADII)
    - 12/31 co-morbid SUDs (4 on Bup, 3 on MTD, all in remission)
    - High degrees of suicidality, prior PICU admissions
      - High utilizers of the system

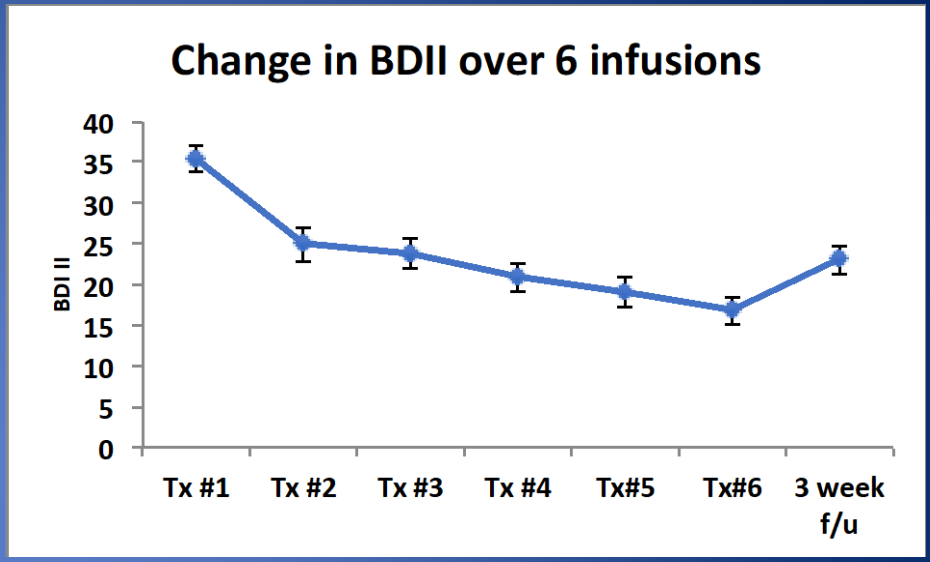
  - 4 non-completers
    - 2 did not like dissociative experience
    - 1 found ECT to have "more kick"

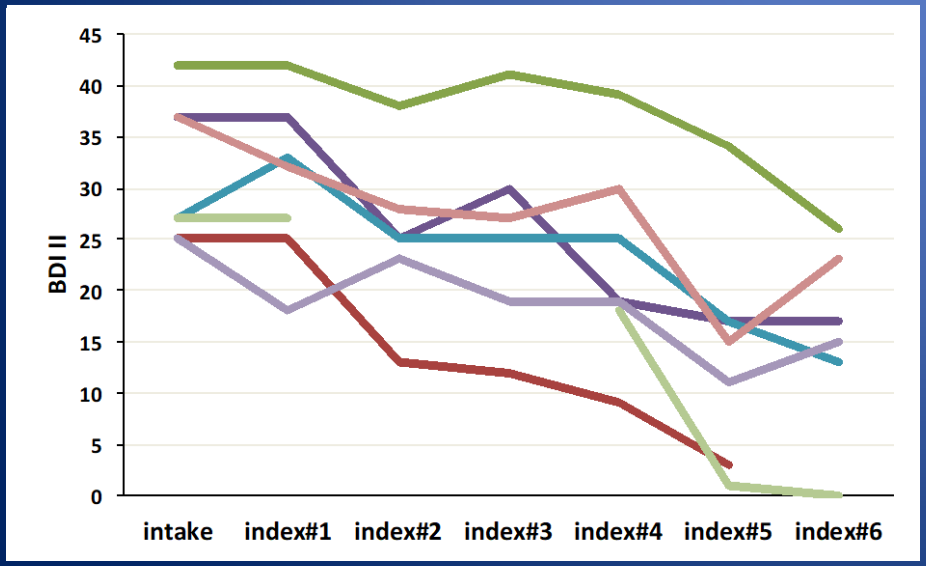
Clinical Protocol

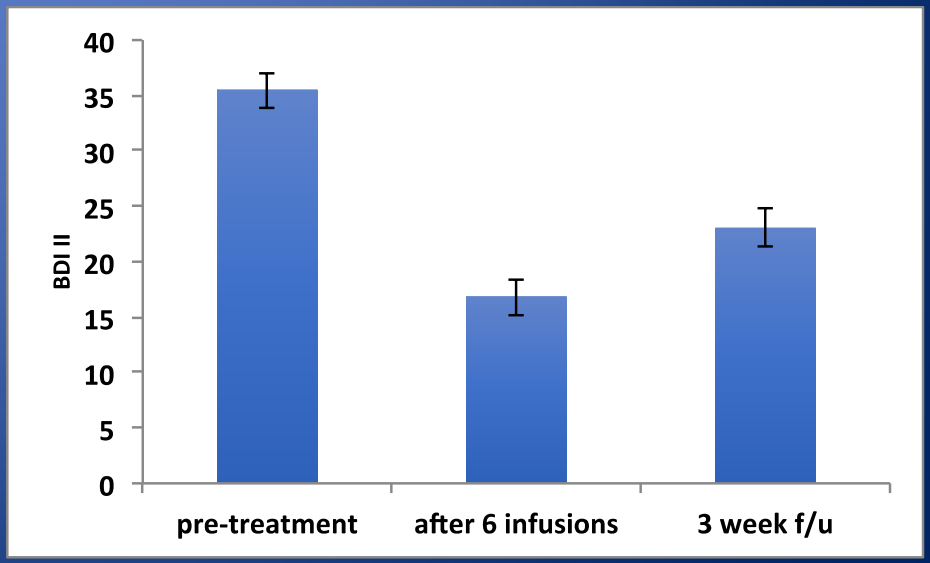
- No active SUDs x 30 days (flexibility re: cannabis). Uncontrolled HTN, LFTs.
- 6 infusions over 3 weeks
- Then ~q 3 weekly maintenance

SFVAHCS Ketamine Infusion Outcomes

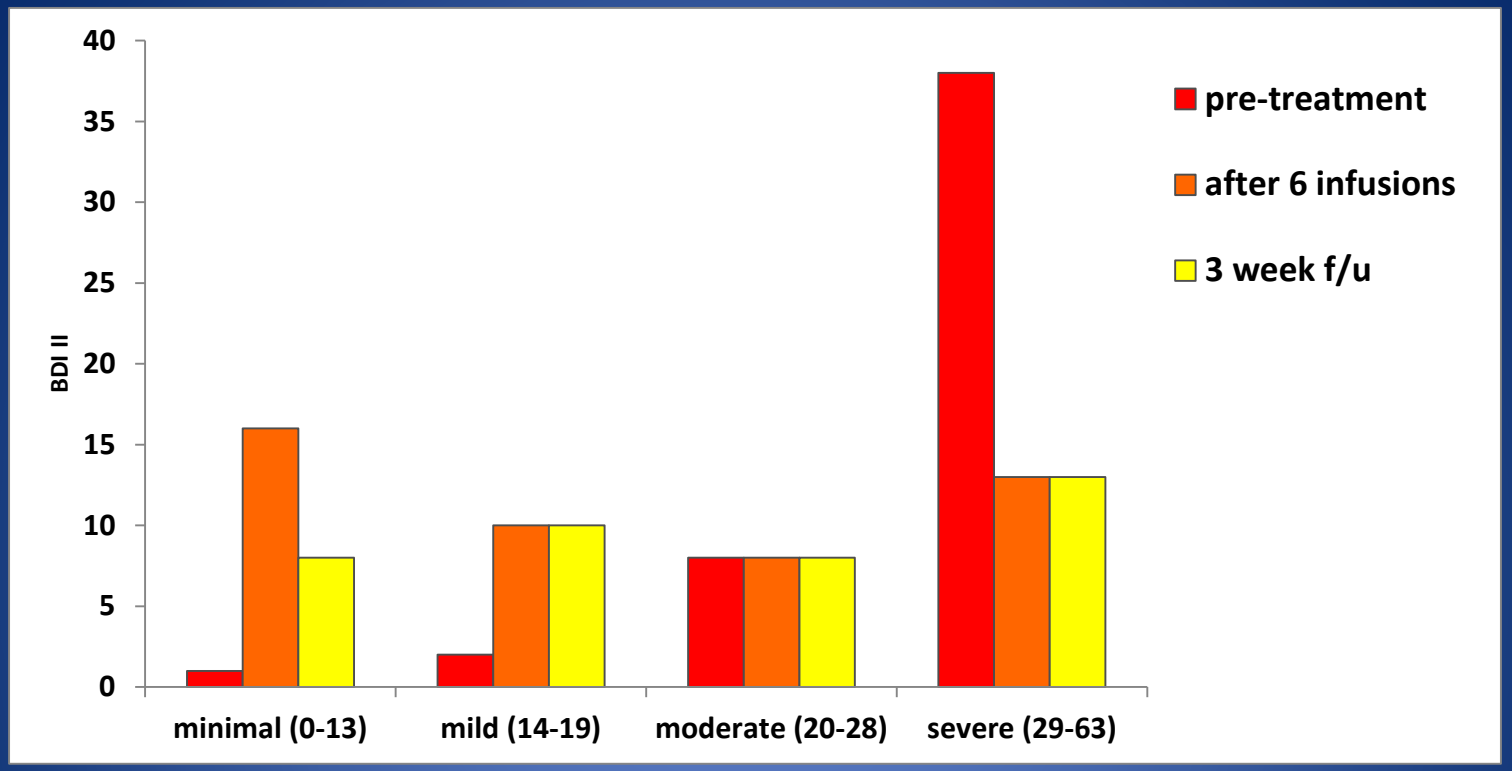
- 49 patients completed at least 5/6 infusions
- Average reduction 19 points BDI II (36 -> 17)
- Average increase of 6 point BDI II at 3 week f/u (17 ->23)







SFVAHCS Ketamine Infusion Outcomes



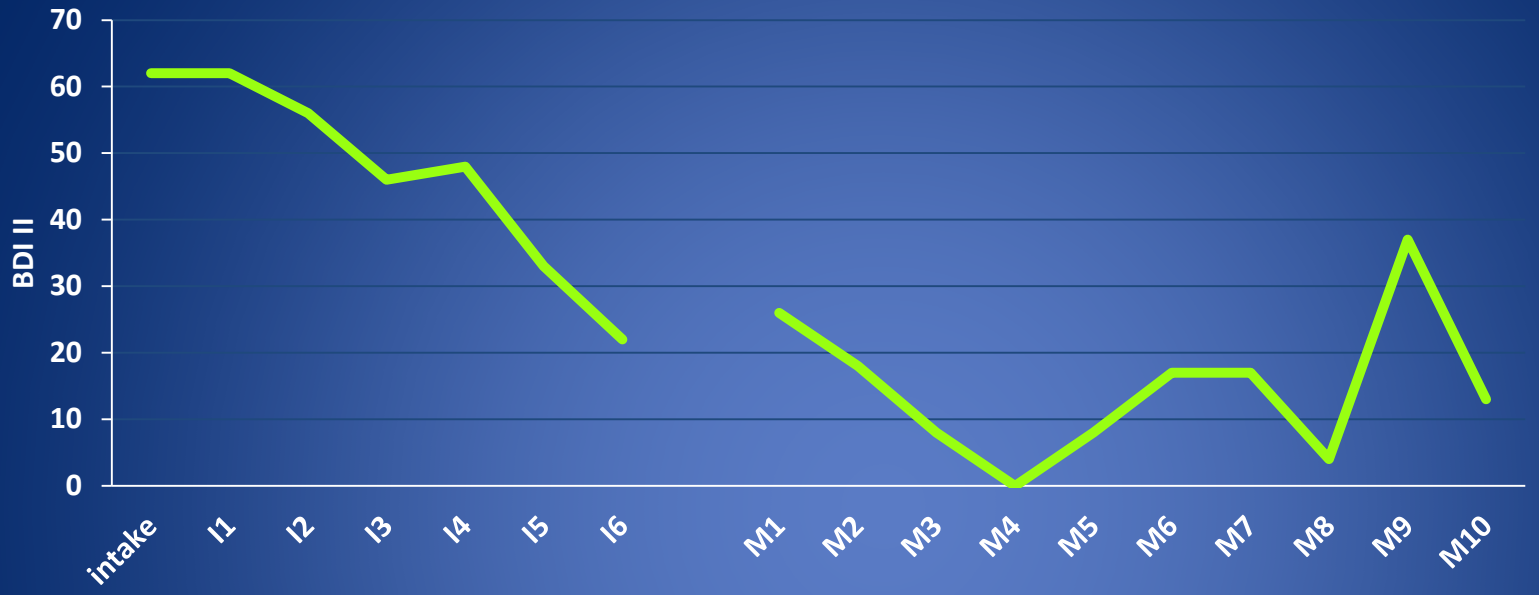
- BDI II -> 26/49 completers with final BDIs in "minimal" to "mild" range
- 50% remission rate, 72% response rate
- Favorable with ECT response/remission rates
- At 3 weeks: 18/49 remain in "mild" or "minimal" group
- No relapses into "severe" range

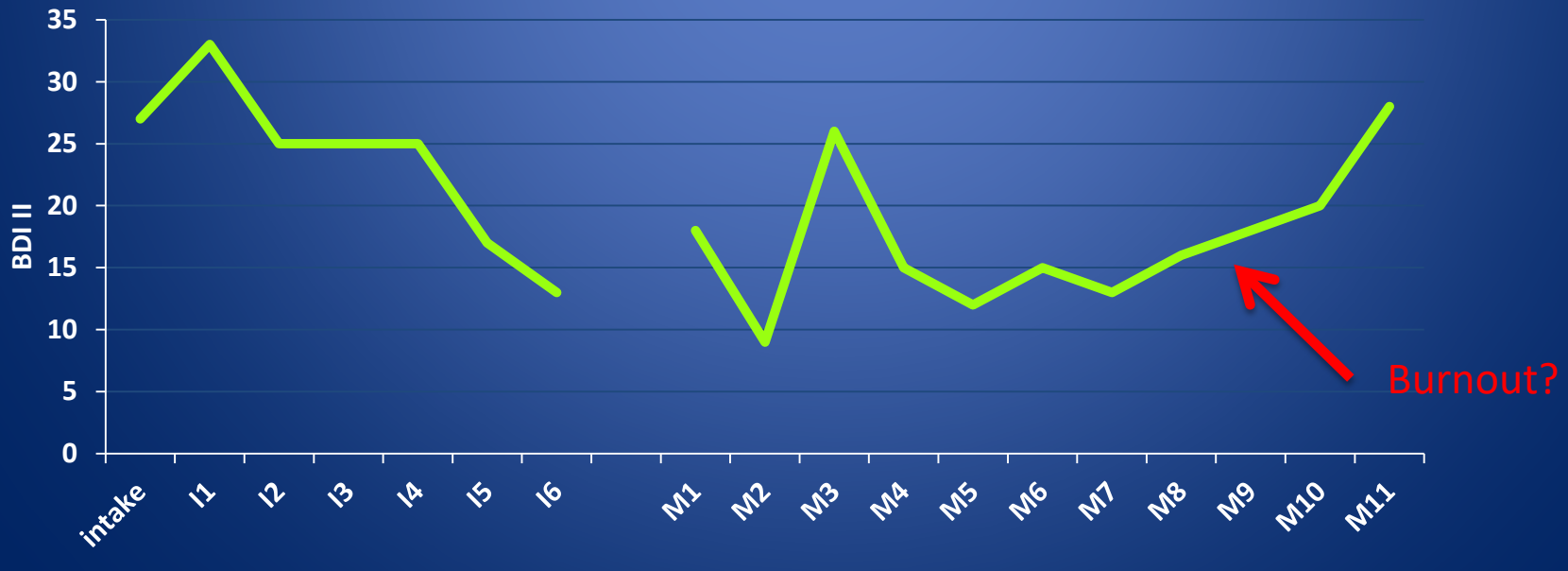
What about maintenance?

- >1/3 of our patients are in active maintenance (~q2-4 week infusions). Often start relapsing at 18 days
  -Longest patient >24 months (~40 + infusions)
  -several more ~1-2 years

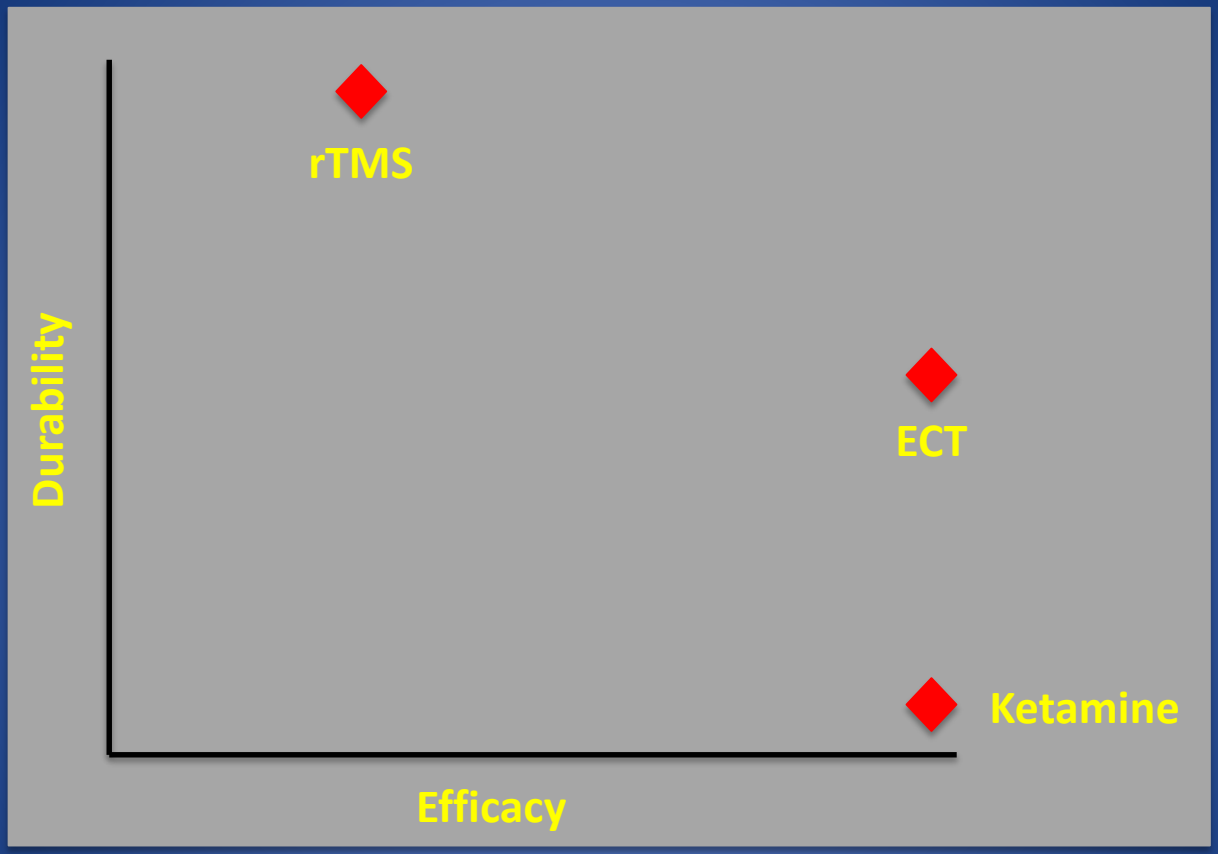
- Logistical/clinical difficulties:
  - Growth of clinic – now doing 15-25 infusions/week
  - Lost to f/u -> depressive relapse
  - How/when to stop?
  - Safety of long term treatment? – no adverse events this far
  - Burnout could be a problem with patients in treatment >1 year?

Maintenance examples





Ketamine: High Efficacy, low durability



- Ketamine demonstrates high efficacy but very low durability of treatment response in TRD (and PTSD) patients as compared to other somatic therapies (ECT and rTMS)
  - Requires ongoing maintenance infusions in responders (~q 18 days) to maintain response
  - Extending durability of response should is a critical area for research

Acknowledgements

- Ketamine Clinic SFVAHCS
  - Art Wallace, MD PhD
  - Isabella Fernandez, MD
  - Alvin Lau, MD
  - Chuck Primich, NP

  - SFVAHCS PACU staff

- Ketamine Research
  - Art Wallace
  - Anusha Badathala
  - Josh Woolley
  - Dan Mathalon