Icahn School of Medicine at Mount Sinai

Developing a Potential New Treatment for Chronic PTSD
Ketamine Combined with Written Exposure Therapy

Adriana Feder, MD

Professor of Psychiatry

Director, Trauma and Resilience Program

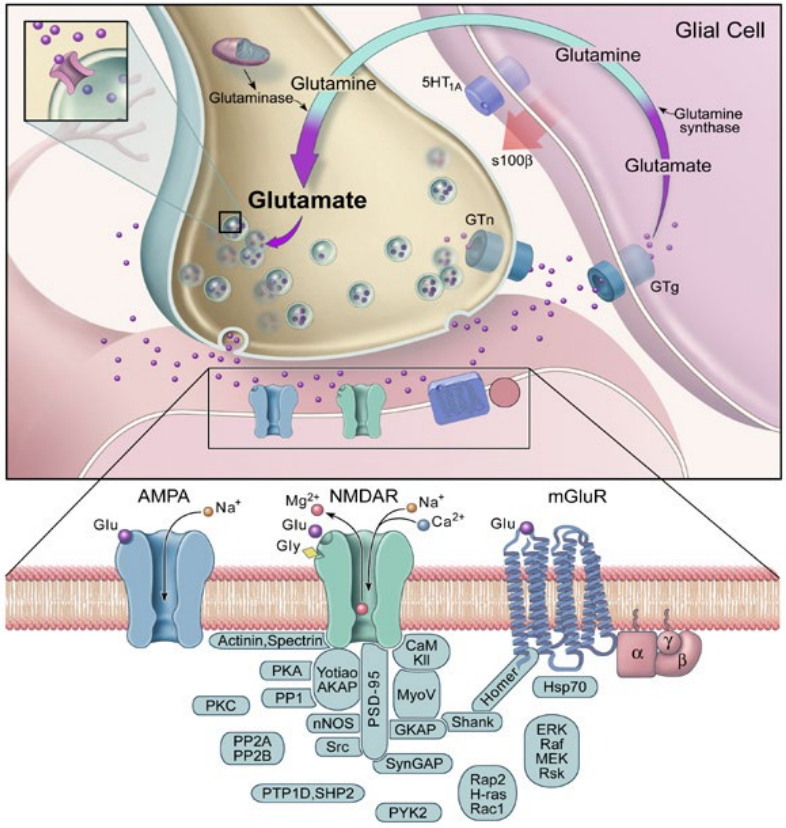
Investigator, Depression and Anxiety Center for Discovery and Treatment

Disclosure: I am named co-inventor with Dennis Charney on issued patents in the US and outside the US, filed by the Icahn School of Medicine at Mount Sinai (ISMMS), related to the use of ketamine for the treatment of PTSD.

ISMMS has just entered into a licensing agreement with Frontier Pharmaceuticals, Inc. (April 2025), to develop intranasal ketamine as a treatment for PTSD. As a part of this agreement, ISMMS will receive consideration in the form of royalties, milestones payments, and equity.

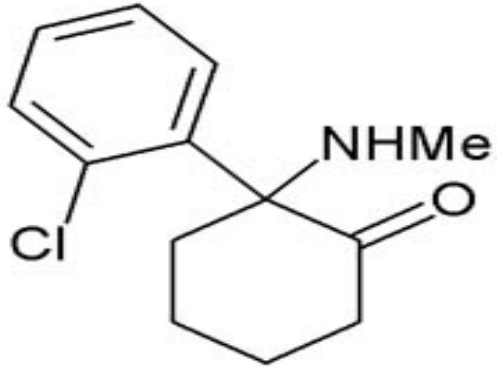
As named co-inventors, Drs. Feder and Charney are entitled under ISMMS's intellectual property policy to a portion of any consideration received by ISMMS.

Ketamine
Pharmacology and NMDA Glutamate Receptor



Receptor Subunit Types

Ionotropic			Metabotropic		
NMDA	AMPA	Kainate	Group I	Group II	Group III
NR1	GluR 1	GluR 5	mGlu 1 a-b-c-d	mGlu 2	mGlu 4 a-b
NR2 A-B-C-D	GluR 2	GluR 6	mGlu 5 a-b	mGlu 3	mGlu 6
NR3 A-B	GluR 3	GluR 7			mGlu 7 a-b
	GluR 4	KA 1			mGlu 8 a-b
		KA 2			

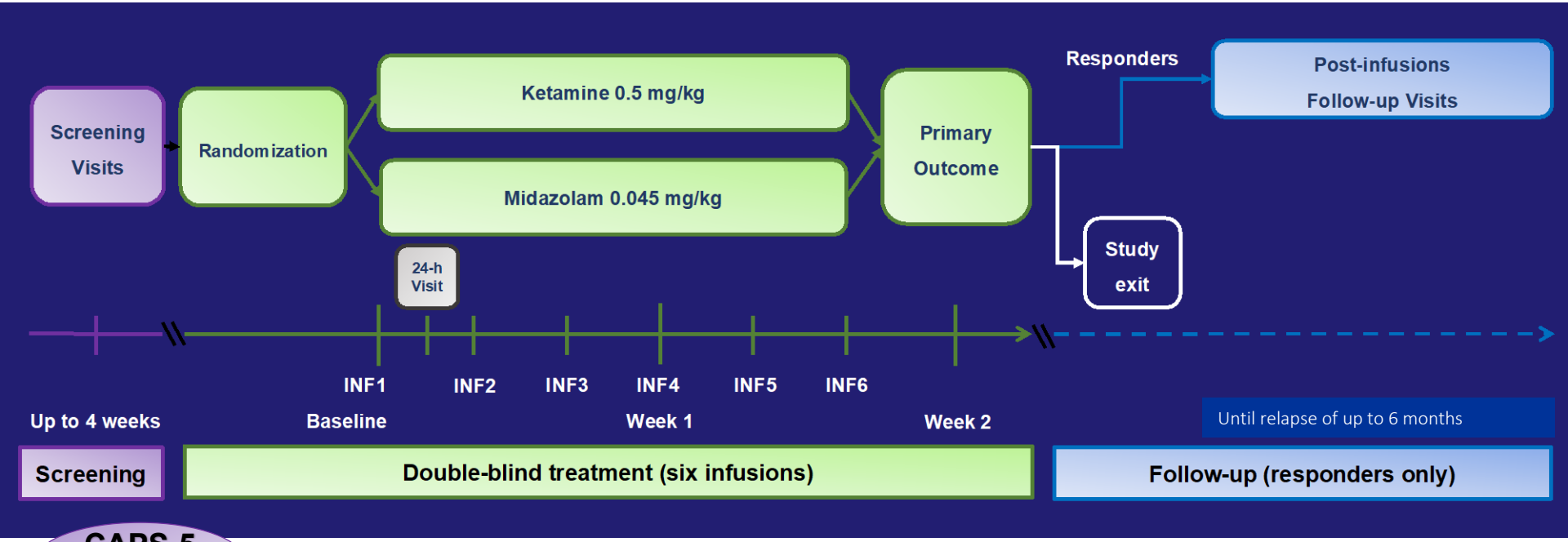


- Non-competitive high-affinity NMDA receptor antagonist
- IV ketamine: Demonstrated antidepressant efficacy in patients with TRD; rapid response
- Repeated IV infusions are necessary to maintain improvement
- Esketamine (Spravato), its S-enantiomer, is FDA-approved for intranasal administration as adjunct to oral antidepressant for TRD and for MDD with acute suicidal ideation or behavior

Ketamine for Chronic PTSD

- First proof-of-concept RCT of *single* IV ketamine infusion (compared to IV midazolam infusion) in patients with chronic PTSD (n=41, civilians, 54% male) (Feder et al 1014)
  - Mean time to loss of response
- First RCT of *repeated* IV ketamine infusions (compared to repeated IV midazolam) in patients with chronic PTSD (n=30, *civilians*, 77% female) (Feder et al 2021)
  - Total 6 infusions, 3 times a week over 2 consecutive weeks
  - Rapid and robust PTSD symptom improvement in the ketamine group (67% ketamine responders vs. 20% midazolam responders)
  - Among ketamine responders, median time to loss of response was 4 weeks following course of infusions
- Open-label clinical trial of *repeated* IV ketamine infusions in pts with co-morbid PTSD and TRD (n=15, *veterans*, 67% male) (Albott et al 2018)
  - Total 6 infusions, 3 times a week over 2 consecutive weeks
  - Rapid improvement in PTSD and depression symptoms; median time to relapse among PTSD remitters was 41 days
- RCT of *repeated* IV ketamine infusions (compared to repeated IV saline) in *veterans and active duty military personnel* with *antidepressant-resistant PTSD* (n=178, military, 77% male) (Abdallah et al 2022)
  - Total 8 infusions, 2 times a week over 4 consecutive weeks
  - PTSD symptoms (PCL-5) were significantly reduced over time but did not differ between treatment groups; significant antidepressant effect from ketamine.

Randomized Controlled Trial of Repeated-Dose Intravenous Ketamine for PTSD Study Flow Chart



CAPS-5 PM=30

CAPS-5 severity scoring range

0-10	asymptomatic/few symptoms
11-22	mild PTSD/subthreshold
23-34	moderate PTSD
35-46	severe PTSD
47+	extreme PTSD

Mean age = 39 years, 77% female
Mean CAPS-5 score at screening= 41
Mean PTSD duration= 15 years
Primary trauma:
- 43% sexual assault/molestation
- 27% physical assault/abuse

Feder et al 2021

Selected quotes from ketamine responders

Obtained as part of clinical assessment

"I don't feel my life is going to end anymore, it made it impossible to plan a future. I want a life now too." *[After interacting with someone who had been harassing her]: "One huge thing I noticed that is different. Before I would have panicked. He's been very aggressive, I don't feel panicky or afraid."*

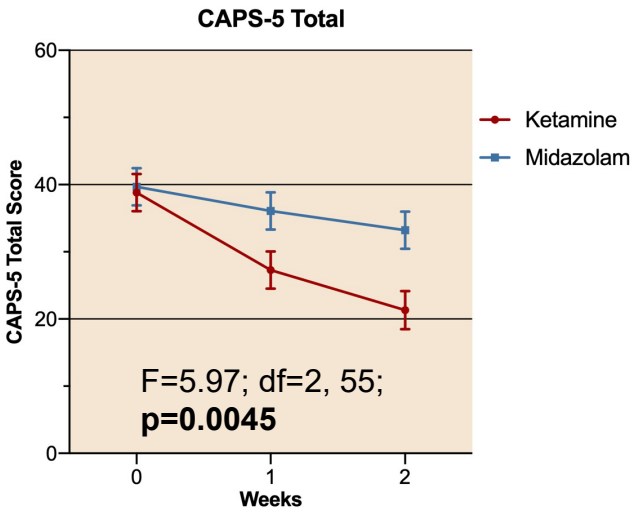
"I feel like a normal person. I seem like a normal person. My brain doesn't [any longer] let me envision or picture a thought of suicide". [Now, when she thinks about her past trauma], "it doesn't make me feel weighed down" "I have to dig out the memory as if from an attic". "Before, talking about it used to make me feel a terrible feeling."

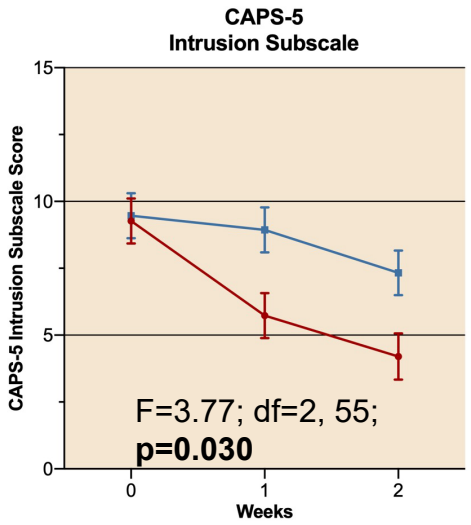
[Feeling] "like I have energy and want to do things again. I felt safe and able to confront feelings [about the trauma] without problems. I could just feel it, and figure out what happened and why it happened."

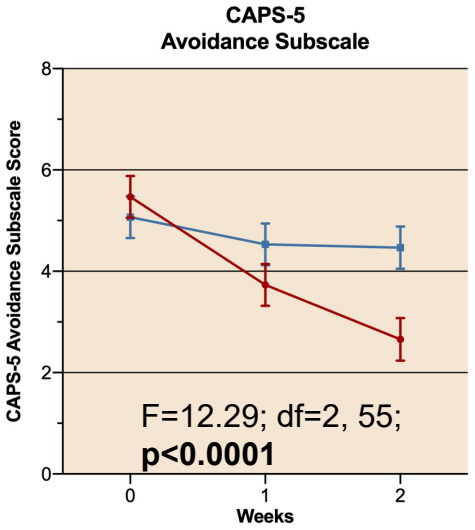
[Reported that during infusions, she felt] "like I made peace, I could go past it, I could, can let it go. [It's been a] gradual acceptance. I haven't felt this safe in a long time."

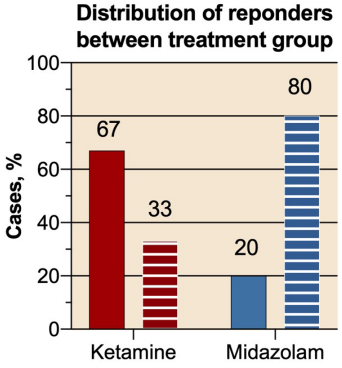
Feder et al 2021, Am J Psychiatry

Effect of Treatment with Ketamine Compared to Midazolam on PTSD Severity in Patients with Chronic PTSD

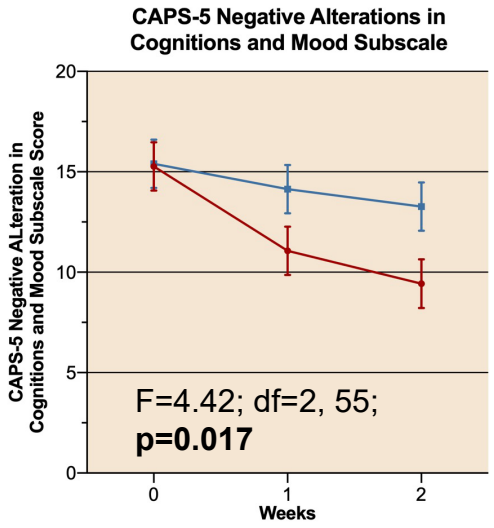


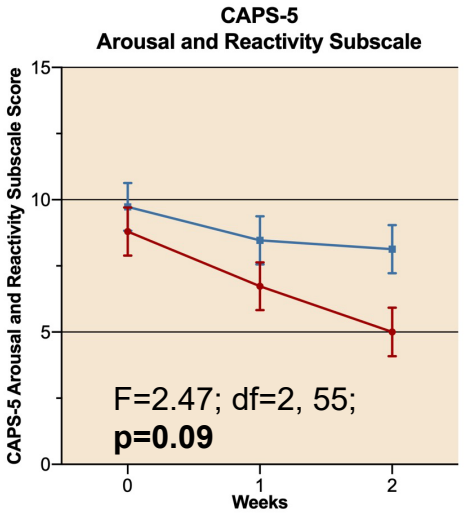






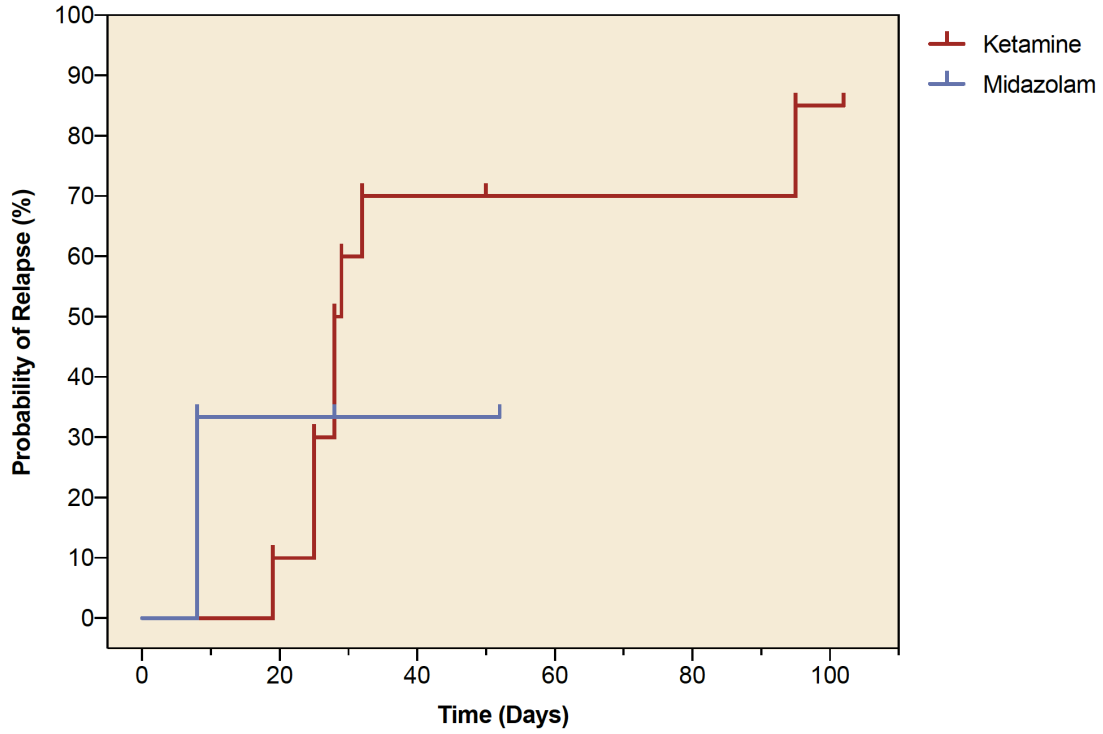
χ^2=4.89,
p=0.027





Feder et al 2021

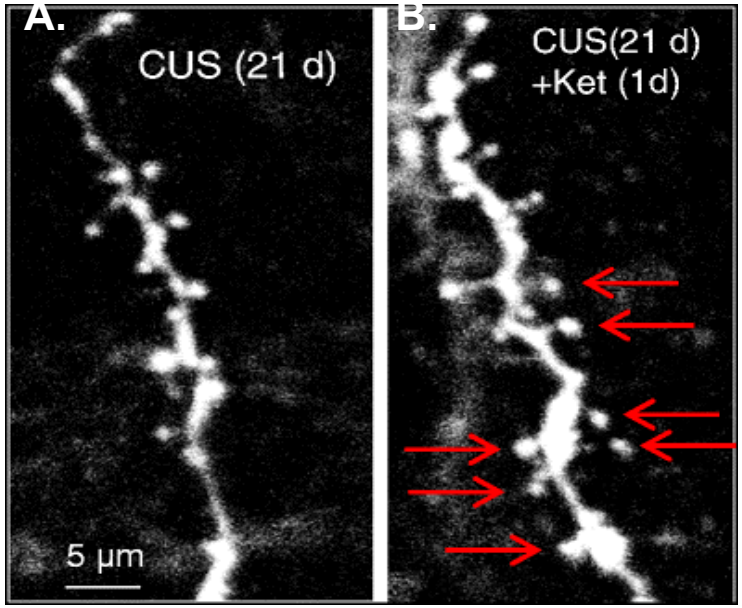
Risk of Relapse Among Responders to Repeated Ketamine and Midazolam Infusions in Posttraumatic Stress Disorder



- Among ketamine responders, median time to relapse was 27.5 days from the primary outcome assessment day;
- 25th and 75th percentiles were 23 and 32 days;
- Two participants had not relapsed by their last assessment (50 and 102 days after the primary outcome assessment)

Feder et al 2021

Animal Model of Chronic Stress
Rapid Reversal of Synaptic Atrophy by Ketamine



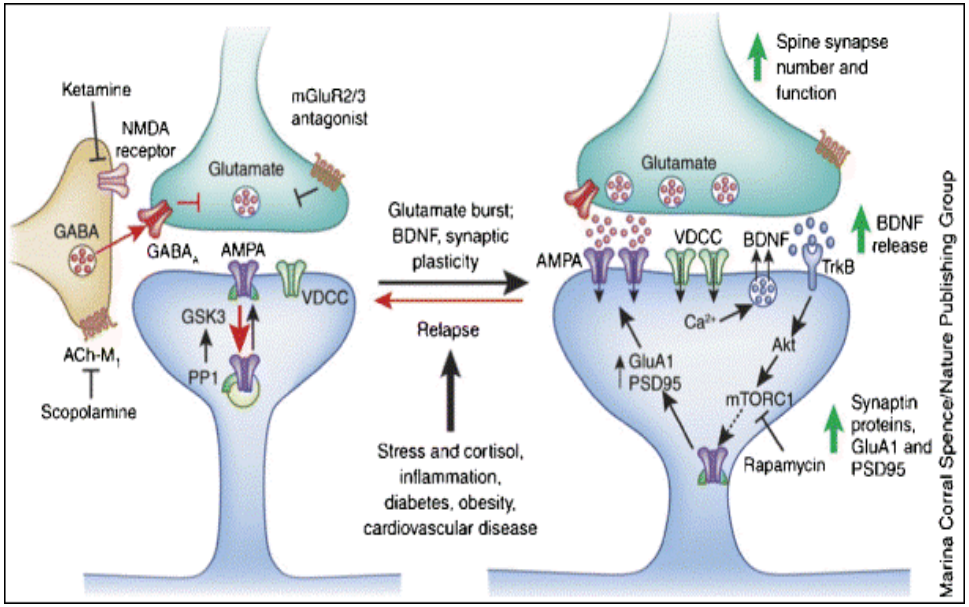
A. Low numbers of dendritic spines present in the dendrites of layer V pyramidal neurons after 21 days of chronic uncontrollable stress (CUS).

B. Reversal following a single dose of ketamine 1 day later.

Ketamine [N-methyl-D-aspartate (NMDA)-type glutamate receptor antagonist] → burst of glutamate → stimulates AMPA receptors → activation of intracellular pathways → increased protein synthesis → synapse maturation and formation

Reversal of abnormal connectivity patterns in key brain regions.

PTSD, a "synaptic disconnection syndrome"



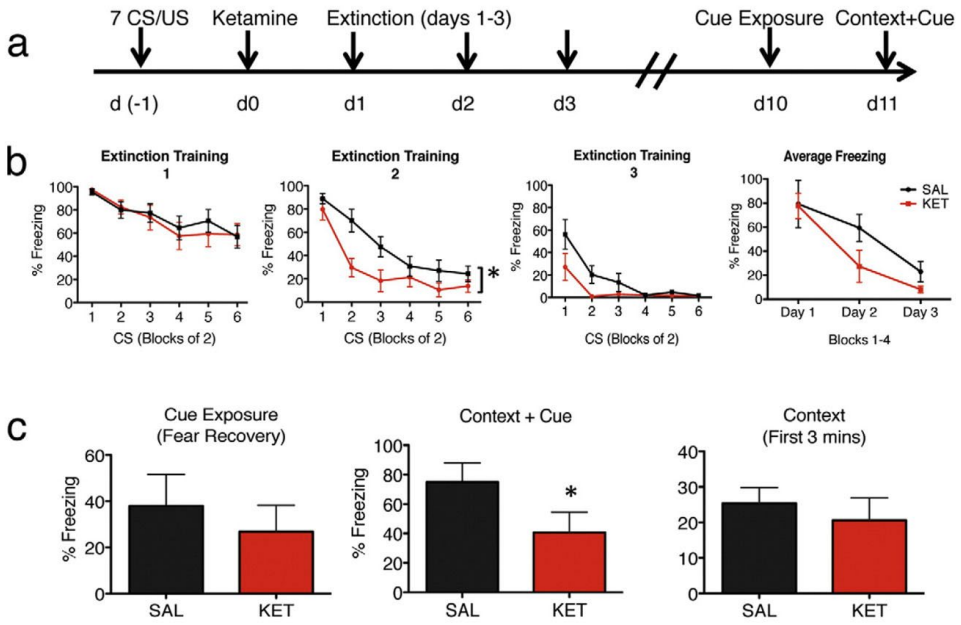
Li et al 2011
Krystal el al 2017

Trauma-focused Psychotherapies

- Trauma-focused psychotherapies are thought to rely on adequate threat processing and emotion regulation
- Findings from published fMRI studies of trauma-focused (exposure-based) psychotherapies suggest that poorer PFC inhibition of amygdala activation a pre-treatment baseline predict poorer response
- Response to these therapies might be hampered by impaired function of neural circuitry subserving emotion regulation, threat learning and extinction, including amygdala and PFC, in a substantial proportion of patients with chronic PTSD

- Wide interest in investigating combination of ketamine + *trauma-focused psychotherapy* for PTSD (Shiroma et al 2020, Duek.. Harpaz-Rotem et al 2023)

Ketamine accelerates fear extinction via mTOR signaling



Girgenti et al… Duman 2017

Acute ketamine facilitates fear memory extinction in a rat model of PTSD along with restoring glutamatergic alterations and dendritic atrophy in the prefrontal cortex

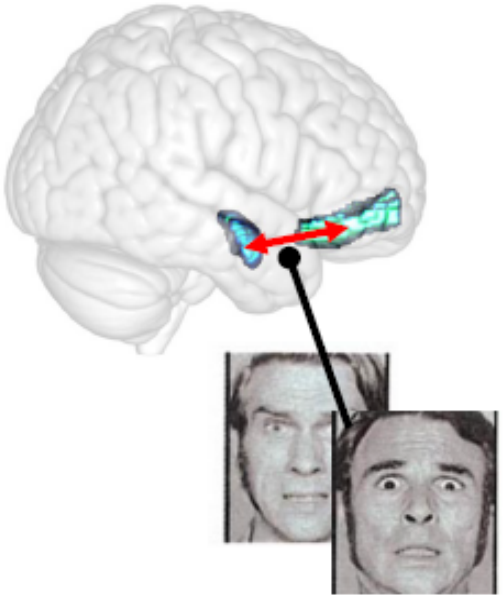
Sala et al… Musazzi 2022

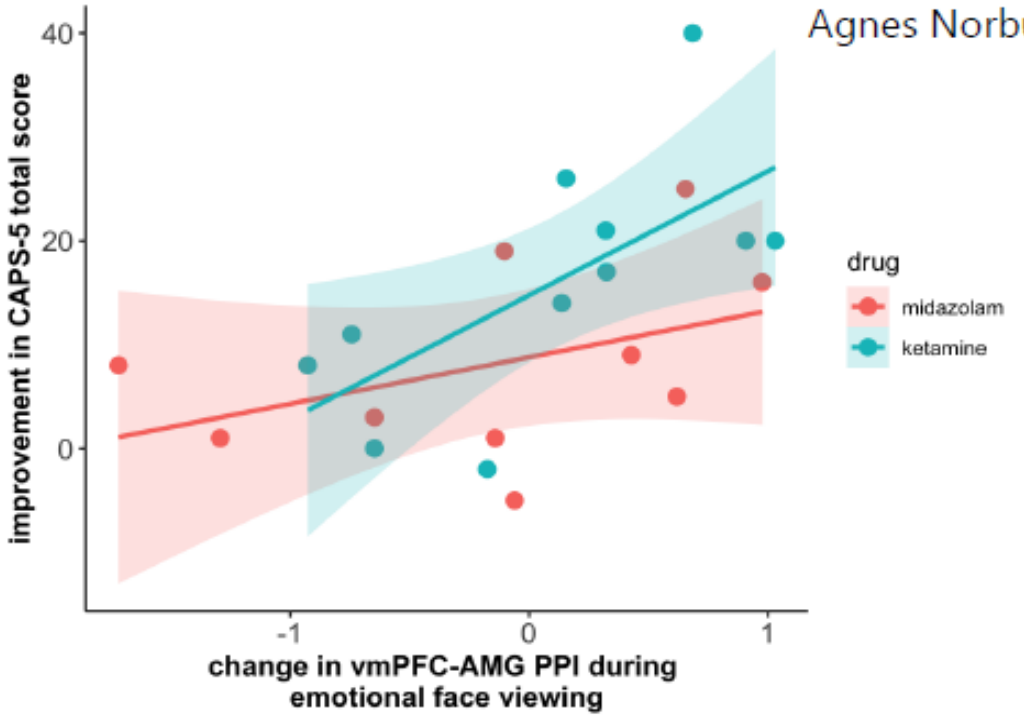
Adjunct treatment with ketamine enhances the therapeutic effects of extinction learning after chronic unpredictable stress

Paredes et al… Morilak 2022

Correlates of PTSD symptom improvement: interaction with drug

Agnes Norbury, PhD

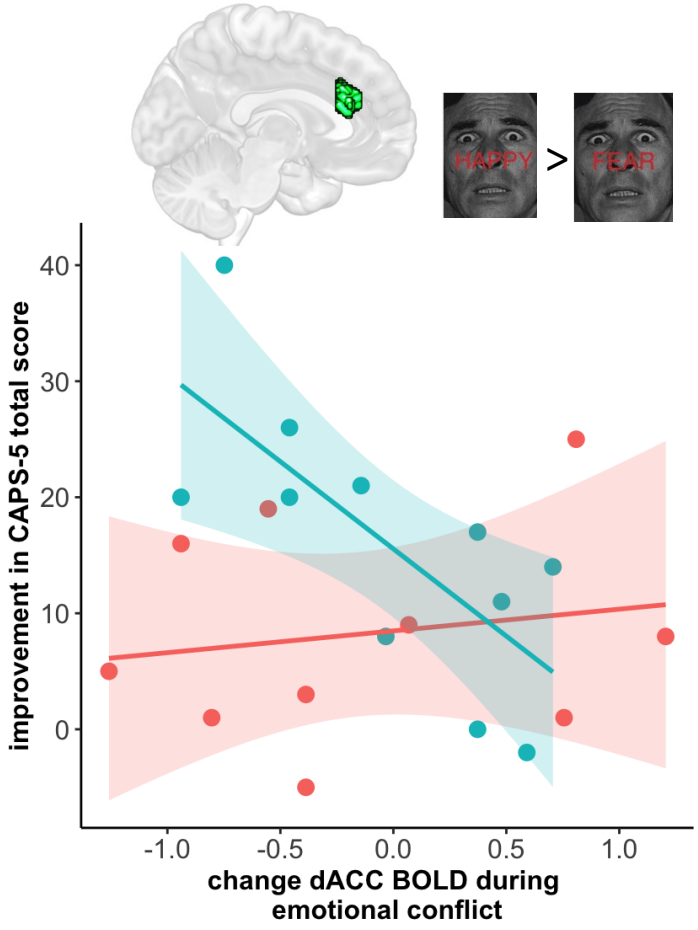


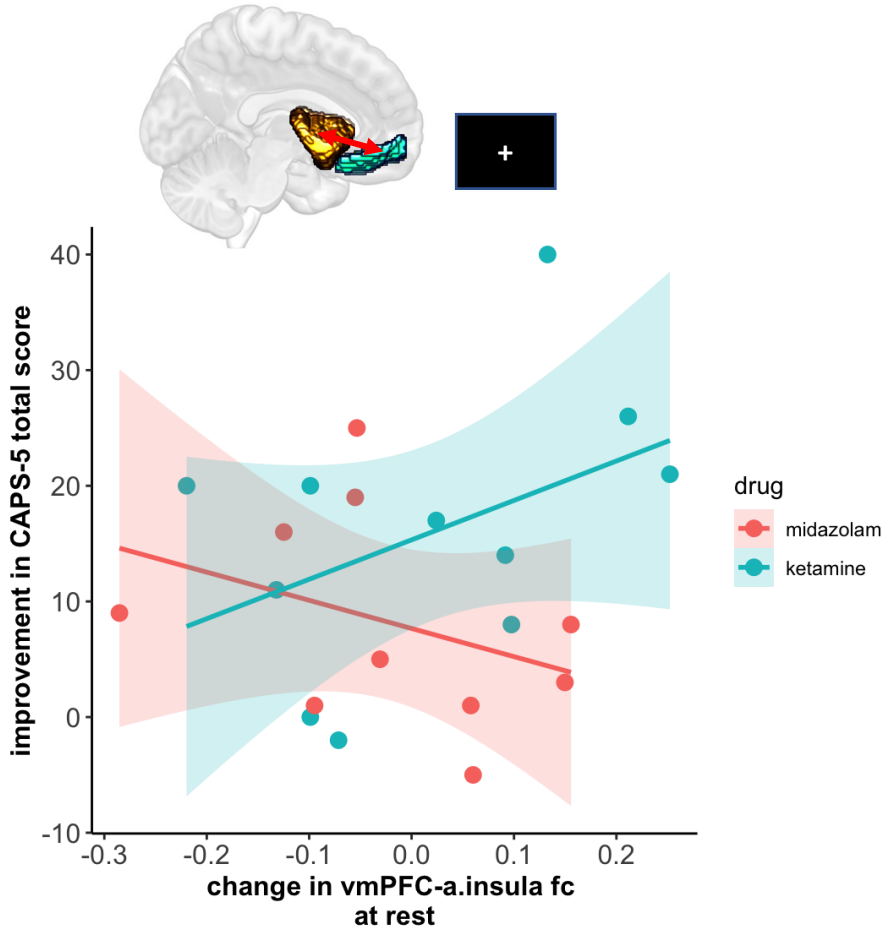


An interaction between drug and face-related increase in vmPFC-AMG connectivity was retained in the winning model, suggesting that **the association is stronger in individuals who received ketamine**.

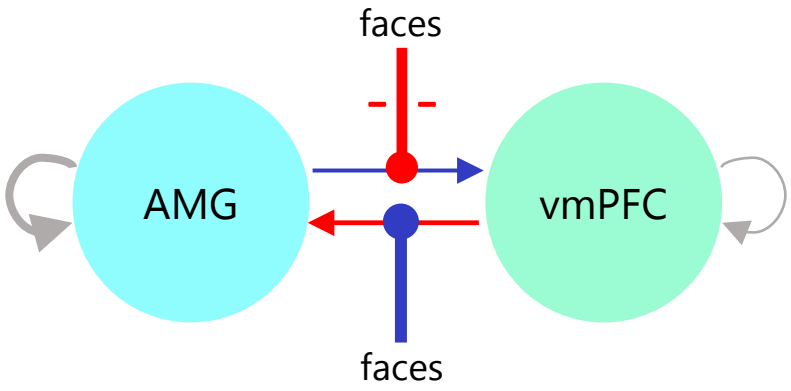
Norbury et al 2021

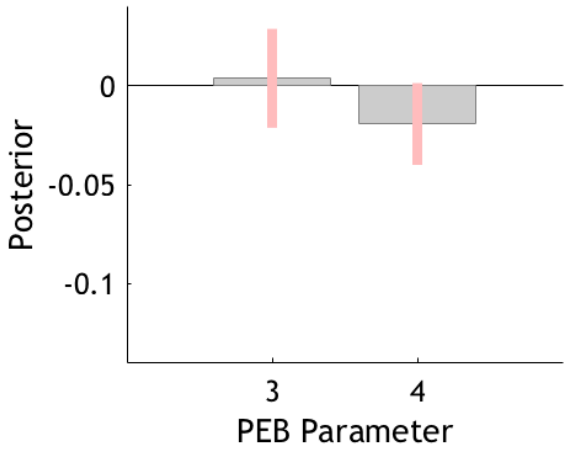
Correlates of PTSD symptom improvement: interaction with drug



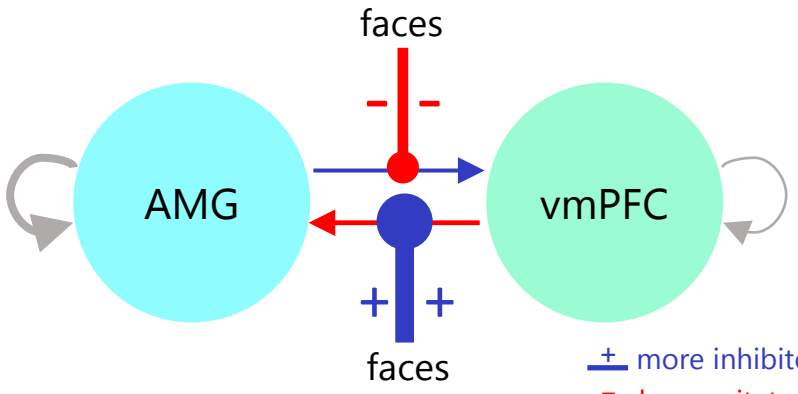


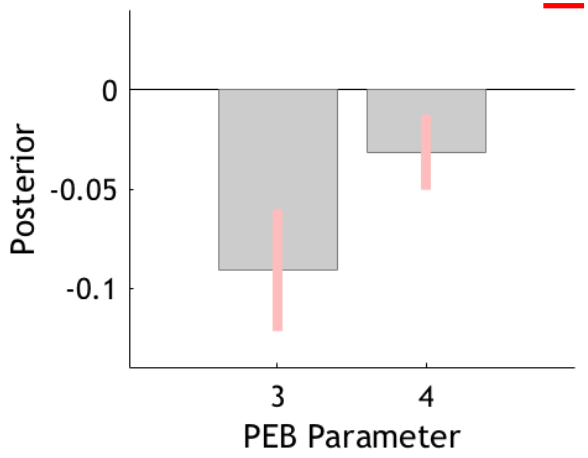
MIDAZOLAM
pre-post infusion*CAPS-5 change interaction
on emotional faces modulation of connectivity





KETAMINE
pre-post infusion*CAPS-5 change interaction
on emotional faces modulation of connectivity



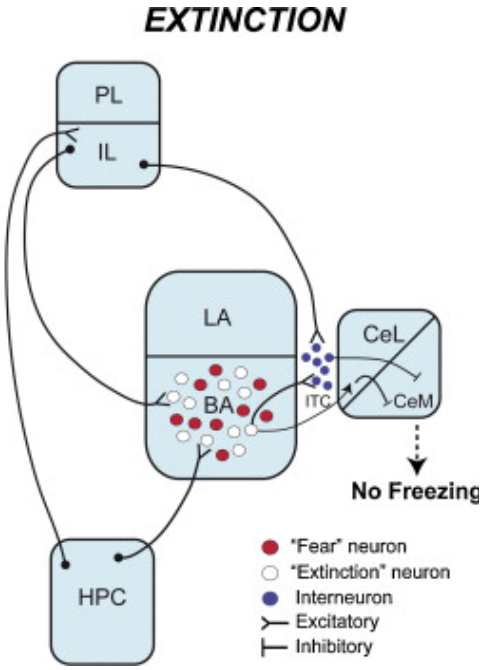


- In both groups, association between greater symptom improvement and less face-related excitation of the vmPFC by the AMG (*Pp*=0.94,1.0).
- However, the relationship between PTSD symptom improvement and greater top-down inhibition of the AMG by the vmPFC was only evident in the ketamine group

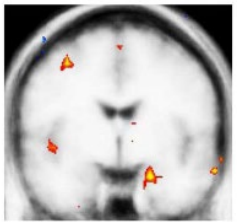
Norbury et al 2021

What does this tell us?

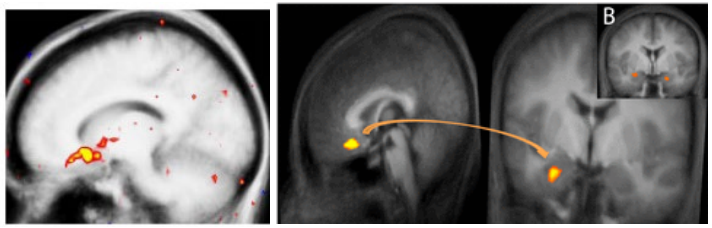
- PTSD symptom improvement following repeated-dose ketamine seems to specifically involve **greater top-down inhibition of the AMG by the vmPFC, in response to emotional stimuli** (whereas lessening AMG→vmPFC excitation seems to be a drug non-specific marker of response).
- This has intriguing parallels to neural mechanisms implicated in **successful extinction learning.**



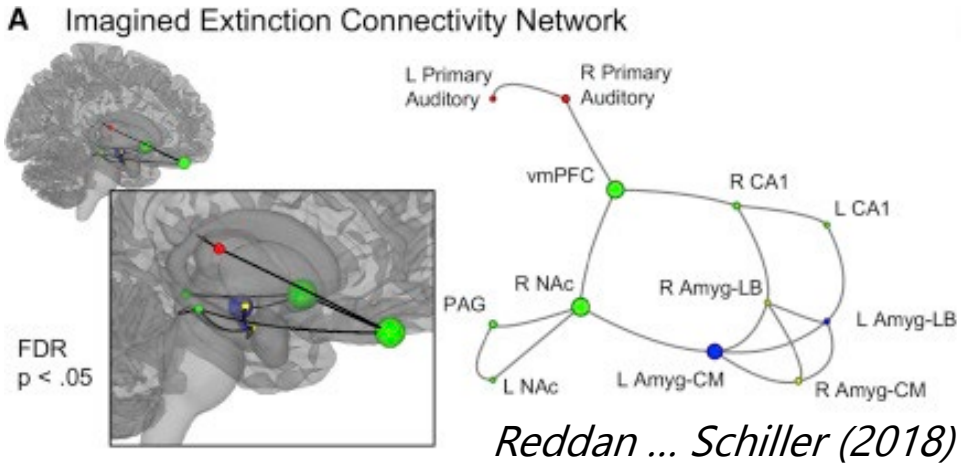
Orsini & Maren (2012)



Milad et al. (2007)



Schiller et al. 2013



Reddan … Schiller (2018)

Ketamine and Trauma-focused Psychotherapy

Potential Synergism?

Chronic PTSD –*Abnormalities in Sustained Threat System*

Synaptic disconnection and dysregulation of amygdala reactivity to threat

Ketamine administration

Increased neuroplasticity and top-down inhibition vmPFC → amygdala

and reduced representational dissimilarity in amygdala responses to fearful vs. neutral faces

Delivery of brief trauma-focused psychotherapy: Written Exposure Therapy

Ketamine may enhance the efficacy of written exposure therapy in individuals with chronic PTSD

Combining Ketamine with Trauma-focused Psychotherapy

- Shiroma et al 2020 (open-label, 3 weekly infusions):
  - Proof-of-concept study of IV ketamine combined with PE in Veterans with PTSD (N= 10), CAPS-5 ≥ 23
  - 10 weeks of weekly PE and 3 IV ketamine infusions 24 hours before the first 3 PE sessions
  - 5 participants completed the full treatment; 5 others did not complete full PE (3-8 sessions)
  - CAPS-5 scores decreased significantly from baseline to end of treatment,
    Mean change CAPS-5 [95% CI]= -15.25 [7.27 – 23.23]
- Duek et al… Harpaz-Rotem 2023 (RCT, single infusion):
  - RCT of single ketamine infusion (vs. single midazolam infusion) after retrieval of traumatic memory (N= 27 individuals with PTSD). Following infusion (24 hours later), all participants received a 4-day trauma-focused psychotherapy (modified PE). Primary outcome measure: PTSD Checklist for DSM-5 (PCL-5).
  - Clinical outcome: No significant difference between ketamine and midazolam groups (PTSD symptoms significantly improved in both groups): effect size in full sample [95% HDI]= 0.8 [0.23, 1.39].
  - Changes in neural function: Potential larger reduction in neural reactivity associated with the trauma memory in the ketamine group (lower amygdala reactivity to recalled trauma, reduced connectivity amygdala-posterior hippocampus at end of treatment).
  - Korem et al… Harpaz-Rotem 2024: Secondary analyses: Early changes (post-treatment) in functional connectivity, RSFC hippocampus-vmPFC ←→ sustained changes (short-term and 30-day follow-up) in anatomical connectivity (UNC FA) ←→ PTSD symptom improvement.

Combining Ketamine Treatment with Written Exposure Therapy for Chronic PTSD

An Open-label Clinical Trial

Choice of Trauma-focused Therapy
Written Exposure Therapy (WET)

- Brief, evidence-based, tolerable and efficient, very low dropout rates
- Extinction learning is thought to underlie exposure-based therapies
- Total 5 sessions:
  - Treatment rationale, psychoeducation
  - Pts write repeatedly about details of trauma linked to their symptoms
    - Particular attention to felt emotions and meaning of the traumatic event

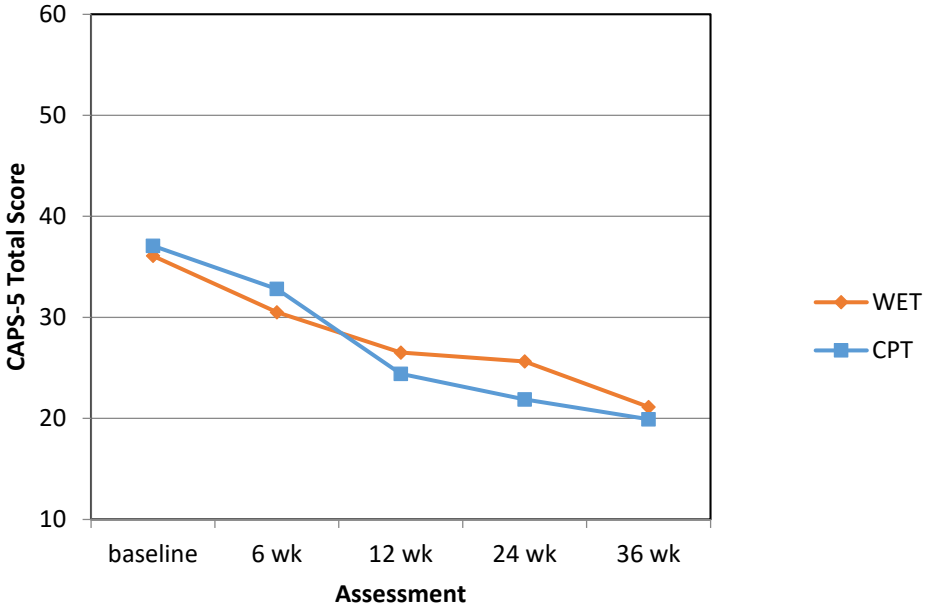
To date, three non-inferiority RCTs in PTSD:

- Sloan et al 2018: WET non-inferior to CPT (n=126, 74% civilians)

- Sloan et al 2022: WET non-inferior to CPT (n=169, active duty military service members)

- Sloan et al 2023: WET non-inferior to PE (n= 178, veterans)

Fig. 2: Non-inferiority RCT

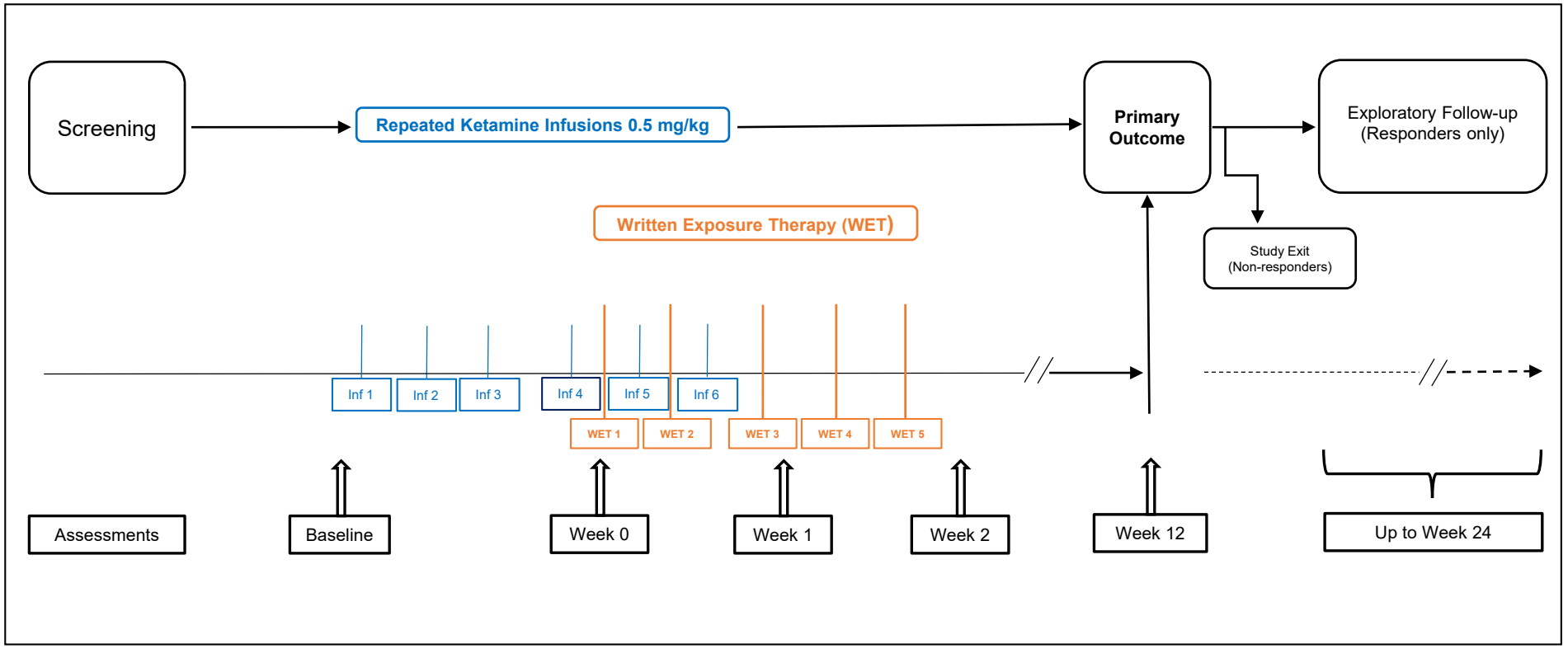


Sloan et al 2018

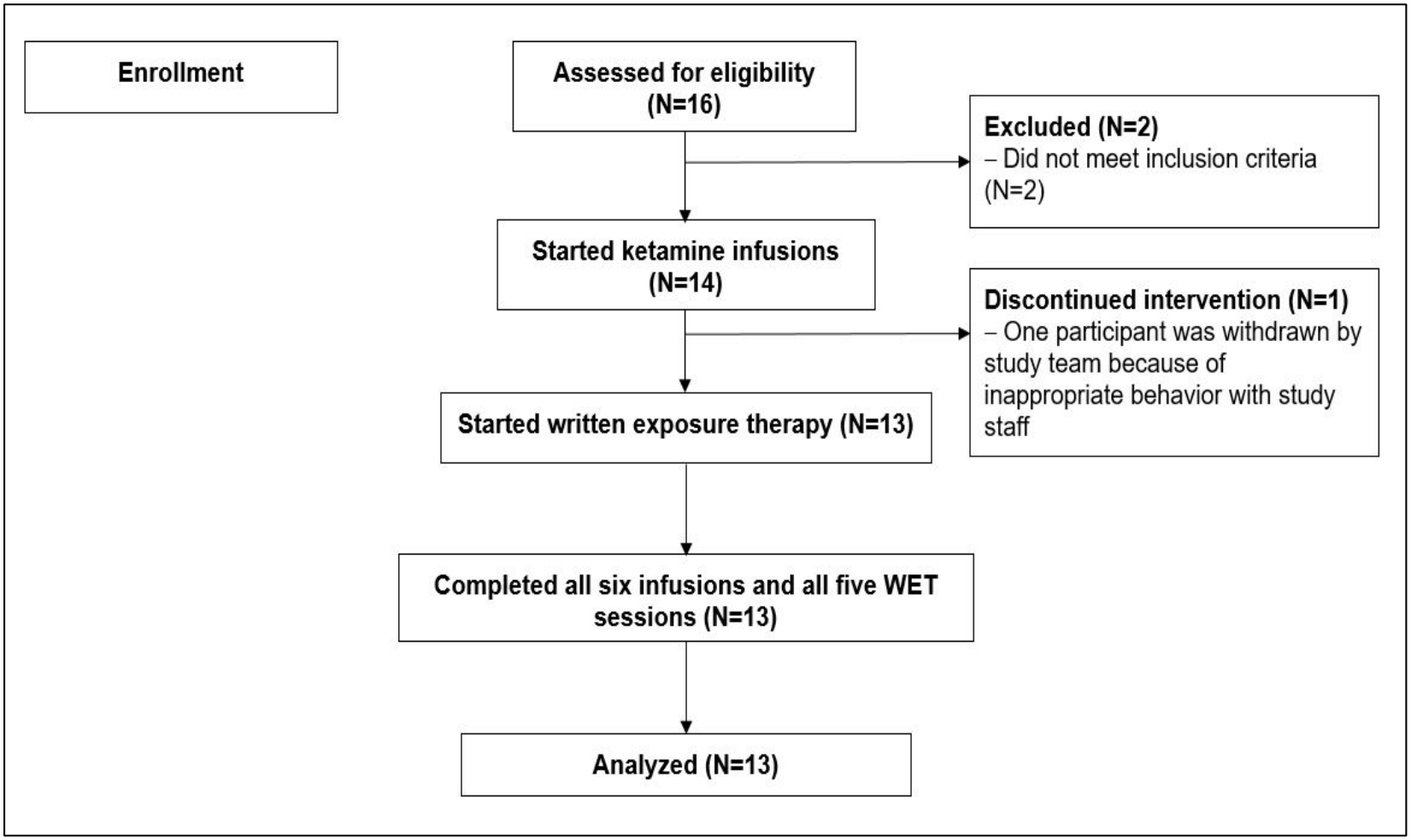
Standard Written Exposure Therapy Instructions

- Session 1: Write about your trauma from the beginning (how it happened, who was involved, what you saw/heard/smelled) + details, thoughts, feelings during trauma (and immediately after) as you remember it now
- Session 2: Trauma – continue where you left off or write about entire trauma again as you look back upon it now + details (setting, people involved, saw/heard/felt), thoughts, feelings
- Session 3: Trauma – write about trauma again or pick "worst" part (most upsetting/stressful) + begin to write about how trauma changed your life (the way you view life, meaning of life, how you relate to others) + thoughts, feelings
- Session 4: Trauma – pick "worst" part (most upsetting/stressful) + how trauma has changed your life (the way you view life, meaning of life, how you relate to others) + thoughts, feelings
- Session 5: Thoughts and feelings related to trauma and how trauma changed your life + how trauma is related to your current life and future + thoughts, feelings

Study Flowchart



CONSORT Diagram



Demographic and Clinical Characteristics of Study Participants (N=13)

Characteristic		
Continuous Variables	**Mean**	**SD**
Age, years	38.3	7.5
BMI	27.3	7
Duration of PTSD, years	18.1	14.0
CAPS-5 score (past month)	40.5	3.9
MADRS score (past week)	31.4	6.5
Categorical Variables	**N**	**%**
Female, sex	13	100
Race		
Black	0	0
Asian	1	7.7
White	9	69.2
Other/ More than 1 race	3	23.1
Hispanic ethnicity	4	30.8
Education		
Some college or trade school	2	15.4
Graduated 4 years of college	4	30.8
Some graduate/professional degree	1	7.7
Completed graduate/professional degree	6	46.2
Unemployed	2	15.4
Married or cohabiting	2	15.4
Primary trauma		
Sexual assault or molestation	8	61.5
Physical assault or abuse	2	15.4
Other (accident, assault witness, 9/11 survivor)	3	23.1
Current Comorbid Diagnoses:		
Major Depressive Disorder	10	76.9
Persistent Depressive Disorder	6	46.2
Generalized Anxiety Disorder	10	76.9
Social Anxiety Disorder	5	38.5
Concomitant treatment with psychotherapy	7	53.8
Concomitant treatment with psychotropic medication	6	46.2
Marijuana use during treatment phase	1	7.7
Marijuana use during follow-up phase	2	15.4

Pre- and Post-treatment Scores on Primary and Secondary (Exploratory) Measures

	Pre-Treatment	Post-Treatment	F	P	d (95%CI)
	Mean (SD)	Mean (SD)			
CAPS-5 total	**41.6 (6.2)**	**20.8 (14.8)**	**22.00**	**<.001**	**1.9 (1.0-2.8)**
Intrusions	9.2 (2.1)	5.8 (4.1)	6.98	0.014	1.1 (0.3-1.9)
Avoidance	5.3 (1.3)	1.7 (2.1)	26.99	<.001	2.1 (1.2-3.1)
NACM	16.7 (2.9)	8.0 (6.6)	18.75	<.001	1.8 (0.9-2.7)
AAR	10.4 (2.6)	5.2 (3.6)	17.17	<.001	1.7 (0.8-2.6)
MADRS	31.4 (6.5)	19.1 (13.2)	8.96	0.006	1.2 (0.4-2.1)
CGI-S	4.9 (0.6)	3.2 (1.2)	19.23	<.001	1.8 (0.9-2.7)
CGI-I	N/A	2.0 (0.9) 77% ≥ 2	--	--	--
SDS work[a]	4.1 (3.2)	3.4 (3.1)	0.25	0.63	0.2 (-0.6-1.0)
SDS social	6.1 (2.5)	3.1 (3.6)	6.02	0.022	1.0 (0.2-1.8)
SDS family/home	5.7 (2.9)	2.4 (2.4)	10.17	0.004	1.3 (0.5-2.1)

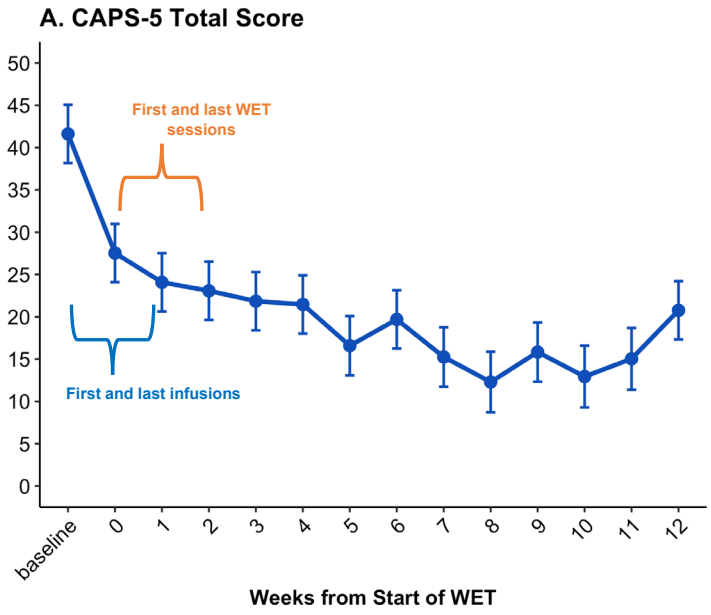
Note: CAPS-5: Clinician-Administered PTSD Scale for DSM-5; NACM: negative alterations in cognition and mood; AAR: alterations in arousal and reactivity; MADRS: Montgomery-Åsberg Depression Rating Scale; CGI-S: Clinical Global Impressions-Severity; CSI-I: Clinical Global Impressions-Improvement; SDS=Sheehan Disability Scale.

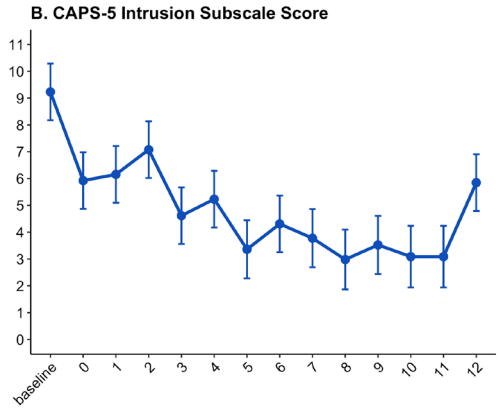
[a] SDS work scores were assessed in 10 participants who reported current employment.

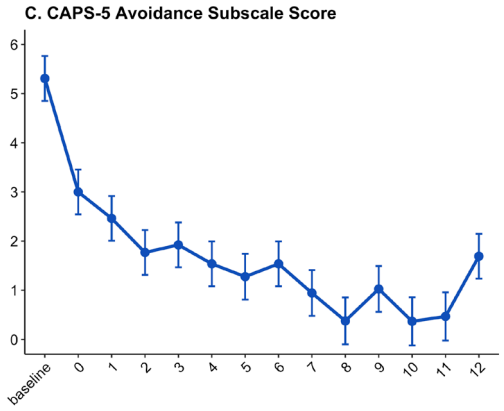
Safety and Side Effects

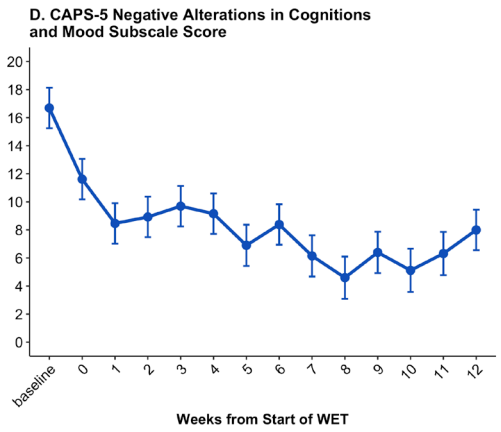
- One participant was withdrawn early for reasons unrelated to infusions
- All other participants completed the full treatment
- Any acute dissociative symptoms during infusions were transient, resolving after infusion end
- Most frequent general side effects on infusion days:
  - Fatigue (38%), dizziness (31%)
  - Blurred vision (23%), body numbness (23%), headache (15%)
- A few patients experienced slowdown in PTSD symptom improvement following initial WET sessions
- One patient (ketamine responder, non-responder to combined treatment) found it very difficult to tolerate WET

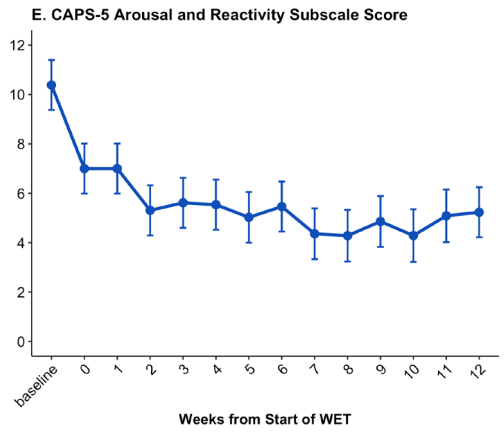
Effect of the Combined Treatment on PTSD Symptom Severity (N=13)



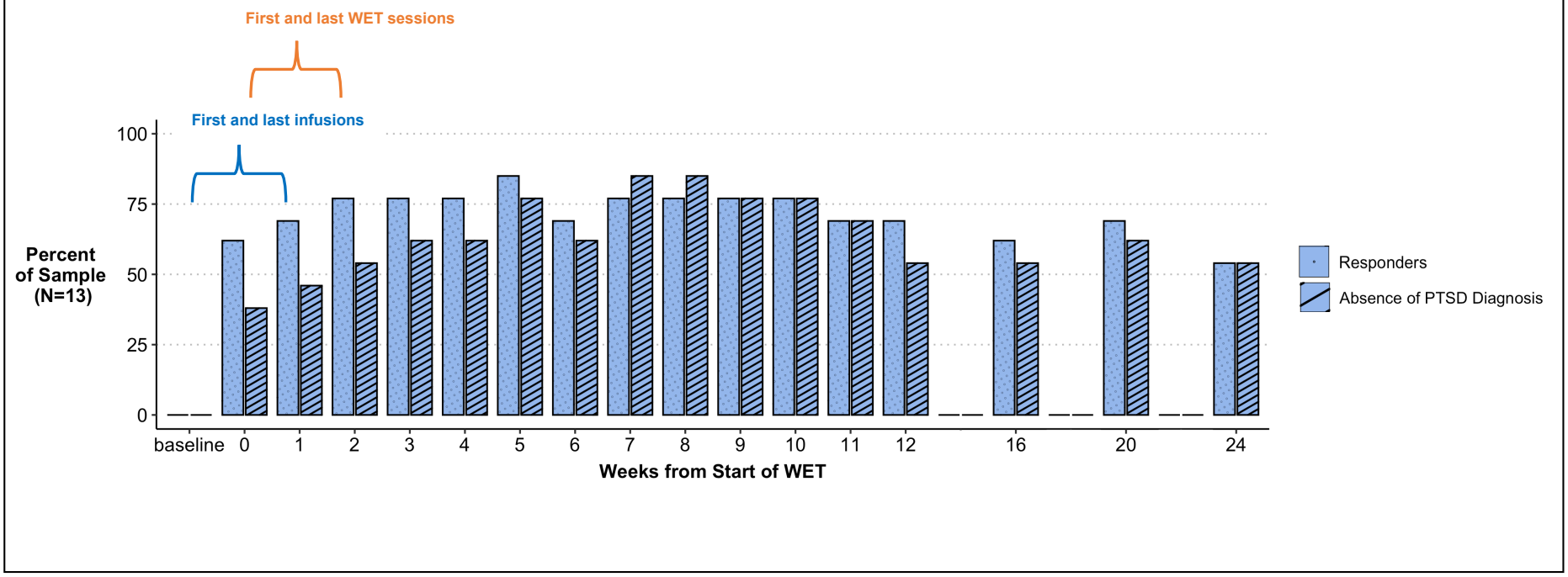








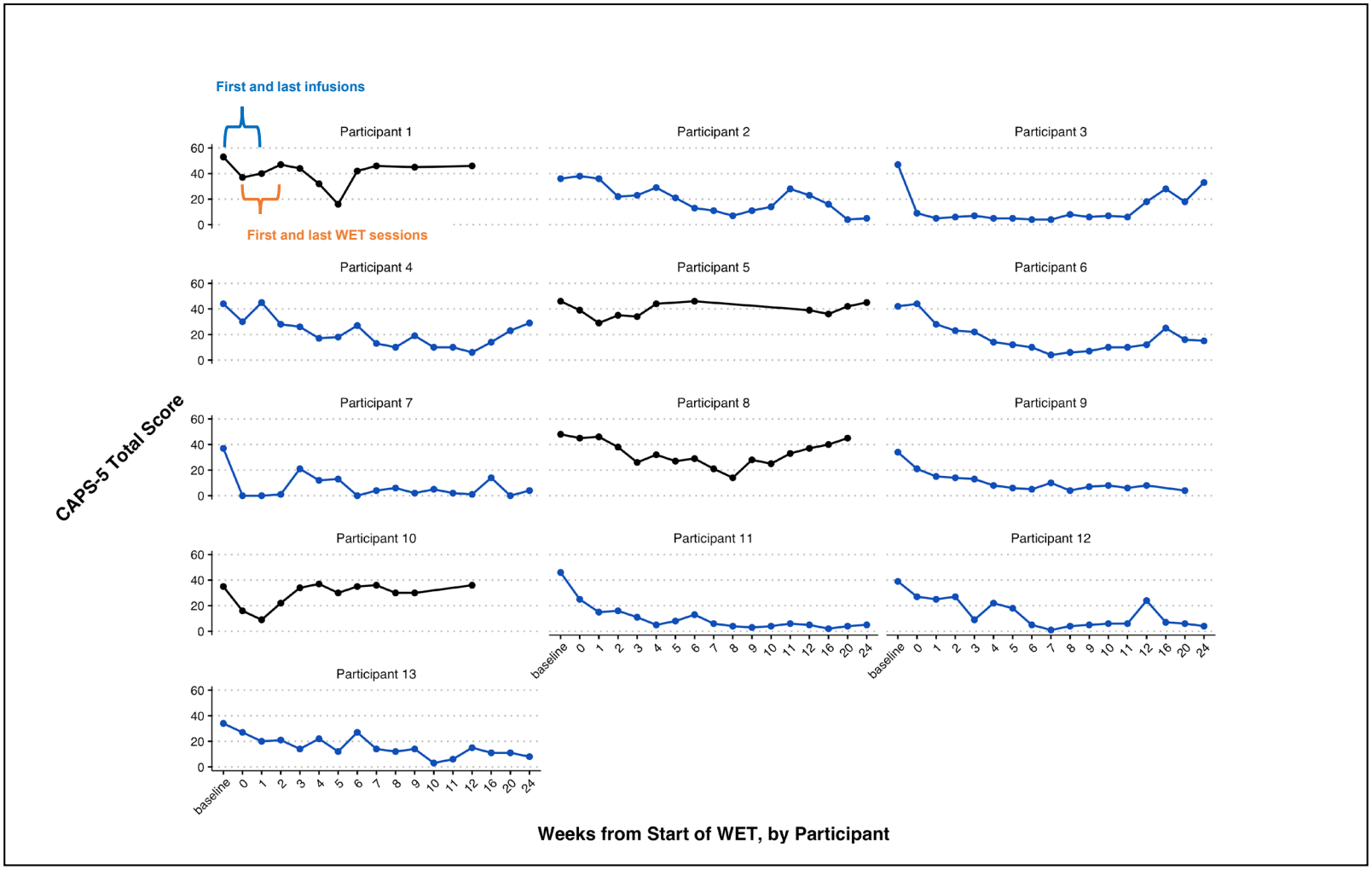
Percentage of Treatment Response and Loss of PTSD Diagnosis (N=13)



Note: Treatment responders (TR) = at least 30% improvement from baseline on the total CAPS-5 score.
Loss of PTSD diagnosis (0_PTSD) = no longer met DSM-5 diagnostic criteria for PTSD.

Week 3: TR=10 (77%), 0_PTSD= 10 (77%)
Week 12 (primary outcome): TR= 9 (69%), 0_PTSD= 7 (54%)
Week 24 (maintenance): TR= 7 (54%), 0_PTSD= 7 (54%) – plus 8th participant last assessed at Week 20

Effect of the Combined Treatment on PTSD Symptom Severity by Participant (N=13)



Note: In blue, treatment responders (69%) at Week 12; in **black**, treatment non-responders (31%) at Week 12.

Summary and Future Directions

- Repeated ketamine infusions are associated with rapid and robust improvement in PTSD symptoms in patients with chronic PTSD, but maintenance ketamine infusions are needed over time
- Patients with PTSD can receive ketamine infusions at ketamine clinical practices
- IV ketamine is currently off-label, not FDA-approved for the treatment of psychiatric disorders
- Intranasal administration of esketamine is FDA-approved as adjunct treatment for TRD or depression with suicidal ideation

Summary and Future Directions

- Ketamine opens a window of increased neuroplasticity in brain regions subserving emotion processing/regulation and threat processing/fear extinction learning
  - Ketamine might enhance efficacy of exposure-based psychotherapy

- Open-label clinical trial aimed to maximize potential synergistic effect of ketamine + WET
  - Several infusions administered prior to starting WET to "prime the brain"
  - Full course of WET administered within the estimated window of ketamine-related increased neuroplasticity

- fMRI studies of exposure-based psychotherapies for chronic PTSD:
  - Pts with poorer PFC inhibition of amygdala activation at pretreatment baseline are *least* likely to respond
- Repeated ketamine RCT for chronic PTSD:
  - Pts with poorer PFC inhibition of amygdala activation at pretreatment baseline are *more* likely to respond

Summary and Future Directions

- Feasibility, safety and preliminary efficacy open-label trial:
  - No participants dropped out
  - *Rapid response*
  - *Large-magnitude improvement* in PTSD symptoms assessed 3 months from baseline (69% treatment responders)
  - All responders improved early in treatment
  - *Maintenance of response:* Treatment response maintained in 54-62% of the sample 6 months from baseline
  - Combined treatment → Mean ES (*d*= 1.9) at *3 months* comparable to standalone ketamine at *2 weeks*
  - Mean ES at *3 months* larger than standalone WET at at *3 months* ?
  - Avoid/reduce need for maintenance ketamine infusions?

Summary and Future Directions

- Findings from open-label clinical trial support feasibility and preliminary safety/efficacy of combined treatment
- Larger randomized controlled trial is needed.
- Future mechanistic neuroimaging study examining changes in threat and emotion regulation circuitry function

Acknowledgments

Depression and Anxiety Center for Discovery and Treatment

James Murrough
Oneysha Brown, Sarah Rutter
Leah Cahn
Agnes Norbury
Abby Collins
Sara Costi
Manish Jha
Rachel Fremont
Kate Collins
Sarah Horn, Marin Kautz
Brittany Cho, Morgan Corniquel
Saren Seeley
Philip Bonanno

Office of the Dean

Dennis Charney

Department of Anesthesiology

Andrew Glasgow & Jess Brallier
Alex Yu
Ethan Bryson

Yale University

Robert Pietrzak

Psychiatry Department Nursing Personnel

Lorna Green
Hugo Gavilanez
Ramuel Abuedo
and others

Research Pharmacy

Ivy Cohen
Alla Khodzhayeva
Giuseppe Difiore

Clinical Research Unit

Margaret Garrett
Betty Chen
Christian Malatesta

Other Mount Sinai Faculty

Daniela Schiller
Usha Govindarajulu
Jessica Overbey
Andrew Delgado
Rachel Yehuda

Boston University

Denise Sloan

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

Mount Sinai *Innovation Partners*

With additional support from Mr. Gerald Greenwald and Mrs. Glenda Greenwald, and the Ehrenkranz Laboratory for Human Resilience at Mount Sinai.