Is "Special K" a quick fix for Depression?

Wynnie Lau
UBC PharmD Candidate
28 March 2013

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Controversial drug proves highly effective in treating depression

CARLY WEEKS

The Globe and Mail

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"Science is more than a body of knowledge; it's a way of thinking,
a way of skeptically interrogating the universe" -Carl Sagan

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Yale scientists explain how ketamine (AKA "Special K") vanquishes depression within hou

(news.yale.edu)

submitted 4 months ago by TealOcelot

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Controversial drug proves highly effective in treating depression

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Bret Stetka, MD, David Feifel, MD, PhD | Disclosures

Jan 10, 2013

The Globe and Mail

Published Friday, Aug. 06 2010, 8:51 AM EDT

Last updated Thursday, Aug. 23 2012, 3:18 PM EDT

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Treatment

- Meta analysis of 100 RCT (n=27,127) of MDD found average response (≥ 25% ∆) of 54% compared to 37% for placebo
- Treatment resistant MDD (TRD) = any of 3 with 6-8 weeks therapy
  - ≤ 25% ↓ from baseline HAM-D
  - ≤ 50% ↓ from baseline HAM-D
  - fail to achieve remission - HAM-D 17 item score ≥ 7

Undurraga J. Neuropsychopharmacology. 2012; 37:85-64.
Souery D. J Clin Psychiatry 2006; 67 (suppl 6):16-22.

Pathophysiology hypotheses

- Monoaminergic theory of depression
- GABAergic and glutamatergic theory
- Neutrophic hypothesis
  - ↓ Brain derived neutrophic factors (BDNF)

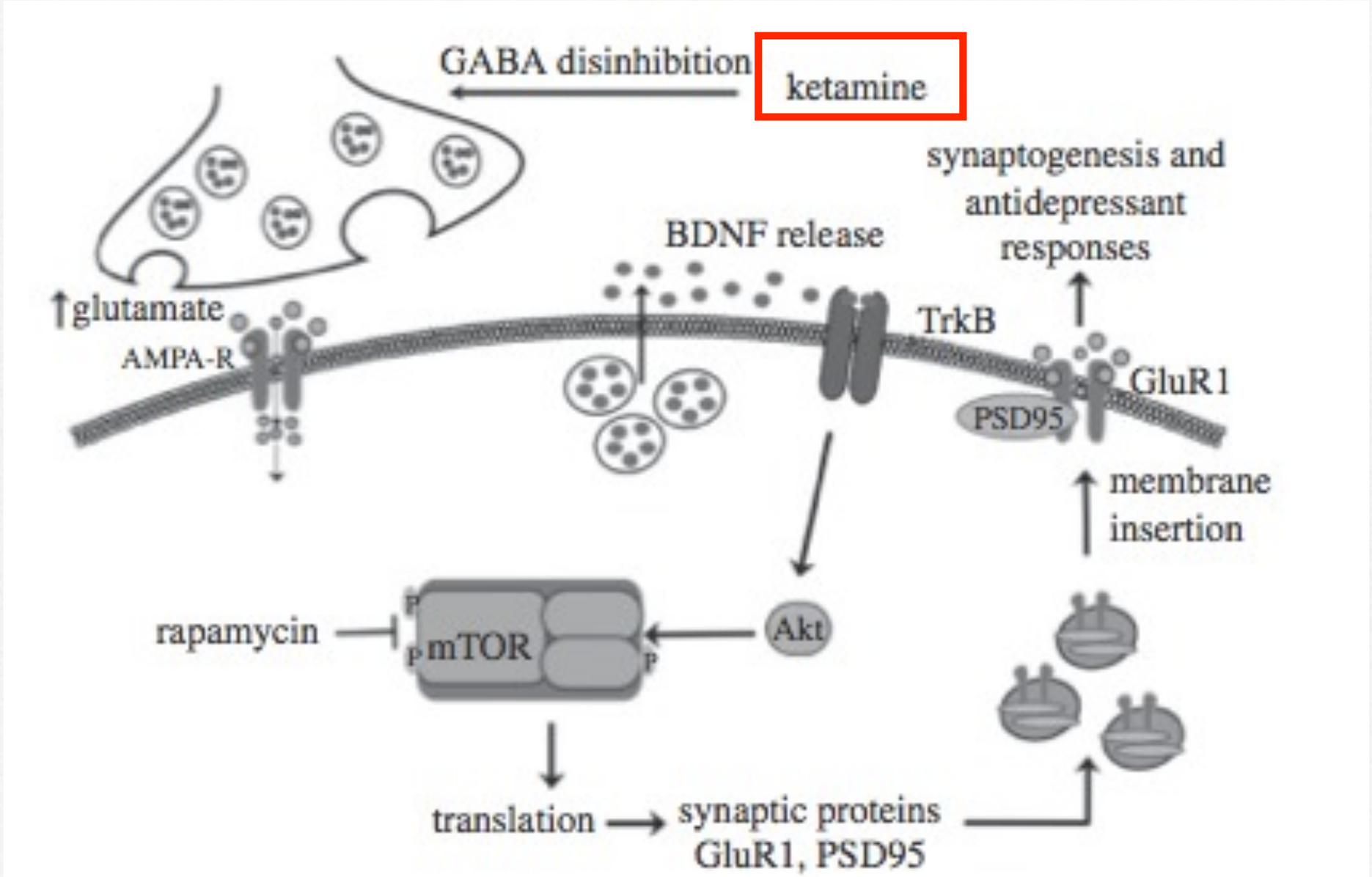
Covvey. Annals of Pharmacotherapy; 2012; 46:117-23.
Wieronska JM. Clinical, Research and Treatment approaches to affective disorders. 2012 ISBN 978-953-51-0177-2

Ketamine

- Synthesized in 1963 and approved since 1970 for 3 indications:
  - Sole anesthetic agent; induction of anesthesia; as supplement for low potency anesthetics
- NMDA antagonist but many different effects
  - inhibit nicotinic ACh receptor activation
  - ↑ BDNF
  - inhibit transport of 5HT, NA and DA
  - modulate GABA-A activity

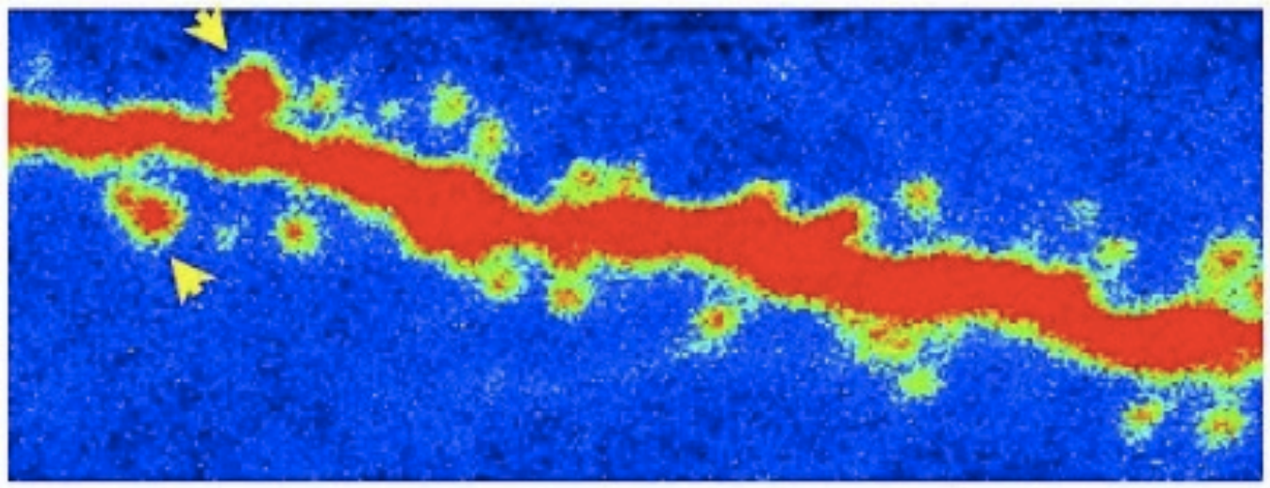
Duman RS. Phil Trans R Soc B 2012; 367; 2475-84
Duman RS. Science 2012; 338, 68- 72

How does it work?



Duman et al. Phil Trans R Soc B. 2012; 367:2475-84.

What is synaptogenesis?



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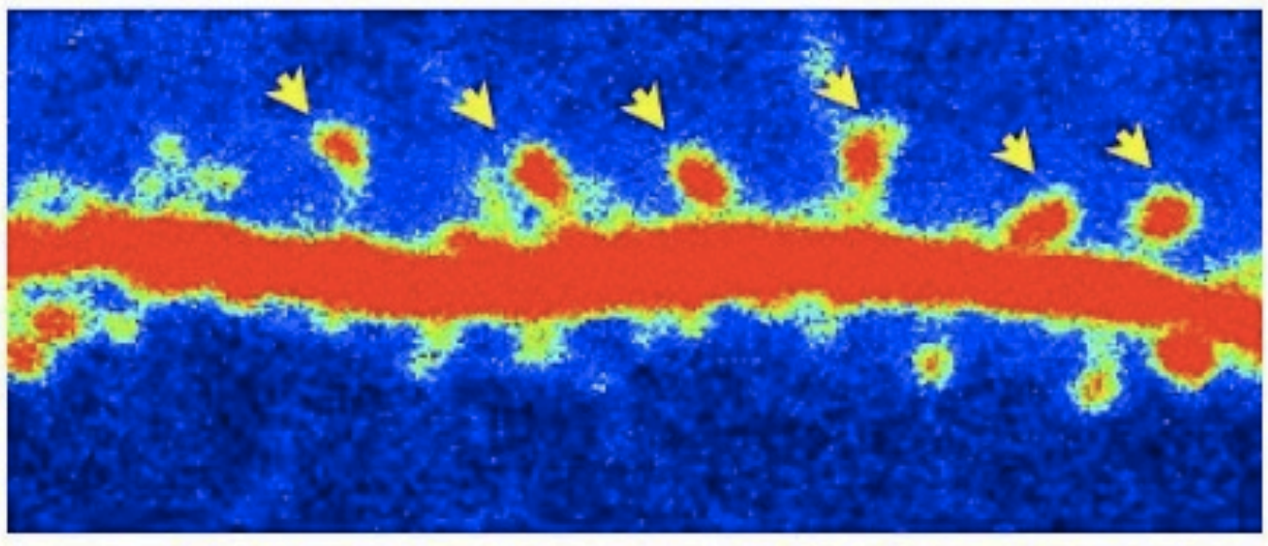


Ketamine

Duman et al. Phil Trans R Soc B. 2012; 367:2475-84.

Clinical Question

P	TRD patients having failed ≥ 2 adequate antidepressant trials
I	Ketamine
C	Placebo or active antidepressant
O	Efficacy: - Prevention of suicide - Reduction in symptoms as measured by validated tool - Reduction in duration of depressive episode - Improved QoL Safety

Search results

Databases	Medline, EMBASE, Cochrane database, Google scholar
Search Terms	Ketamine, N-methyl-D-aspartate receptor, Depression, Treatment resistant depression,
Limitations	Humans, English
Results	2 Systematic Review 3 RCTs 13 Open Label trials 15 Case reports

Rating scales for depression

	Hamilton Depression Rating Scale -17 (HAM-D) (1960)	Montgomery and Asberg Depression Rating Scale (MADRS) (1979)	Beck Depression Inventory (BDI-II) (1996)	Inventory of Depressive Symptomatology (IDSC-C30) (1980)
# of items	17	10	21	30
Frequency	weekly	weekly	q2week	weekly
Administered by	Clinician	Clinician	Patient	Clinician (IDS-C) Patient (IDS-SR)
Max time for admin (mins)	12	15	10	15min
Max Score	54	60	63	84
Clinically relevant Δ	≥ 11 point	≥ 23 point	≥ 10 pt	No interpretative guideline

http://www.ids-qids.org/idsqids.pdf

Furukawa. Journal of Psychosomatic Research 68 (2010) 581-9.

Rating scales for side effects

- Brief Psychiatric Rating Scale 1976 (BPRS)
  - Clinician rating scale
  - 18 items
- Clinician Administered Dissociative States Scale (CADSS)
  - Self report measure
  - 56 items, not validated

Furukawa. Journal of Psychosomatic Research 68 (2010) 581-9.

Antidepressant Effects of Ketamine in Depressed Patients

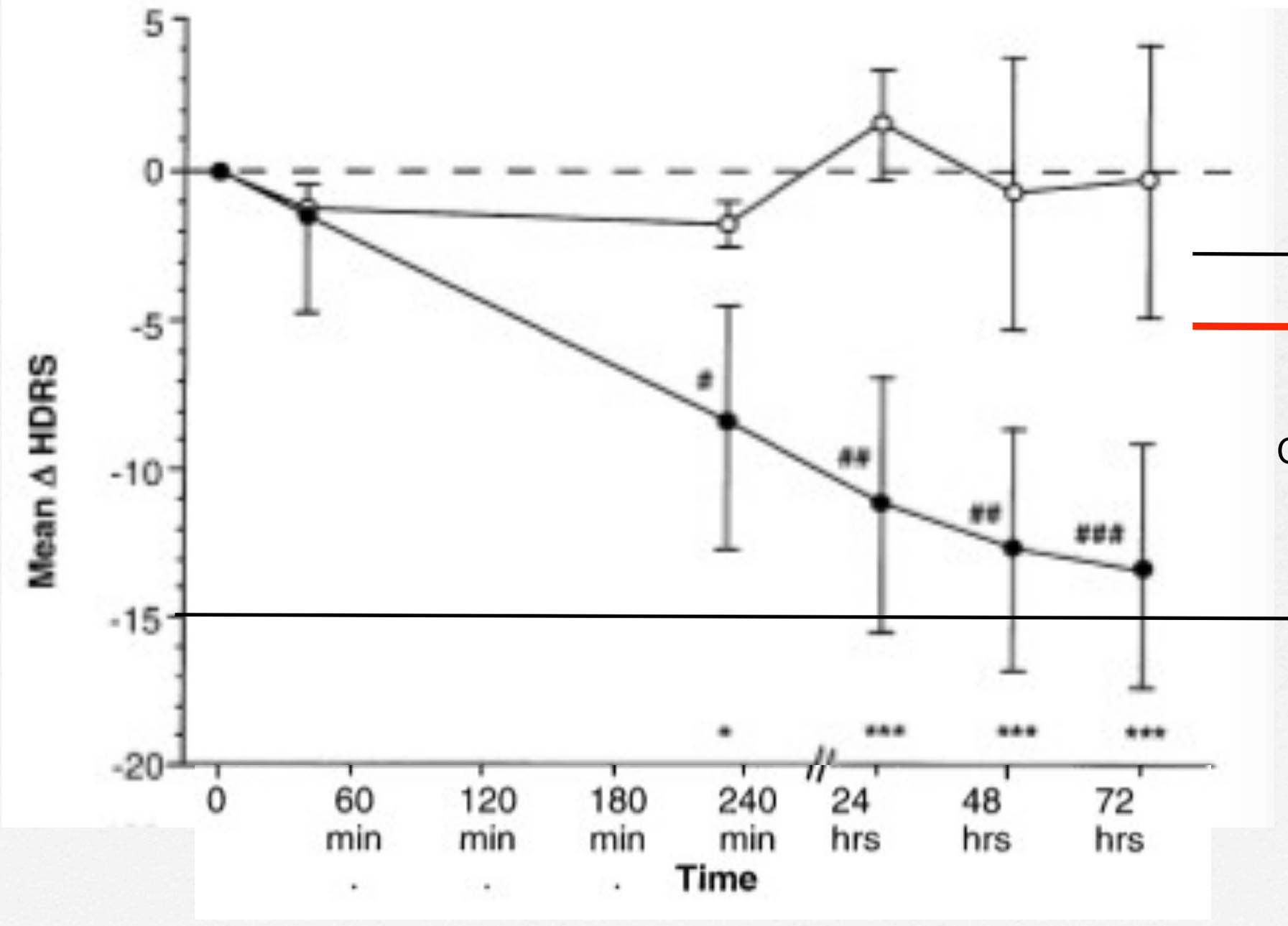
Robert M. Berman, Angela Cappiello, Amit Anand, Dan A. Oren, George R. Heninger, Dennis S. Charney, and John H. Krystal

Biol Psychiatry 2000; 47:351-4.

Berman et al. 2000

D	R, DB, Single centre (Yale University), cross over
P	n = 9, 56% women, 37 ± 10 years old, 8 (unipolar TRD) and 1 (bipolar disorder, depressed), 2 week washout
I	Ketamine 0.5mg/kg IV over 40min, cross over 1 week apart
C	0.9%NS IV over 40min
O	Evaluate potential antidepressant effects using: - 25- item Hamilton Depression Rating Scale (HDRS) - Beck Depression Inventory (BDI) Evaluate toxicity using: - Visual Analog Scales (VAS-high) to assess for “high” -- Brief Psychiatric Rating Scale (BPRS)

Berman et al 2000



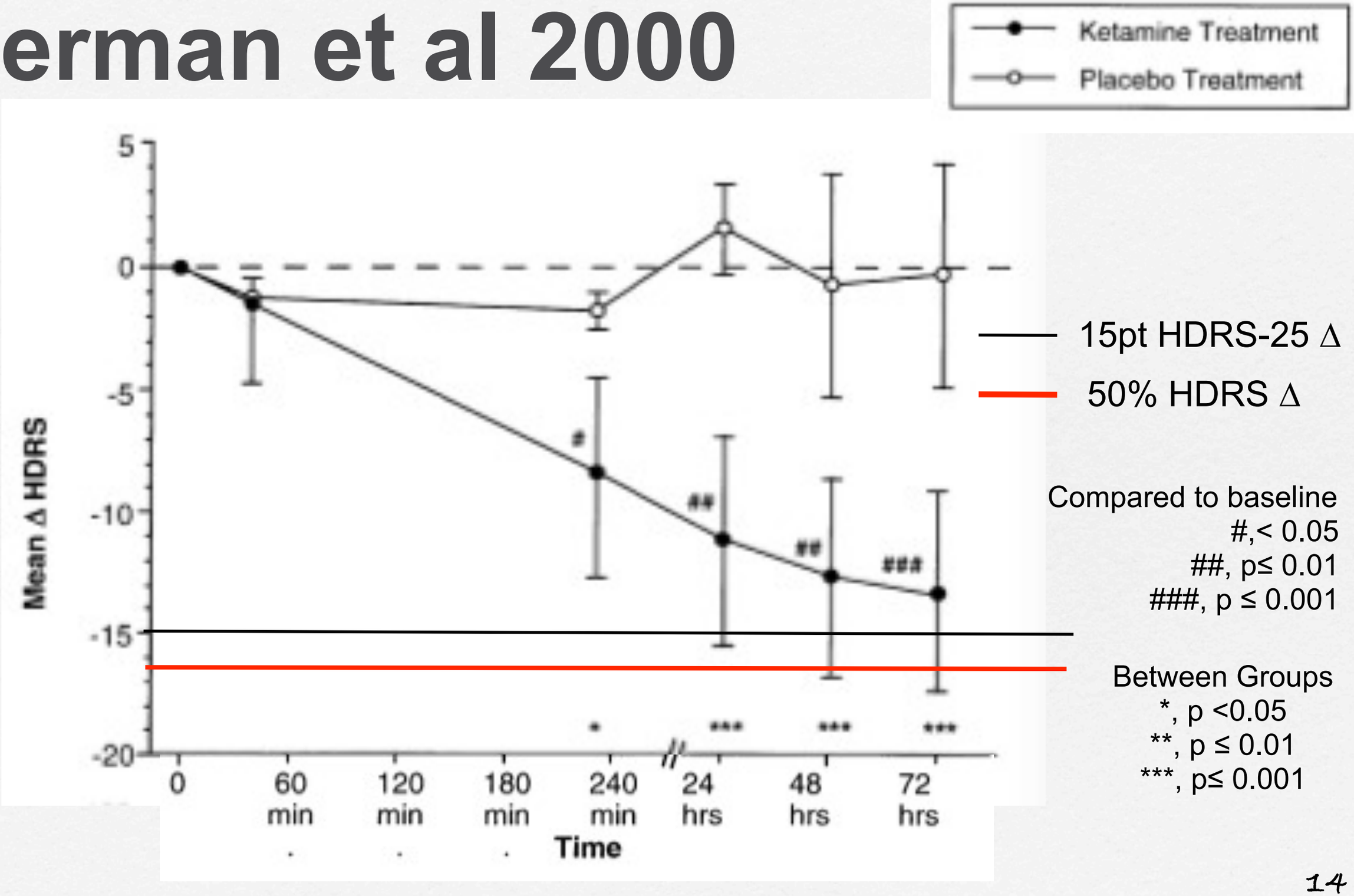
15pt HDRS-25 Δ

50% HDRS Δ

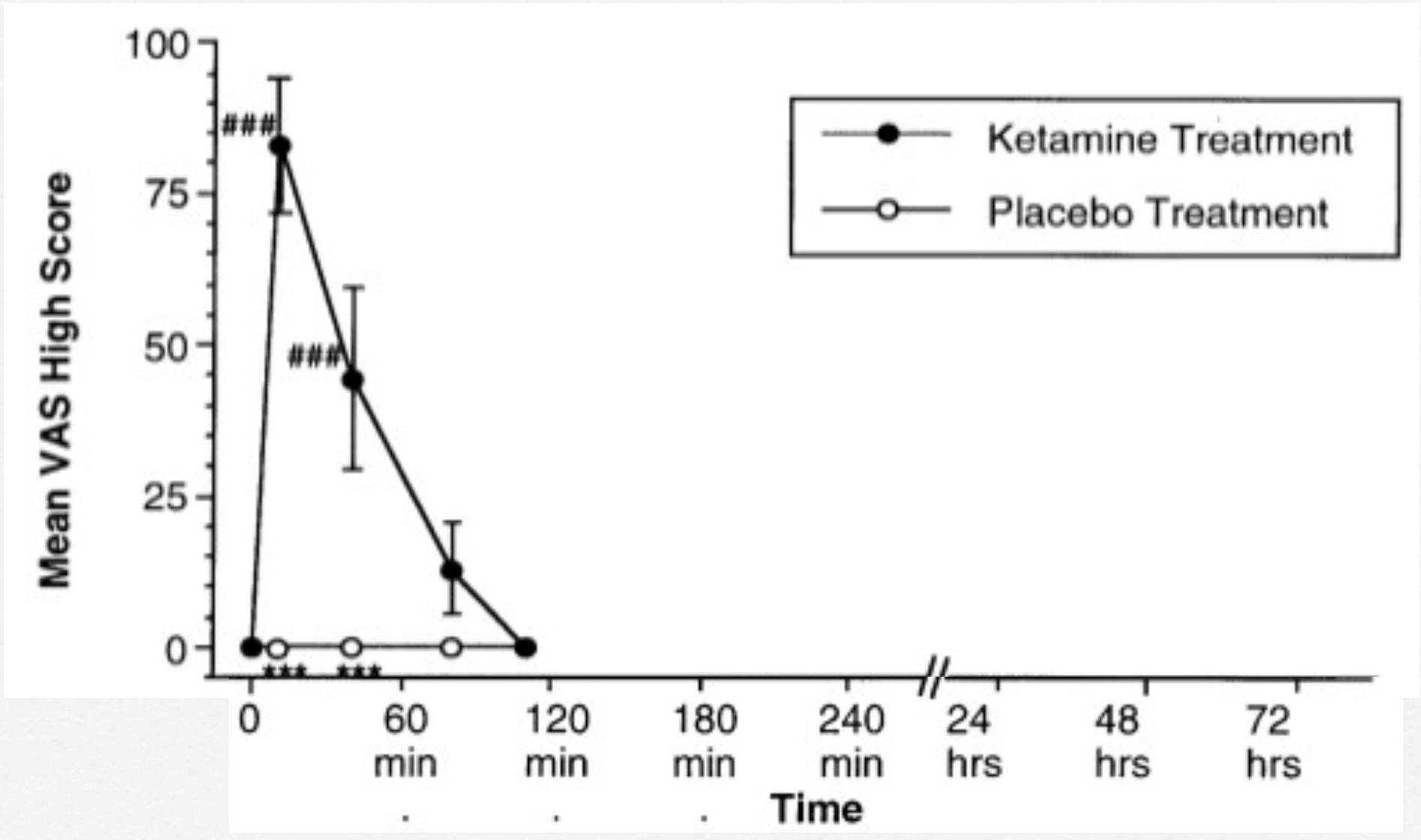
Compared to baseline
#,< 0.05
##, p≤ 0.01
###, p ≤ 0.001

Between Groups
*, p <0.05
**, p ≤ 0.01
***, p≤ 0.001

Berman et al 2000



Berman et al 2000



Compared to baseline
#,< 0.05
##, p≤ 0.01
###, p ≤ 0.001

Between Groups
*, p <0.05
**, p ≤ 0.01
***, p≤ 0.001

Author's conclusions

- "Low-dose ketamine infusion, compared to placebo, is associated with robust decreases in depressive symptoms progressively within 3 days"
- "Profound and transient cognitive deficits and euphoria ... were induced by ketamine"

Limitations

- Did not describe recruitment strategy
- Lack of information on pt's baseline resistance
- Inconsistent reporting for measured results
- No details about raters or reliability of assessment
- HAM-D rating may not be most appropriate for measuring change
- Blinding compromised with perceptual disturbances and "high"

A Randomized Trial of an *N*-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression

Carlos A. Zarate, Jr, MD; Jaskaran B. Singh, MD; Paul J. Carlson, MD; Nancy E. Brutsche, MSN; Rezvan Ameli, PhD; David A. Luckenbaugh, MA; Dennis S. Charney, MD; Husseini K. Manji, MD, FRCPC

Arch Gen Psychiatry. 2006; 63:856-64.

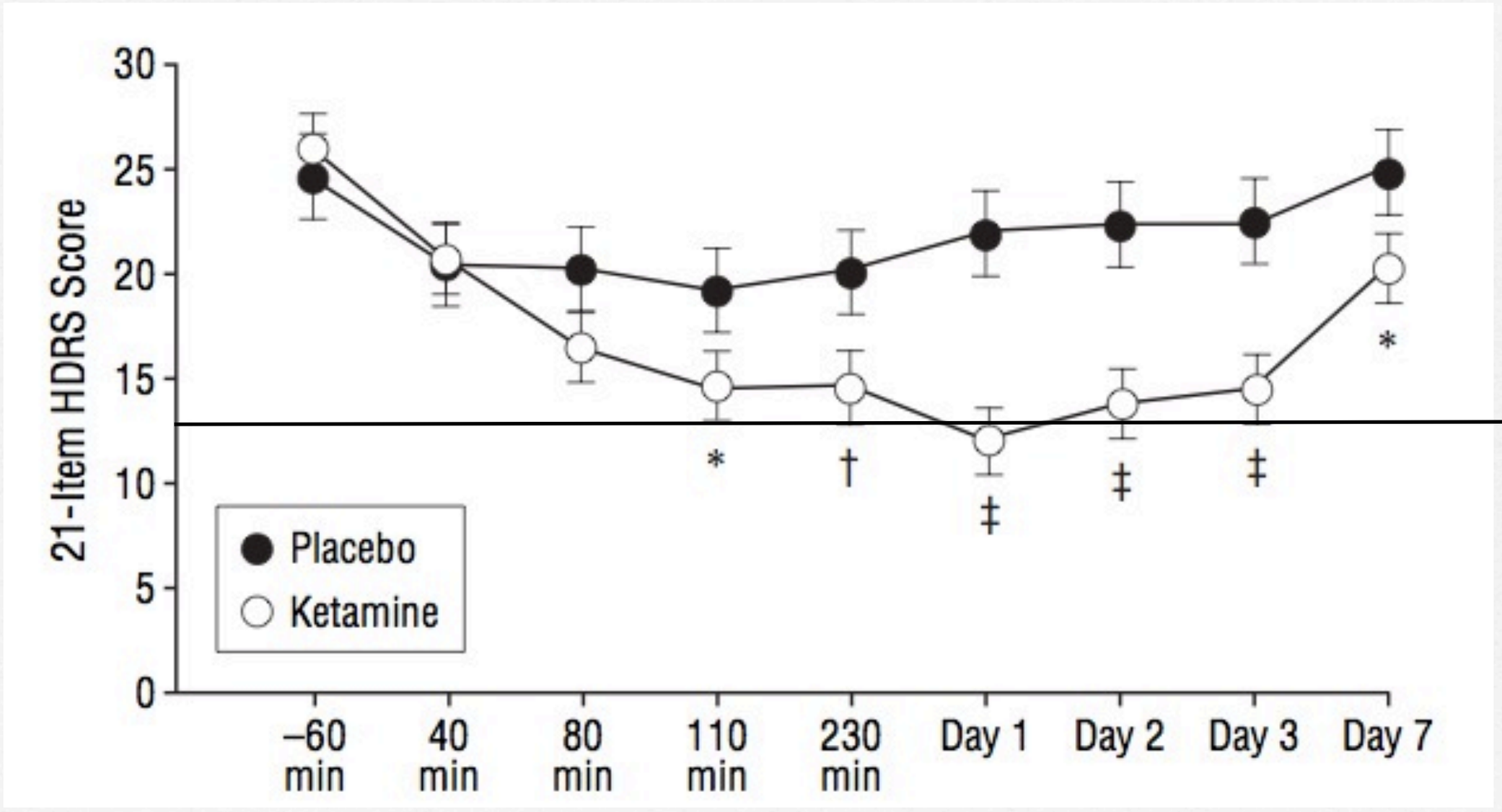
Zarate 2006

D	R, DB, Cross over, Single site (Washington, DC)
P	n = 18, 67% women, mean 46.7 ± 11.2 y/o, current episode 33.6 ± 37.4mo, mean # antidepressant trials 5.7 ± 3.4 (4 had tried ECT), 2 week drug free Excl: Diagnosis Bipolar Disorder or episodes of hypomania or mania
I	Ketamine 0.5mg/kg IV over 40min, cross over 1 week apart
C	0.9%NS IV over 40min
O	Evaluate @ 60min prior, 40, 80, 110 and 230 min after then 1, 2, 3, 7d after 1) Assess antidepressant effects using 21 item- HAM-D scale 2) Assess antidepressant and safety outcomes using BDI, BPRS, YMRS, VAS

Zarate et al 2006

13pt HDRS-21 Δ

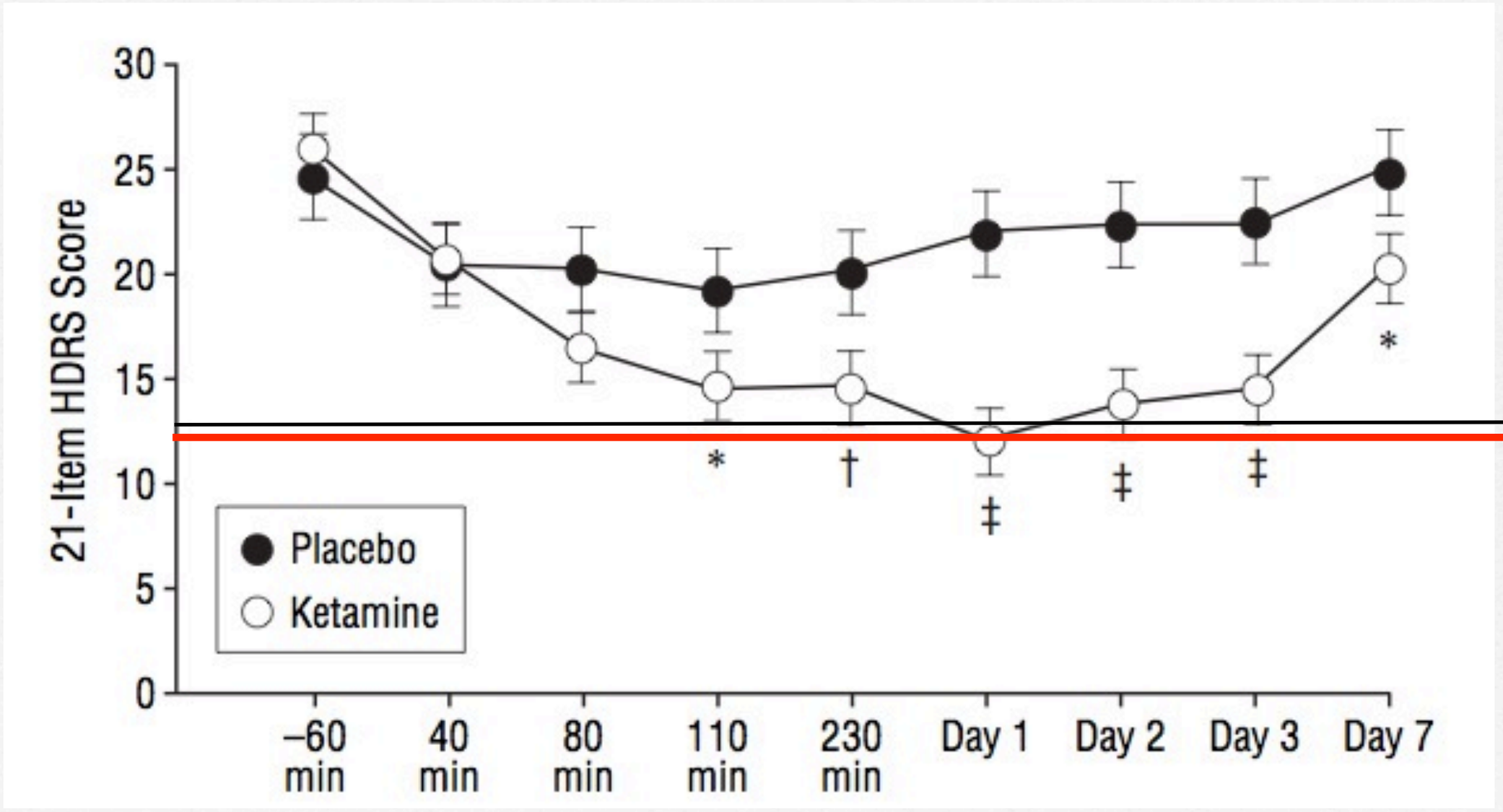
50% HDRS Δ



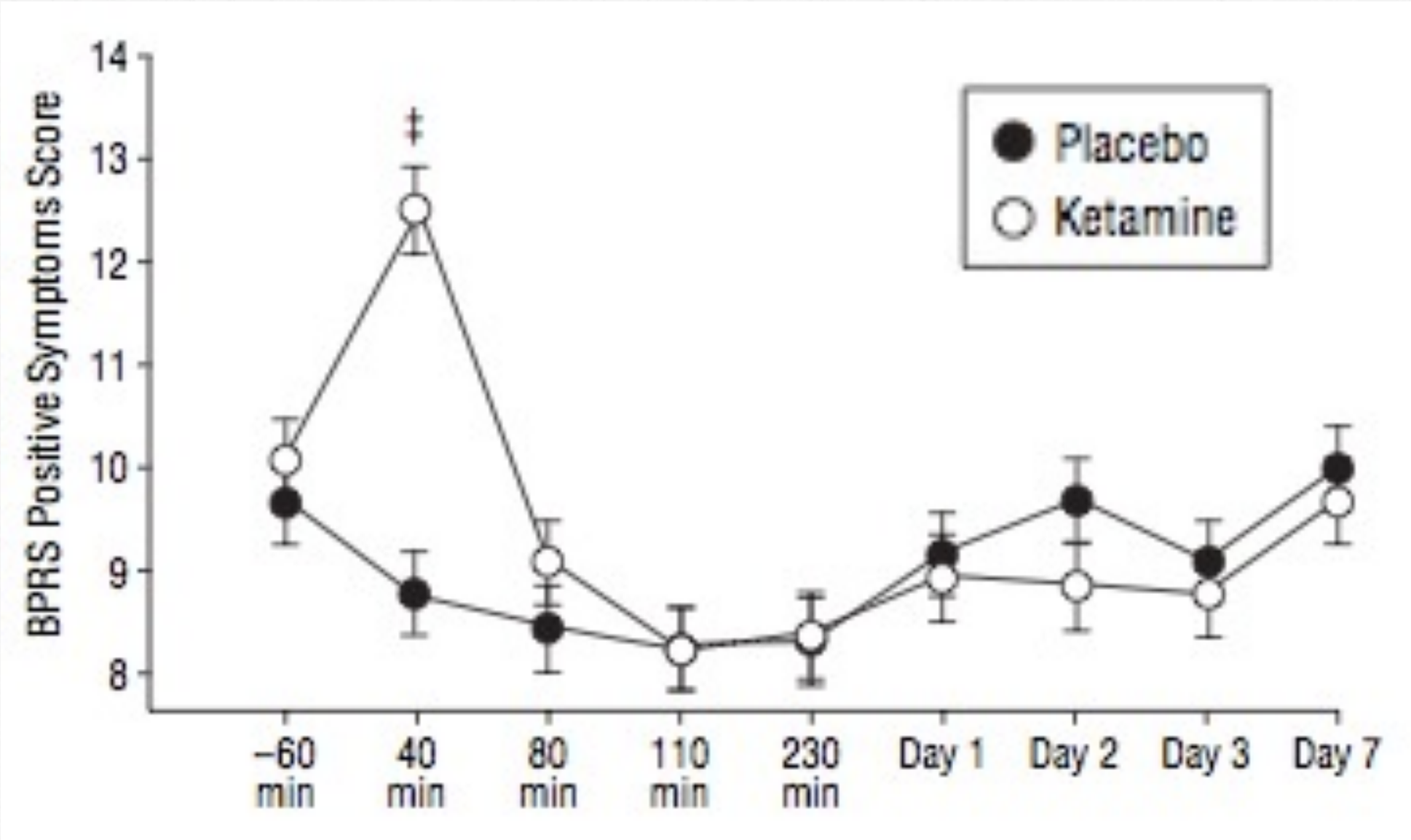
Zarate et al 2006

13pt HDRS-21 Δ

50% HDRS Δ



Zarate et al 2006



Author's conclusions

- "A robust, rapid (hours) and relatively sustained (1 week) response to a single dose of ketamine was statistically significant for 21-HDRS from 110min through 7 days and self related BDI (from 40min through 7 days)" compared to placebo

Limitations

- Consistent perceptual disturbances with ketamine affecting blinding
- HAM-D designed for use weekly
- Early termination - was meant to include 22 patients

M135. Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: a Two-Site, Randomized, Parallel-Arm, Midazolam-Controlled, Clinical Trial

James W. Murrough*, Dan V. Iosifescu, Lee C. Chang, Rayan K. Al Jurdi, Charles M. Green, Syed Iqbal, Sarah Pillemer, Andrew M. Perez, Alexandra Foulkes, Asim Shah, Dennis S. Charney, Sanjay J. Mathew

Mount Sinai School of Medicine, New York, New York

Murrough JW et al. Neuropsychopharmacology.ACNP 2012
Conference publication: 38. (ppS151-S152)

Murrough 2012

Design	2:1 Randomization scheme, parallel- arm, controlled, 2 site
P	n= 73, 52% female, 45.5 ± 12.4 y.o., unipolar TRD with moderate to severe depressive symptoms (IDS-C30), washout of concomitant antidepressants, suicide attempt in 32.9%
I	Ketamine 0.5mg/kg IV infusion over 40 min X 1
C	Midazolam 0.045 mg/kg IV infusion over 40min X 1
O	Discharged 24hrs after infusion with evaluation @ 48hr, 72hr, 7d post infusion 1) Δ in MADRS with “response” criteria @ 24hr (≥ 50% ↓ in MADRS) 2) Safety and tolerability of interventions

Murrough et al 2012

	Baseline	Ketamine	Midazolam	p values
MADRS	32.07 ± 5.9	-16.5 point *	-8.8 point *	p = 0.0001
24 hours				
Response		63.8%	28.0%	p = 0.006
Remission		36.2%	8.0%	p = 0.011
7 Days				
Response		45.7%	18.2%	p = 0.034
Remission		34.8%	18.2%	p = 0.26

*authors controlled for site differences, treatment and time

Author conclusion

- “Associated with higher incidence of ↑ BP compared to midazolam during infusion period”
- Ketamine had rapid and large antidepressant effect at 24hr and maintained 7days post infusion compared to midazolam

Limitations

- Conference abstract
- 73 underwent randomization but only 72 received study drug
- Details about MADRS assessment - raters and reliability

Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression

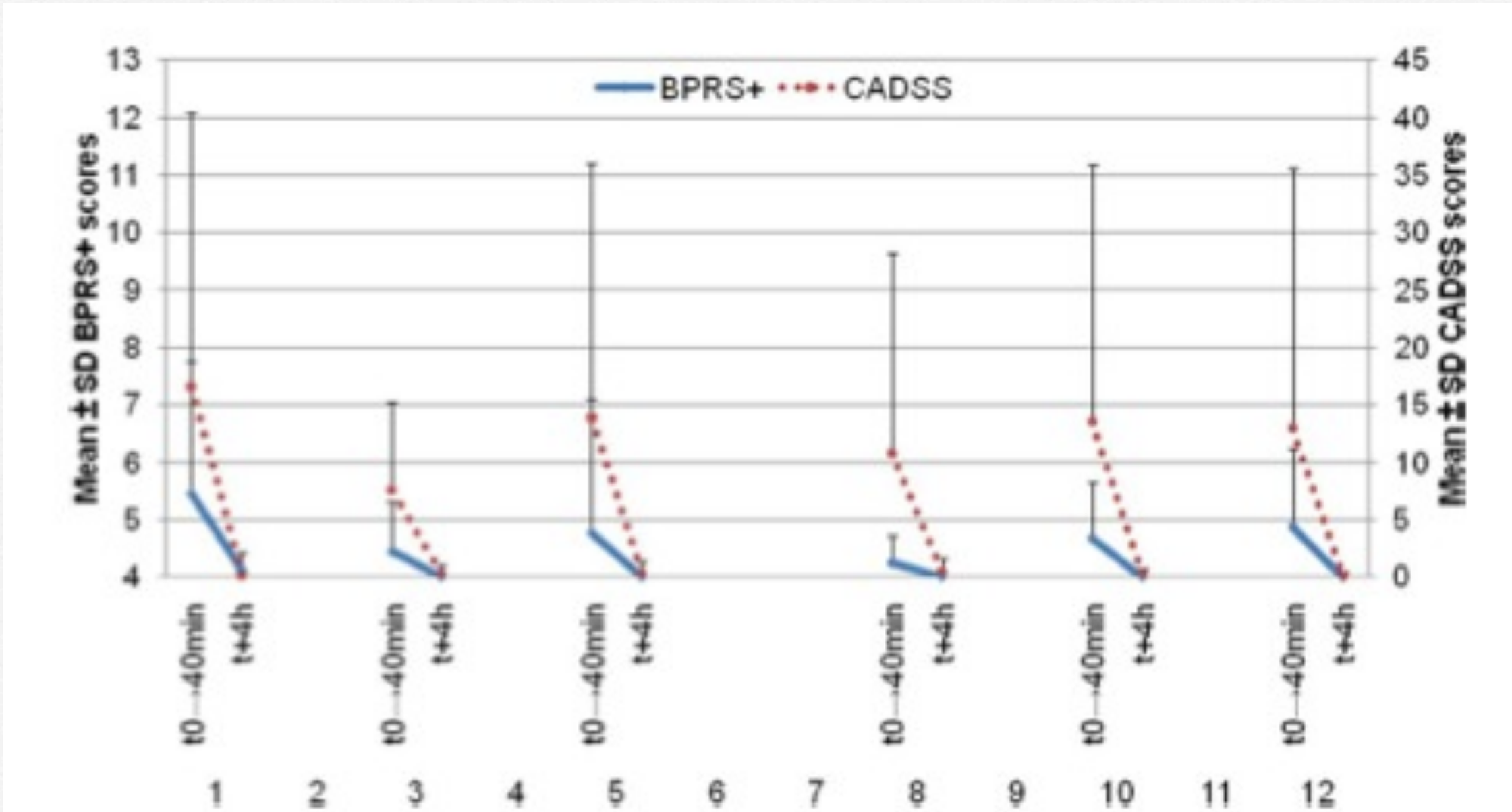
Marije aan het Rot, Katherine A. Collins, James W. Murrough, Andrew M. Perez, David L. Reich, Dennis S. Charney, and Sanjay J. Mathew

Biol Psychiatry 2010; 67:139-45.

Rot 2010

Design	Single centre (Mt. Sinai), Open label
P	n=10, 51.4 ± 14.6 y/o, 50% female, Chronic or recurrent MDD as per DSM-IV-TR, failed ≥ 2 antidepressant trials, all participants were responders from a 2009 study, require IDS-C scores ≥ 32, psychotropic medication free for ≥ 2wks (4 wks if fluoxetine) Excl: psychotic symptoms or (hypo)mania, substance disorder w/in 3 months of screening, current active suicidal ideation
I	Ketamine 0.5mg/kg over 40mins; 5 subsequent q48hr if first resulted in ≥ 50% ↓ in MADRS score
C	None
O	1) Safety and tolerability measured by 3 scales (BPRS+, CADSS, SAFTEE- SI) 2) Efficacy measure done with MADRS, QIDs

Rot 2010


BPRS+
CADSS
Mean ± SD BPRS+ scores
Mean ± SD CADSS scores
13
12
11
10
9
8
7
6
5
4
45
40
35
30
25
20
15
10
5
0
t0→40min
t→4h
1
2
3
4
5
6
7
8
9
10
11
12

Rot et al 2010

Week 1 = infusions 1-3
Week 2 = infusions 4-6

Table 2. Numbers of Patients Who Endorsed Moderate-to-Severe Increases in Specific Symptoms on the SAFTEE-SI

	Moderate		Severe	
Symptom	Week 1	Week 2	Week 1	Week 2
Abnormal Sensations	0	2	1	1
Blurred Vision	0	0	1	1
Diminished Mental Capacity	1	1	1	1
Dizziness or Faintness	1	0	0	0
Feeling Drowsy or Sleepy	2	0	0	0
Feeling Strange or Unreal	1	1	0	0
Headache	1	0	2	1
Hearing or Seeing Things	2	0	0	0
Numbness or Tingling	0	1	1	1
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

Numbers of patients who endorsed moderate-to-severe increases in specific symptoms on the Systematic Assessment For Treatment Emergent Effects Self-Report Inventory (SAFTEE-SI) from pre-infusion (t_0) to 4 hours postinfusion (t_{+4h}) collapsed across infusions 1–3 (week 1) and infusions 4–6 (week 2).

Author's conclusions

- Vital sign changes in 4/10 of patients (2 ↑ BP, 1 ↓ BP, 1 ↓ HR)
- "Observed vital sign changes were transient and did not warrant treatment cessation"
- "Appropriate precautions are necessary, including pre-ketamine ECG and close monitoring by an anesthesiologist"

Limitations

- High selection bias
- Frequent administration of depression scales
- CADSS scale not validated for use
- Cannot ascertain whether reported symptoms on SAFTEE was from same patient
- Lack of information about concurrent medications

Back to PICO question

Prevention of suicide	Not assessed, patients excluded from trials
↓ Duration of depressive episode	Longest follow-up only up to 14days and >50% have remission
Quality of Life	Not assessed
Safety	↑ BP, Δ HR, perceptual disturbances, dissociative reactions, confusion and dizziness commonly reported

Back to PICO question

		Berman (HAM-D 25)	Zarate (HAM-D 21)	Murrough (MADRS)
↓ Symptoms as measured by validated tool	Baseline	33.0 ± 6.7	24.9 ± 6.9	32.07 ± 5.9
	24hrs	- 11 ± 4.1 (33%↓)	-12 ± 2.1 (52%↓)	-16.5 (48%↓)
	3 days	-13.1 ± 3.9 (40%↓)	-10.3 ± 1.2 (41%↓)	N/A
	7 Days	N/A	-4.9 ± 1.2 (19%↓)	N/A

Limitation to use

- Single dose has limited sustainability of effect
- Consistent psychotomimetic effect
- IV formulation limits outpatient use
- All trials done in presence of anesthetist
- Patients in trials often hospitalized for 24hr post infusion

At the moment…

- Online survey by UCSD Medical center identified 6 practitioners across US currently using ketamine
  - 22 TRD unipolar and 6 bipolar using 0.5mg/kg ketamine infusion
  - 50% (11pt) of unipolar and 0% of bipolar showed 50% ↓ in their depression symptom after 1 infusion
  - 2 sites have stopped offering it due to “disappointment in efficacy and sustainability of effects”

Feifel D et al. Neuropsychopharmacology ACNP 2011 Conference abstract.

Future...

- From ClinicalTrials.gov
  - 31 studies found using terms “depression” and “ketamine”
    - 5 open label
    - 2 ECT + ketamine vs ECT alone
    - 7 RCTs with ketamine vs placebo
    - 8 RCTs with ketamine vs different single comparators such as midazolam, clonidine, venlafaxine, lamotrigine and scopolamine
    - 9 studies for different conditions/ ketamine analogs

http://www.clinicaltrials.gov

Questions?

Treatment Resistant Depression

- 3 Strategies for treating TRD currently
    - Optimize antidepressant dose
    - Augment or combine therapies
        - Li, liothyronine, antiepileptic, atypical antipsychotics, psychostimulants
    - Switch therapies
        - another class, within class

Souery D. J Clin Psychiatry 2006; 67(Suppl6): 16-22.

Sample questions for MADRS

1 - APPARENT SADNESS - *Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.*

0 No sadness
1
2 Looks dispirited but does brighten up without difficulty
3
4 Appears sad and unhappy most of the time
5
6 Looks miserable all the time. Extremely despondent.

---

2 - REPORTED SADNESS - *Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.*

0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondency.

---

3 - INNER TENSION - *Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.*

0 Placid. Only fleeting inner tension.
1
2 Occasional feelings of edginess and ill-defined discomfort
3

Sample questions for CADSS

1. Do things seem to be moving in slow motion?
   - 0= Not at all.
   - 1= Mild, things seem slightly slowed down, but not very noticeable.
   - 2= Moderate, things are moving about twice as slow as normally.
   - 3= Severe, things are moving so slowly that they are barely moving.
   - 4= Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.
2. Do things seem to be unreal to you, as if you are in a dream?
   - 0= Not at all.
   - 1= Mild, things seem a little unreal, but I'm well aware of where I'm at.
   - 2= Moderate, things seem dreamlike, although I know I am awake.
   - 3= Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
   - 4= Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.
3. Do you have some experience that separates you from what is happening; for instance, do you feel as if you are in a movie or a play, or as if you are a robot?
   - 0= Not at all.
   - 1= Mild, I feel a little bit separated from what is happening, but I am basically here.
   - 2= Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
   - 3= Severe, I feel extremely separated from what is happening, but I can understand what people are saying.
   - 4= Extreme, I feel as if everyone around me is talking a foreign language, so that I

Ketamine interactions

Ketamine is substrate of CYP2B6, CYP2C9, CYP3A4 - interactsw with

- Atazanavir
- Carbamazepine
- Clarithromycin
- Fluconazole
- Gemfibrozil
- all Azoles
- Phenytoin
- Rifampin