Hallucinogens as Treatment?

Preliminary Data with Ketamine

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Disclosures

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Overview

How might hallucinogens work as treatment?

Why might ketamine work as a treatment?

By any other name

Deliriant
Entheogen
Hallucinogen
Imaginant
Oneirogen
Phanarothyme
Phantasticant
Psychedelic
Psychotomimetic

A diverse group

- **Indoles** - d-lysergic-acid (LSD), dimethyltryptamine (DMT), harmaline, ibogaine, psilocybin,
- **Dissociative Anesthetics** - ketamine, PCP
- **Phenethylamines** -mescaline, 2-CB, DOM, MDA, MDMA
- **Others** - nitrous oxide, salvia divinorum, THC, fly agaric mushroom

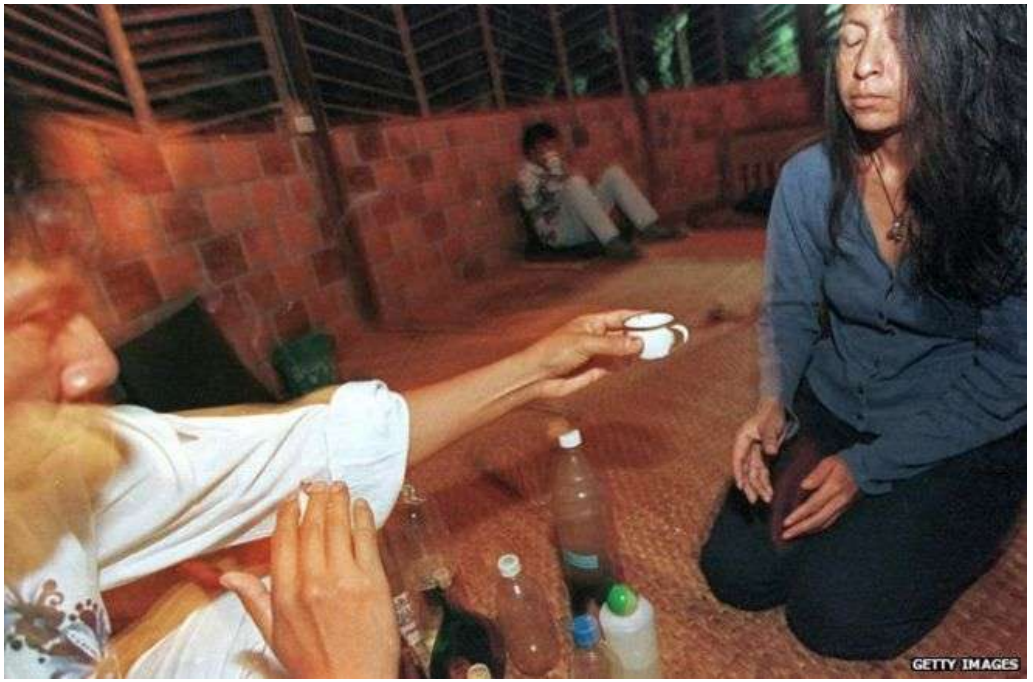
Effects

Produce in a time-limited manner non-ordinary experiences comparable to:

- trance
- psychosis
- ecstasy
- dreaming
- mystical experience

Ancient Uses

- Ritual
- Divination
- Initiation
- Pleasure
- Healing
- Witchcraft
- Protection/fortification



Modern Uses

Classical hallucinogens were investigated in the 1950s through the early ’70s in various settings.

- psychiatric treatment
- quality of life improvement
- investigations of consciousness
- criminal justice
- warfare

“Psychedelic” and “Psycholytic” treatment models

Concern over recreational use obscured promising clinical data and clinical research was largely aborted due to criminalization in 1973. But has recently resumed via private foundation funding

Set and Setting

A valuable heuristic for optimizing benefits, minimizing risks

Set: the recipient's expectations, past experiences, intentions, psychology, preparation

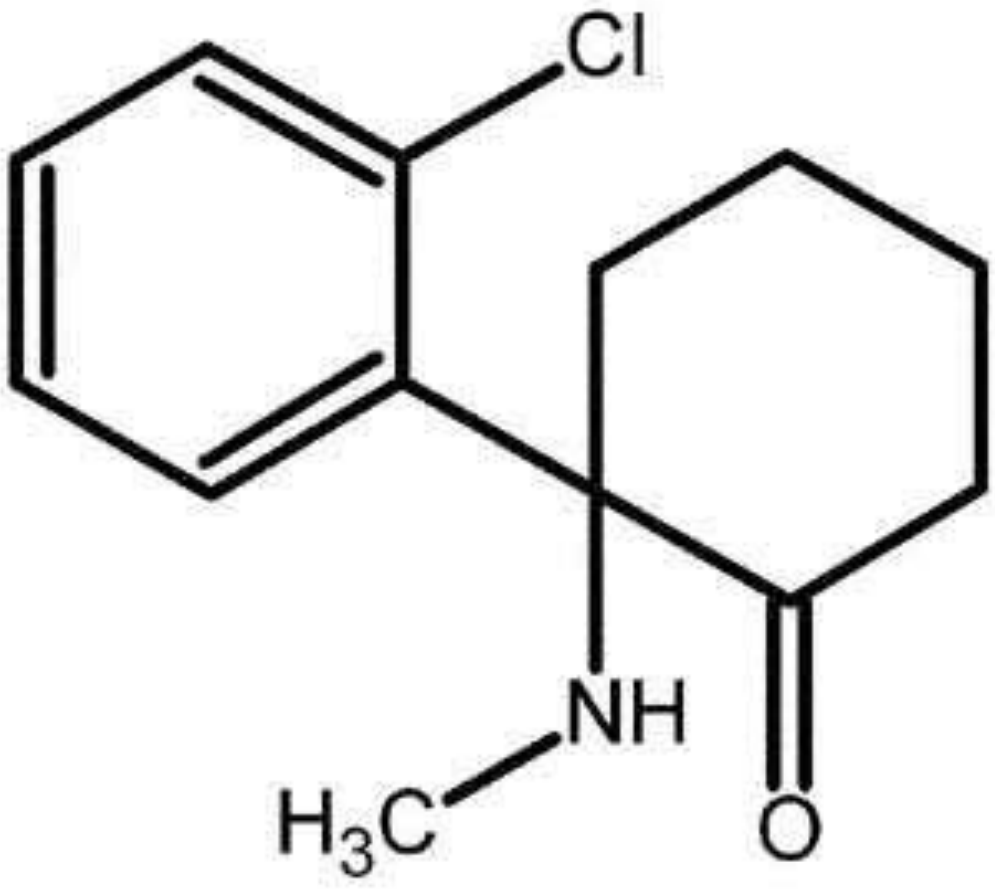
Setting: the environment, context, involvement of others, mode of administration

"Set and setting" comparable to other medical frameworks governing the safe use of high-risk interventions (e.g., surgery).

Medicalization

To be integrated into current medical settings, the ideal "hallucinogen":

- Can be administered in a manner that does not lend itself to abuse or behavioral toxicity
- Has an established safety record
- Has reliable, "lawful" psychoactive effects
- Can be legally provided to patients


Cl
NH
H3C
O

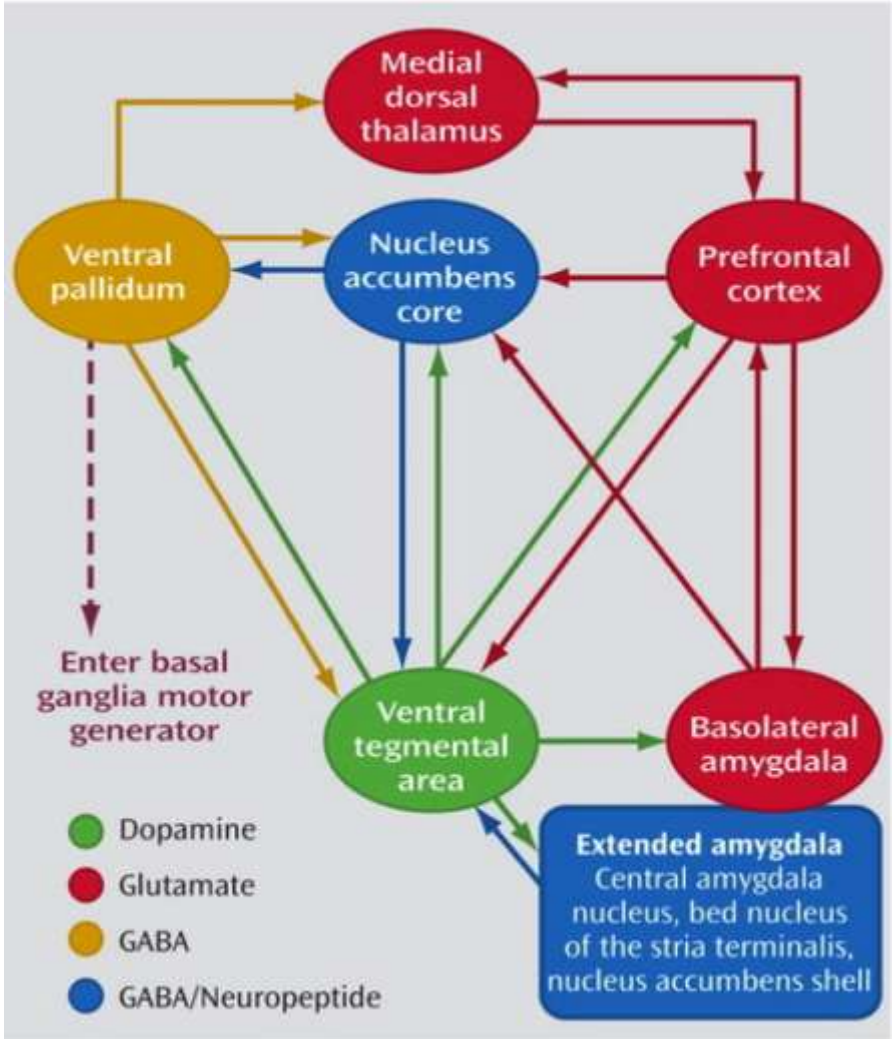
What is the role of medications in cocaine use disorders?

Disruptions in cortico-limbic-striatal communication are implicated in cocaine-related deficits

- behavioral reactivity, craving, impulsivity, blunted salience of non-drug reward

These adaptations occur with other drugs of abuse

Pharmacotherapy may work to address these disruptions



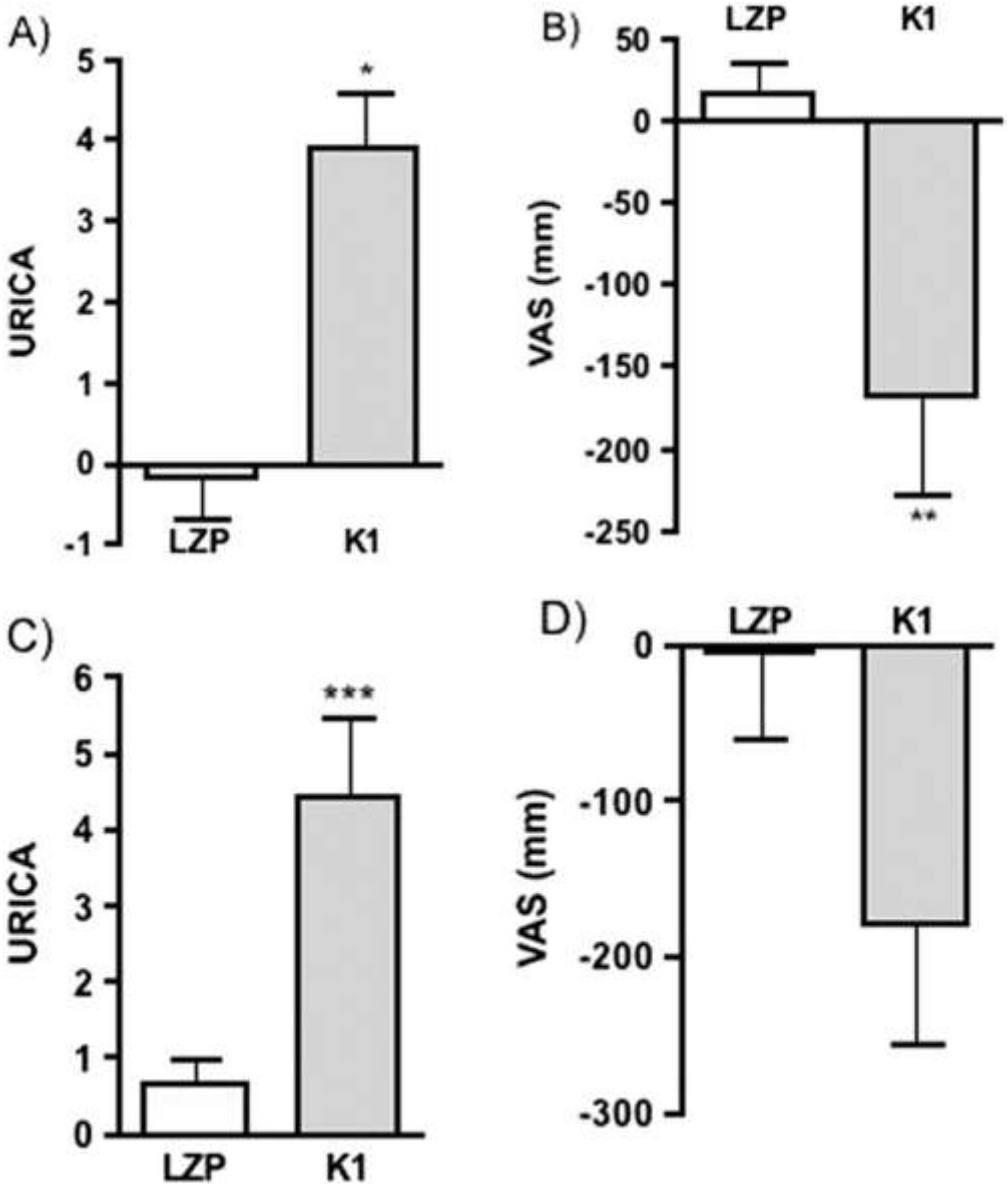
Kalivas and Volkow, 2014

Therapeutic implications

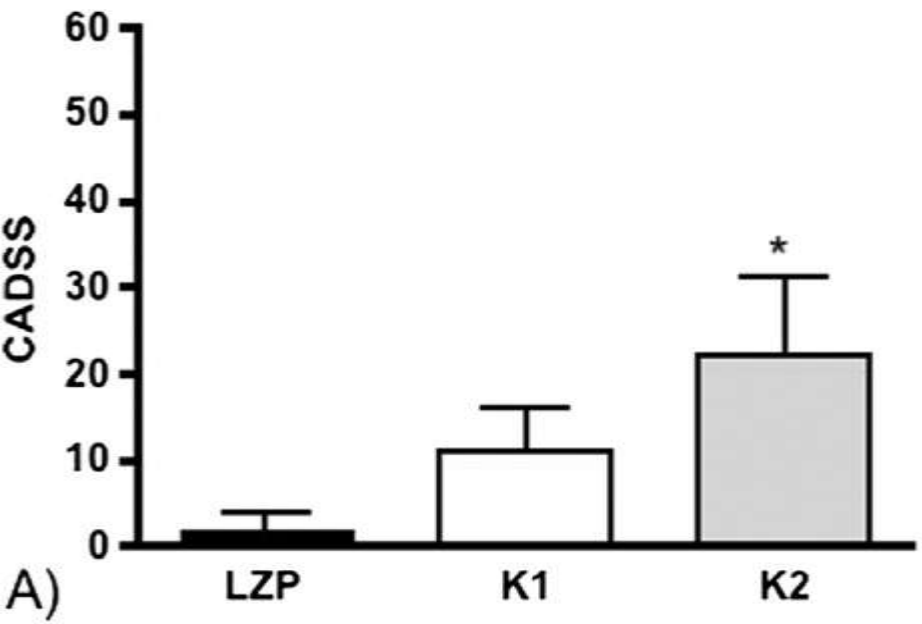
The unique anti-depressant effect of ketamine has been attributed to:

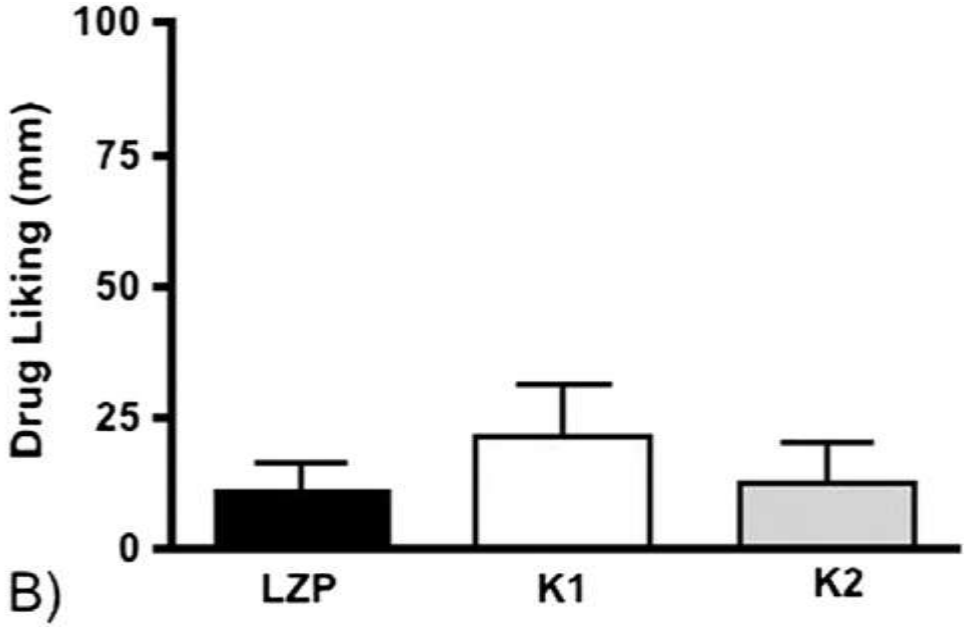
- The promotion of prefrontal neural plasticity
- Improvements in glutamate homeostasis
- Modulation of prefrontal activity
- Attenuation of resting-state connectivity and activity
- Psychological mechanisms?

IM ketamine has shown promise as a treatment for opioid and alcohol dependence in the context of a psychedelic framework



Dakwar et al., 2013, Bio Psych





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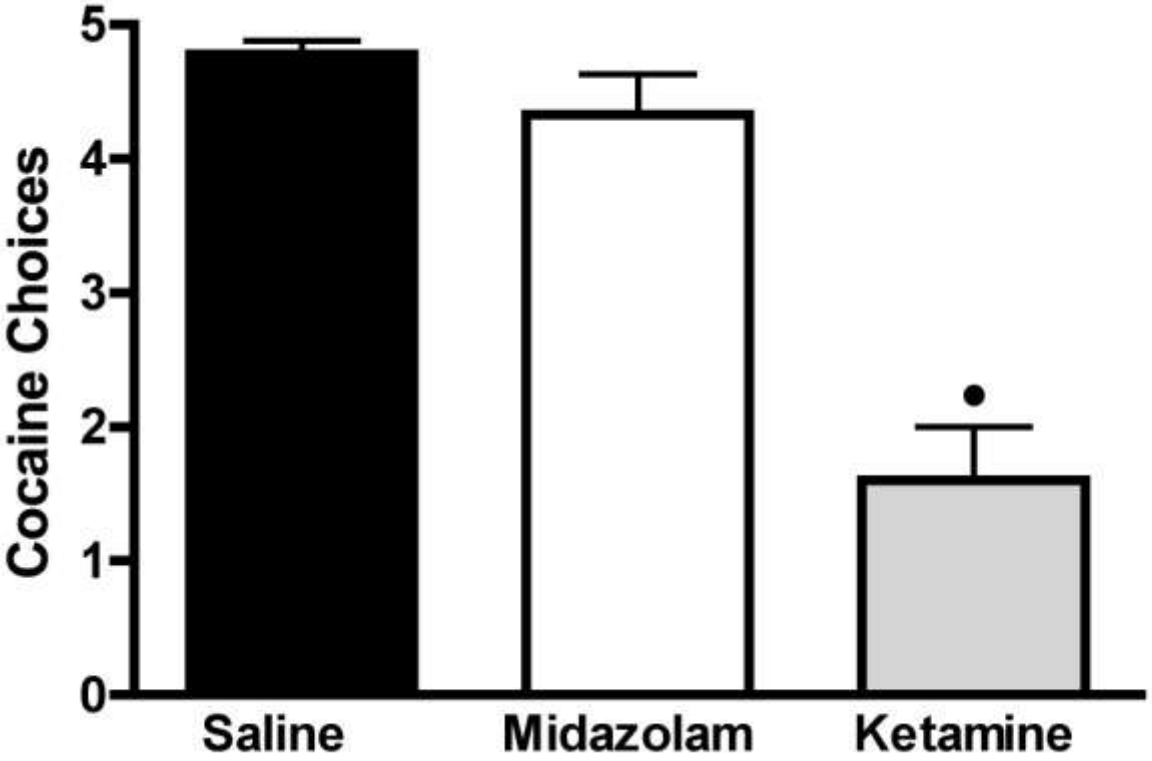
Design (1st hospitalization)

- 20 cocaine dependent individuals, not seeking treatment and otherwise healthy
- Hospitalized up to 3 times for 6-day stays, with intervals of 2 weeks between each stay
- 1st hospitalization: admitted on a Fri, receive 2 doses of crack cocaine Monday, a saline infusion Tues, and five choices (crack vs. money) on Wed.
- Those who choose cocaine more than 3 times continue with the study

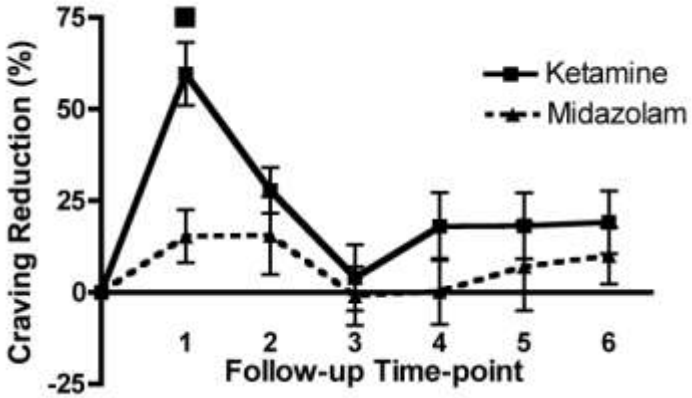
Design (2nd and 3rd Hospitalizations)

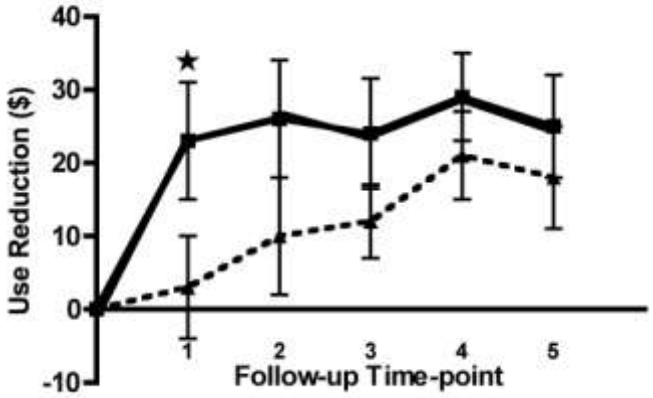
- During the 2nd and 3rd hospitalizations, admitted Friday, receive 2 doses cocaine Monday, counter-balanced 52 min infusions of midazolam (0.025 mg/kg) vs. ketamine (0.71 mg/kg) Tuesday, and 5 choices Wednesday

- We hypothesized that ketamine would lead to greater reductions in cocaine choices than would midazolam



Dakwar et al., 2016, Mol Psych





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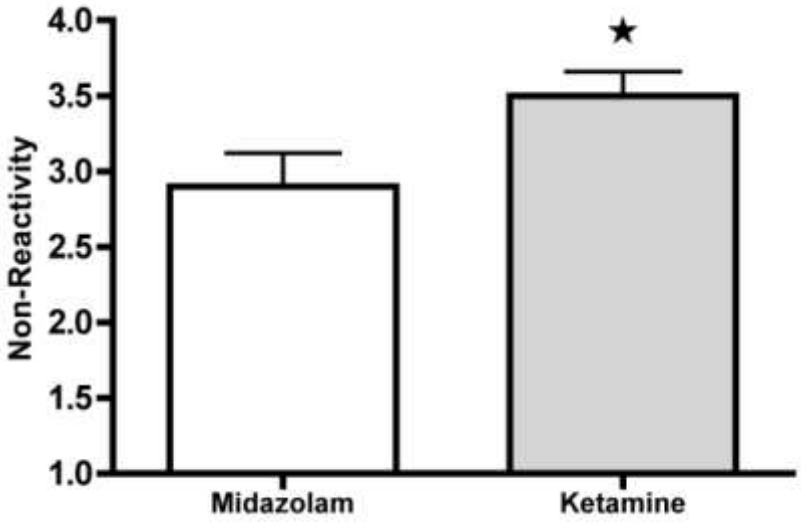
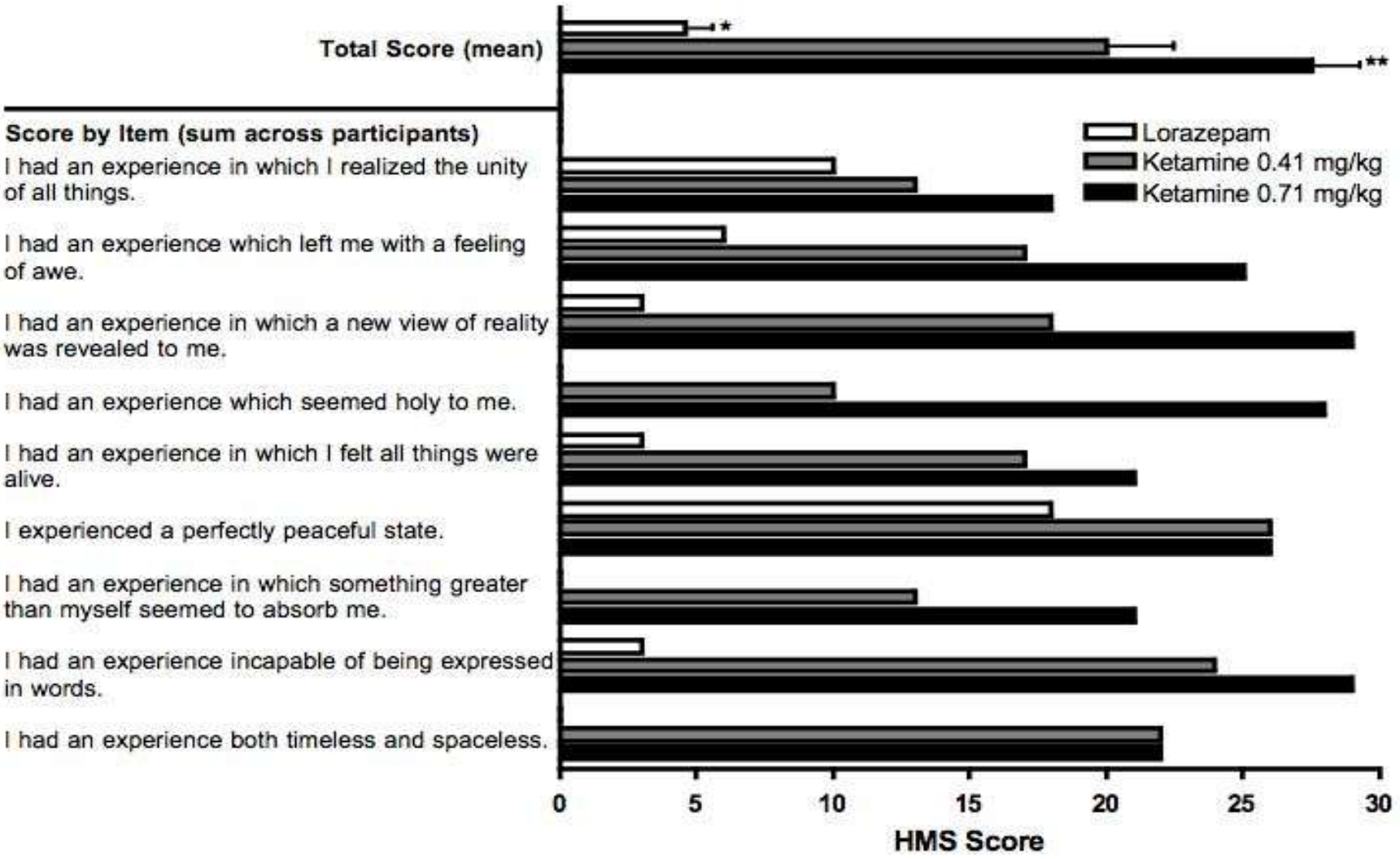


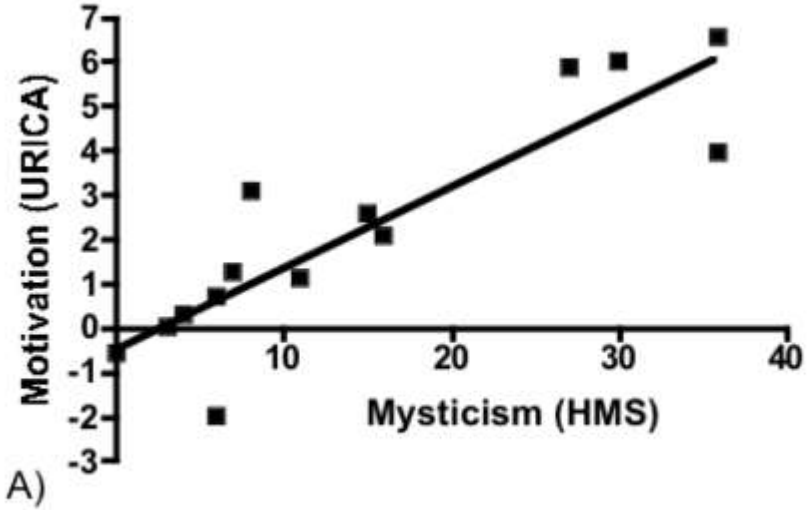
Dakwar et al., 2016, Mol Psych

Do the psychoactive effects matter?

- Sub-anesthetic ketamine is associated with dose-dependent alterations in consciousness
- These alterations in consciousness may have therapeutic implications, as in a psycholytic or psychedelic model
- Dissociative effects well studied, but mystical-type effects remain unclear



Dakwar et al., DAD, 2014

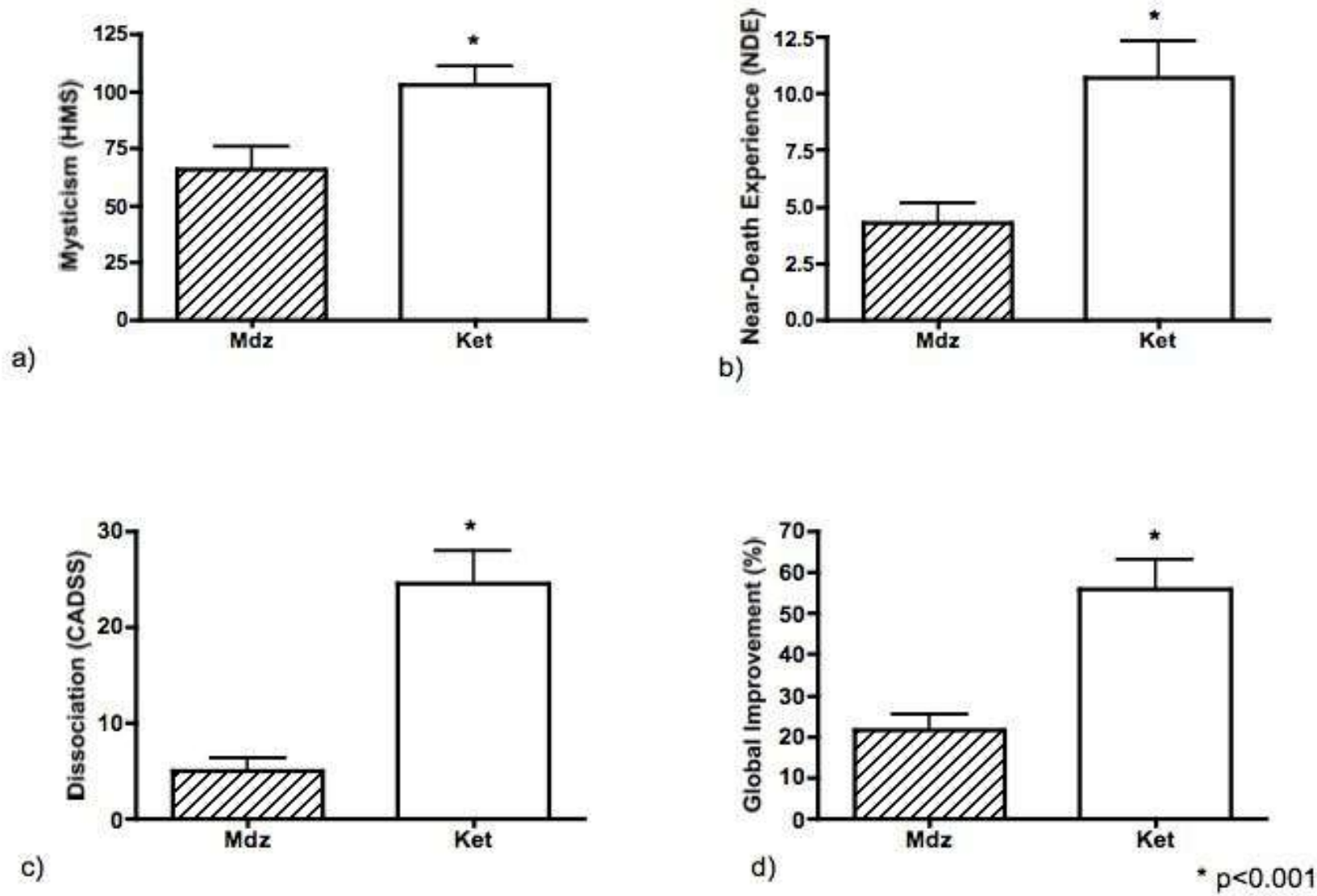


A)

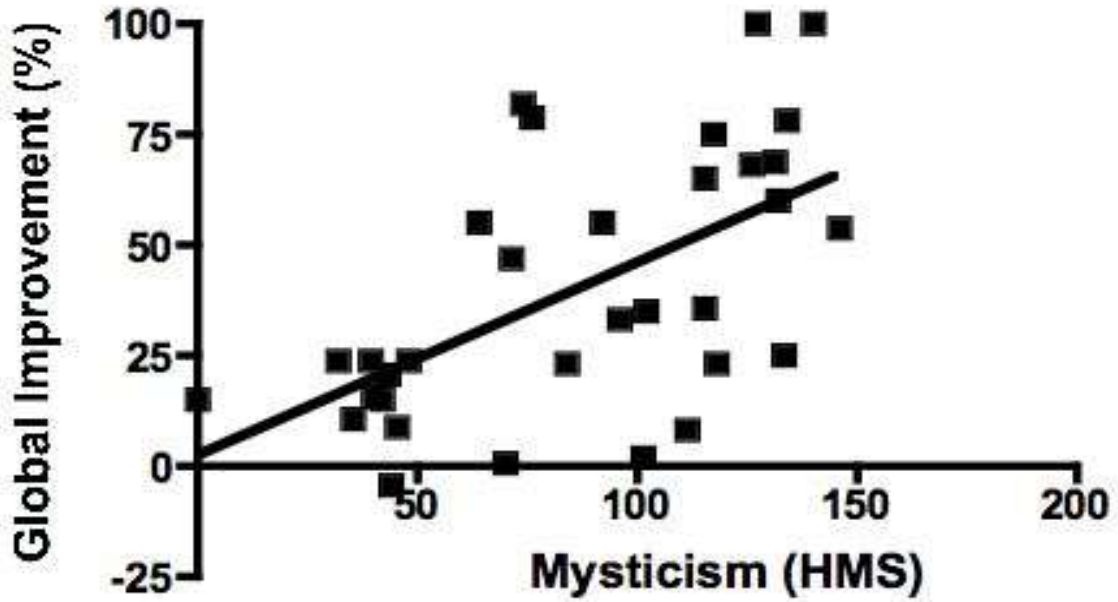
B)

	Simple Regression		Mediation Analysis		
	Infusion Type (β)	Psychoactive Effect (β)	Infusion Type (β)	Psychoactive Effect (β)	
Dissociation	0.776*	0.681**	0.329	0.535	Motivation
	0.580	0.655**	0.287	0.479	Craving
Mysticism	0.776*	0.881***	0.274	**0.678****	Motivation
	0.580	0.647**	0.223	0.482	Craving

Dakwar et al., DAD, 2014



Dakwar et al., 2017



a)

b)

	Simple Regression		Mediation Analysis	
	Ketamine Dose (β)	Psychoactive Effect (β)	Ketamine Dose (β)	Psychoactive Effect (β)
CADSS	.553*	0.552*	0.337[c]	0.334[c]
NDES	.553*	0.513**	0.420[d]	0.358[e]
HMS	.553*	0.586***	0.382[f]	**0.437****

Dakwar et al., 2017

Safety

- No psychosis (by BPRS)
- No persistent dissociation
- No symptoms of hypertension
- No robust drug-liking
- Most common physiological effects: sedation, modest blood pressure elevation, lightheadedness, headache
- All effects resolved within 15 minutes to 1 hr post-infusion

A medication to promote behavioral change

Ketamine appears to address vulnerabilities that typically undermine efforts behavioral modification (craving, high reactivity, tenuous motivation, aberrant reward processing), and thus may work to facilitate addiction-oriented behavioral treatment.

There is mechanistic and behavioral overlap between ketamine and mindfulness training specifically.

Ketamine may enhance mindfulness-based behavioral treatment:

- Eliciting neurobiological effects that render mindfulness easier to practice
- Motivating engagement in mindfulness training/behavioral treatment
- Providing an experiential stepping-stone
- Promote perspectival shifts (openness, curiosity) conducive to the cultivation of mindfulness

Clinical Trial

- Investigate the efficacy of ketamine for promoting abstinence and preventing relapse in cocaine dependent individuals

- Randomized controlled trial of ketamine vs. midazolam for cocaine dependent individuals receiving mindfulness-based relapse prevention therapy (n=55)

- A single infusion occurs in the first week of this 5 week trial

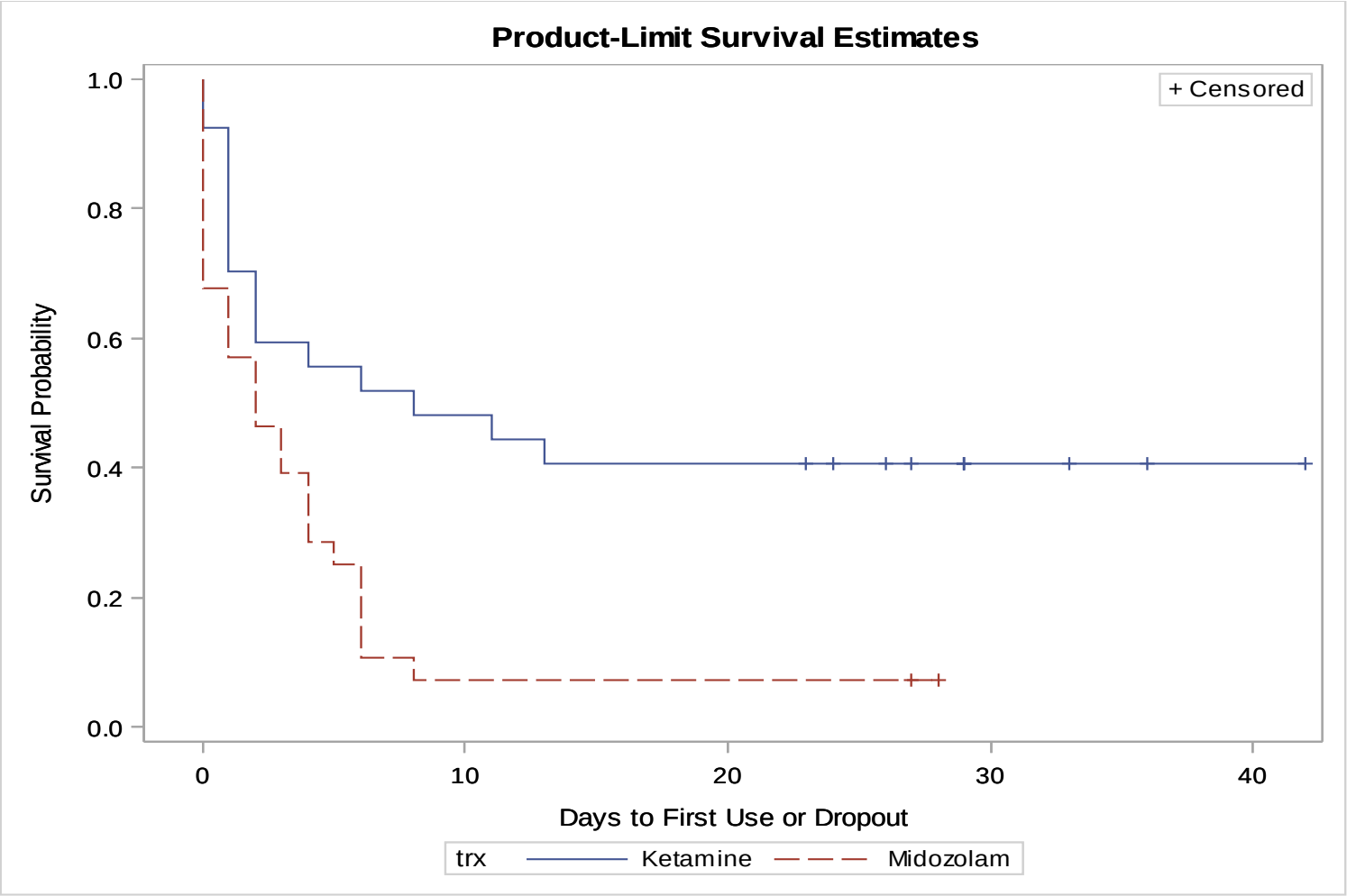
Main outcome

48.3% of individuals receiving ketamine were abstinent in the last two weeks of the trial, compared to 10.8% in the midazolam group.

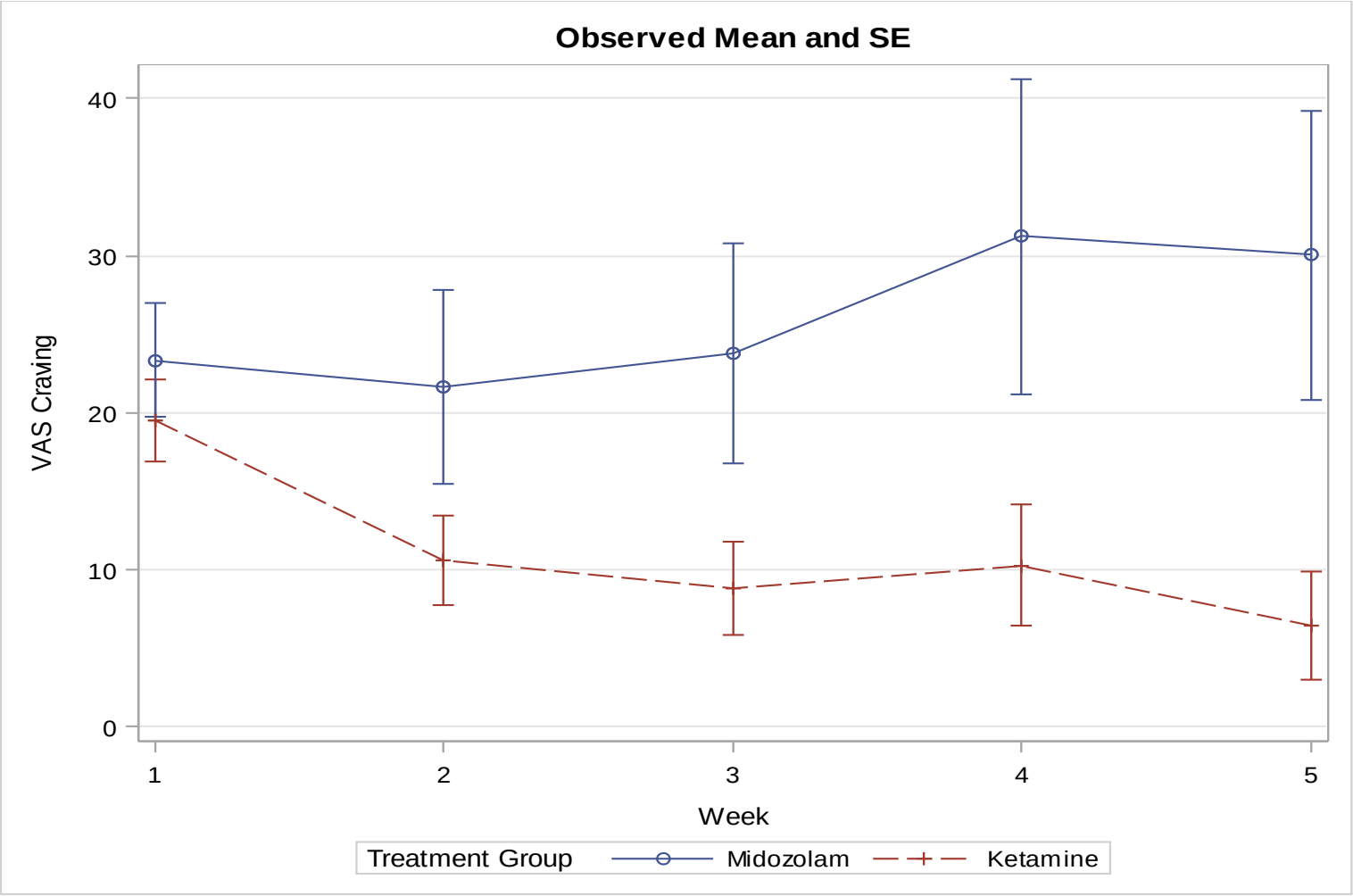
The ketamine group was 6 times more likely to maintain end-of-study abstinence (OR=6, 95% CI = 1.4, 26; p = 0.0159), controlling for route of use.

- Larger trial recently initiated (n=123)

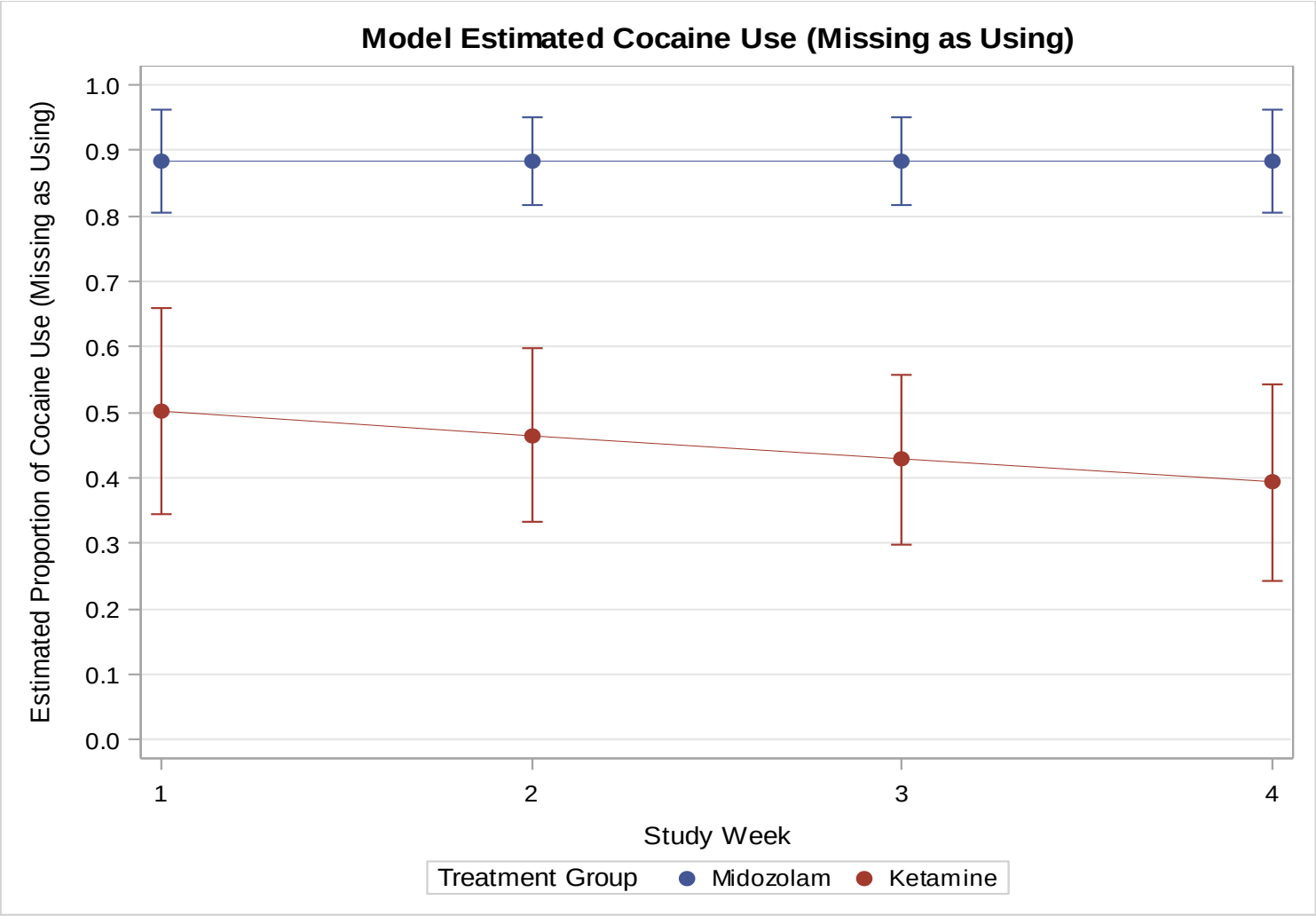
Time to Relapse



Craving Reduction



Likelihood to Use Cocaine



Might ketamine be effective more broadly?

Given the overlap in pathophysiology between different substance use disorders, it is possible that ketamine might be effective more generally.

5-week clinical trial investigating ketamine and motivational interviewing for alcohol dependence

- Ketamine (vs. midazolam) led to a greater proportion of non-drinking days (n=40)
- Similar trajectory as with cocaine users, with early gains maintained throughout the trial

Clinical research, continued

- Clinical trial evaluating the feasibility of ketamine to initiate naltrexone rapidly in opioid use disorder
  - Larger trial (n=100) recently initiated
- Pilot trial investigating ketamine for cannabis use disorder
  - 100% (!) of participants have achieved abstinence thus far (n=6).
- Infusions have been well-tolerated in the >150 individuals who have received it in clinical settings, all of whom with some substance use disorder
  - No emergence of misuse or persistent behavioral toxicity

Conclusions and Future Directions

- Our data suggest that ketamine is effective at disrupting addiction, especially in the context of behavioral treatment, and that it is safe and well-tolerated when administered under controlled conditions

- Our data also suggest that focusing entirely on neural mechanisms is misguided, and that a certain sub-set of psychoactive effects may be critical for behavioral impact

- Future studies can aim to extend these findings of efficacy to more generalizable clinical settings