Beyond the Operating Room

Ketamine, PTSD, and the Veteran Patient

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Parker Neuroscience, LLC · Advancing Clarity. Restoring Lives.

0.75 contact hours | This activity discusses off-label uses of ketamine

Somewhere in our community right now, there is a veteran who has failed two antidepressants, carries a PTSD diagnosis, and is not getting better.

24 years in advanced practice · Emergency medicine · Veteran

Disclosure

Founder and owner, Parker Neuroscience, LLC

Provides IV ketamine and Spravato®. A direct financial interest in interventional psychiatry.

No ineligible company relationships

No pharmaceutical funding, speaking fees, stock, or advisory roles. No commercial support.

Off label use is discussed

Racemic ketamine is FDA approved as an anesthetic. Its psychiatric use is off label.

Treat every speaker on this topic, including me, as someone with a stake.

UPON COMPLETION, PARTICIPANTS WILL BE ABLE TO

Learning Objectives

1. Differentiate the FDA approved anesthetic indication for racemic ketamine from its off label psychiatric use, contrast both with the approved labeling for intranasal esketamine, and describe the factors that guide selection between them.

2. Appraise the current evidence base for ketamine in PTSD, including where findings in veteran and active duty cohorts have diverged from civilian trial results.

3. Describe the evidence supporting reduction of comorbid depressive and anxiety symptoms in patients with PTSD, and explain why this population responds poorly to conventional next step antidepressant strategies.

4. Identify common clinical and public misconceptions about ketamine and describe evidence based responses for patient, family, and colleague conversations.

THE ARGUMENT IN FOUR MOVES

Where this is going

1

Off label is a regulatory status, not an evidence rating

2

PTSD and depressive symptoms can drop substantially and quickly

3

That relief opens a window for trauma focused therapy

4

The real harms follow the delivery model, not the molecule

SECTION 1

What is actually approved

And why off label does not mean unresearched

SECTION 1

Two molecules, two regulatory worlds

Racemic ketamine

(R,S)-ketamine

- FDA approved: anesthesia
- Every psychiatric use is off label
- Schedule III; no REMS

Esketamine (Spravato®)

(S)-ketamine, intranasal

- FDA approved: treatment resistant depression (2019); monotherapy (2025)
- Also: MDD with acute suicidal ideation
- REMS; never sent home

Neither is FDA approved for PTSD. As Myth 1 shows, off label is not the same as unstudied.

SECTION 1

What off label actually changes



Legality

Lawful and routine. Not experimental.

Consent

Name the off label status and the evidence.

Documentation

Chart the indication you are actually treating.

Coverage

Payers follow the label.

MYTH 1

“Off label means it hasn’t been researched.”

Off label is a regulatory status. It is not an evidence rating.

21%

of US office prescriptions are off label

$985M

median cost to bring one drug to market

1970

ketamine approved; long generic, so no sponsor files for depression

The label shows who filed an application. The evidence shows what works.

Radley DC, et al. Arch Intern Med. 2006. | Wouters OJ, et al. JAMA. 2020.

MYTH 1

The FDA's own standard for off label use

> A prescriber has the responsibility to be well informed about the product and to base its use **"on firm scientific rationale and on sound medical evidence."**

U.S. Food and Drug Administration, "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices

That is a standard of evidence, not the absence of one.

SECTION 1 · MYTH 1

You already practice off label medicine

Venlafaxine

Recommended for PTSD by VA/DoD

Not approved for PTSD

Prazosin

Suggested for trauma nightmares

Approved for hypertension

Trazodone

Widely prescribed for insomnia

Approved for depression

Low dose ketamine

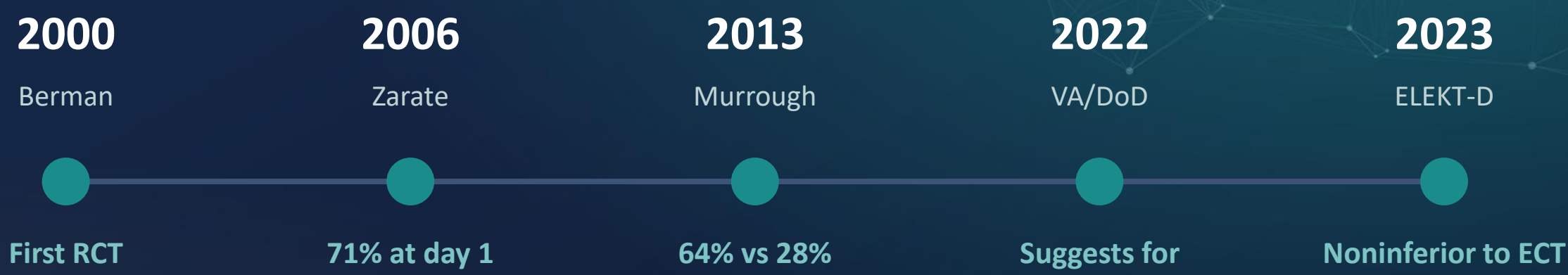
Acute pain consensus guidelines

Approved for anesthesia

If off label meant unresearched, the VA/DoD could not recommend venlafaxine for PTSD.

VA/DoD CPG for PTSD, 2023. | Schwenk ES, et al. Reg Anesth Pain Med. 2018. | Indications per current FDA labeling.

Ketamine for depression: 25 years of controlled trials



Not an evidence gap. A labeling gap.

Berman 2000 | Zarate 2006 | Murrough 2013 (n = 73, midazolam control) | VA/DoD MDD CPG 2022 | Anand, NEJM 2023 (403 randomized)

SECTION 1 · MYTH 1

Same molecule, different stages of evidence

Off label spans the whole evidence spectrum. The label cannot tell you where a use sits.



Unstudied

Well studied

PTSD symptoms: promising

Positive randomized trials; effects are rapid but short lived alone. Veteran data developing.

Resistant depression: established

Multiple RCTs. Noninferior to ECT. VA/DoD guideline: suggests for.

Always ask: what does the evidence show for this indication, in this setting?

SECTION 1

Choosing between routes





Fluctuating blood pressure

Favors IV. An infusion can be paused; an absorbed dose cannot.



Needle phobia

Favors intranasal. Some patients never start IV at all.



Cold and allergy season

Decongestants impede intranasal absorption. Ask first.

No head to head trial shows one route is superior. Assess the patient in front of you.

SECTION 2

Ketamine and PTSD symptoms

What the trials show, and what it means for therapy

SECTION 2

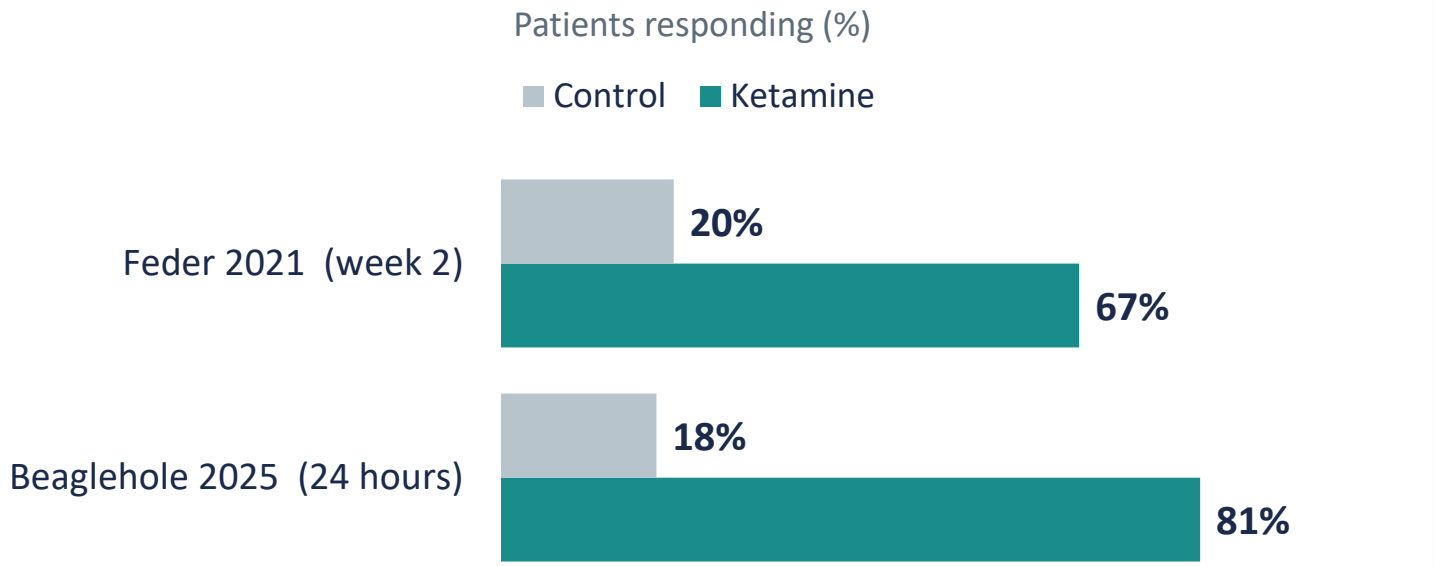
The PTSD evidence at a glance



PTSD symptoms can drop fast. Keeping them down takes more.

SECTION 2

In two controlled trials, most patients responded



Feder 2021

Six IV infusions vs midazolam, n = 30

Beaglehole 2025

IM ketamine vs fentanyl, double blind, n = 33

Relief arrives within days. It lasts weeks, which is why therapy matters.

Feder A, et al. Am J Psychiatry. 2021. | Beaglehole B, et al. BJPsych Open. 2025. | Kwan ATH, et al. CNS Spectr. 2024.

SECTION 2

In veterans, the signal is real and still developing

Albott 2018

Open label, n = 15

Comorbid PTSD and depression. 80% PTSD remission after six infusions.

Artin 2022

VA clinic, n = 35

Intranasal esketamine. PCL-5 and PHQ-9 both fell significantly.

Abdallah 2022

Randomized, n = 158

PTSD scores did not separate from placebo. Depressive symptoms improved rapidly.

A randomized trial of ketamine plus prolonged exposure in veterans is underway.

Albott CS, et al. J Clin Psychiatry. 2018. | Artin H, et al. eClinicalMedicine. 2022. | Abdallah CG, et al. Neuropsychopharmacology. 2022. | Contemp Clin Trials. 2024 (protocol).

SECTION 3

The depression that travels with PTSD

The comorbid burden conventional treatment fails hardest

SECTION 3

A patient you already know

- 41-year-old Army veteran, two combat deployments
- PTSD and major depressive disorder
- Failed an SSRI and an SNRI; stopped trauma-focused therapy
- Not suicidal. Not working. Blames the nightmares.
- Read online that ketamine treats PTSD

What do you tell him?

What do you offer him?

Illustrative composite. Not a real patient.

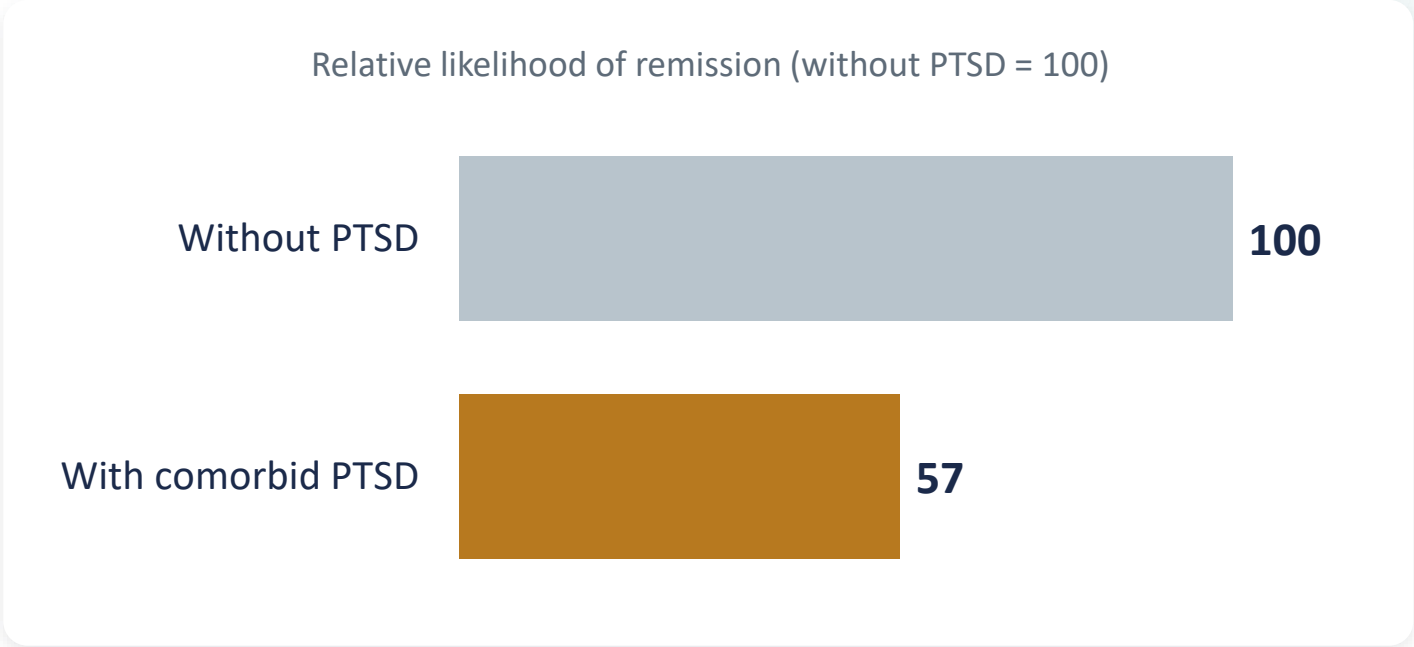
SECTION 3

Comorbid PTSD makes depression harder to treat

43%

lower remission at 12 weeks when PTSD rides along with depression

VAST-D: 1,522 veterans, 35 VA medical centers, three next step strategies



The problem is not which conventional strategy you pick.

Mohamed S, et al. J Clin Psychiatry. VAST-D, NCT01421342. Risk ratios 0.567 (remission) and 0.745 (symptom improvement).

SECTION 3

Anxious depression still responds

Not disqualifying

In a randomized trial of 99 patients, anxious and non-anxious treatment resistant depression responded to ketamine with similar efficacy.

But smaller

Anxiety symptoms improved about half as much as depressive symptoms. Set expectations accordingly.

Baseline anxiety does not appear to disqualify a patient from benefit.

Salloum NC, et al. Depress Anxiety. 2019. | Ionescu DF, et al. J Clin Psychiatry. 2014 (naturalistic, n = 43).

SECTION 4

What the guidelines say

And how to put the evidence to work on Monday



SECTION 4

What the 2023 VA/DoD PTSD guideline says

RECOMMENDED	CPT, EMDR, Prolonged Exposure
RECOMMENDED	Paroxetine, sertraline, venlafaxine*
SUGGESTED	Written Exposure, Present-Centered, and others
SUGGESTED AGAINST	Ketamine as monotherapy (very low quality evidence)
RECOMMENDED AGAINST	Benzodiazepines, cannabis

***Venlafaxine is not FDA approved for PTSD.** The guideline predates the 2025 controlled and combination trials.

VA/DoD CPG for PTSD and ASD, Version 4.0, 2023. Psychotherapy is recommended over pharmacotherapy.

SECTION 4

Two VA/DoD guidelines, one path forward

2022 depression guideline

Suggests for

ketamine or esketamine as augmentation after failed trials

2023 PTSD guideline synopsis

May be considered

for the depression in patients who have both conditions

Treat the depression, track the PTSD symptoms, and bring therapy in while symptoms are lower.

VA/DoD CPG for MDD, 2022 | VA/DoD CPG for PTSD, 2023 | Synopsis: Ann Intern Med. doi:10.7326/M23-2757

SECTION 4

Treat the whole symptom burden

A PTSD diagnosis does not exclude a patient from a treatment resistant depression indication.

Experienced clinicians see it daily: as the depression lifts, PTSD symptoms often ease with it.

Measure both at every visit: PHQ-9 and PCL-5.

SECTION 4

Back to the veteran

1

Relieve the burden

Interventional treatment for his depression, with PTSD symptoms tracked alongside.

2

Re-engage therapy

Bring trauma focused therapy back while his symptoms are lower.

3

Treat the nightmares

Prazosin is suggested for trauma related nightmares.

Relief first. Then the therapy that makes it last.

SECTION 4

Symptom relief opens a window for therapy

Ketamine + prolonged exposure

Veterans, open label, n = 10

Large reductions on CAPS-5 and PCL-5 (d = 1.2 to 1.8). Veterans completed exposure therapy alongside infusions.

Ketamine + written exposure

Chronic PTSD, open label, n = 14

CAPS-5 fell by half (41.6 to 20.8). 69% responded; most kept their gains at six months.

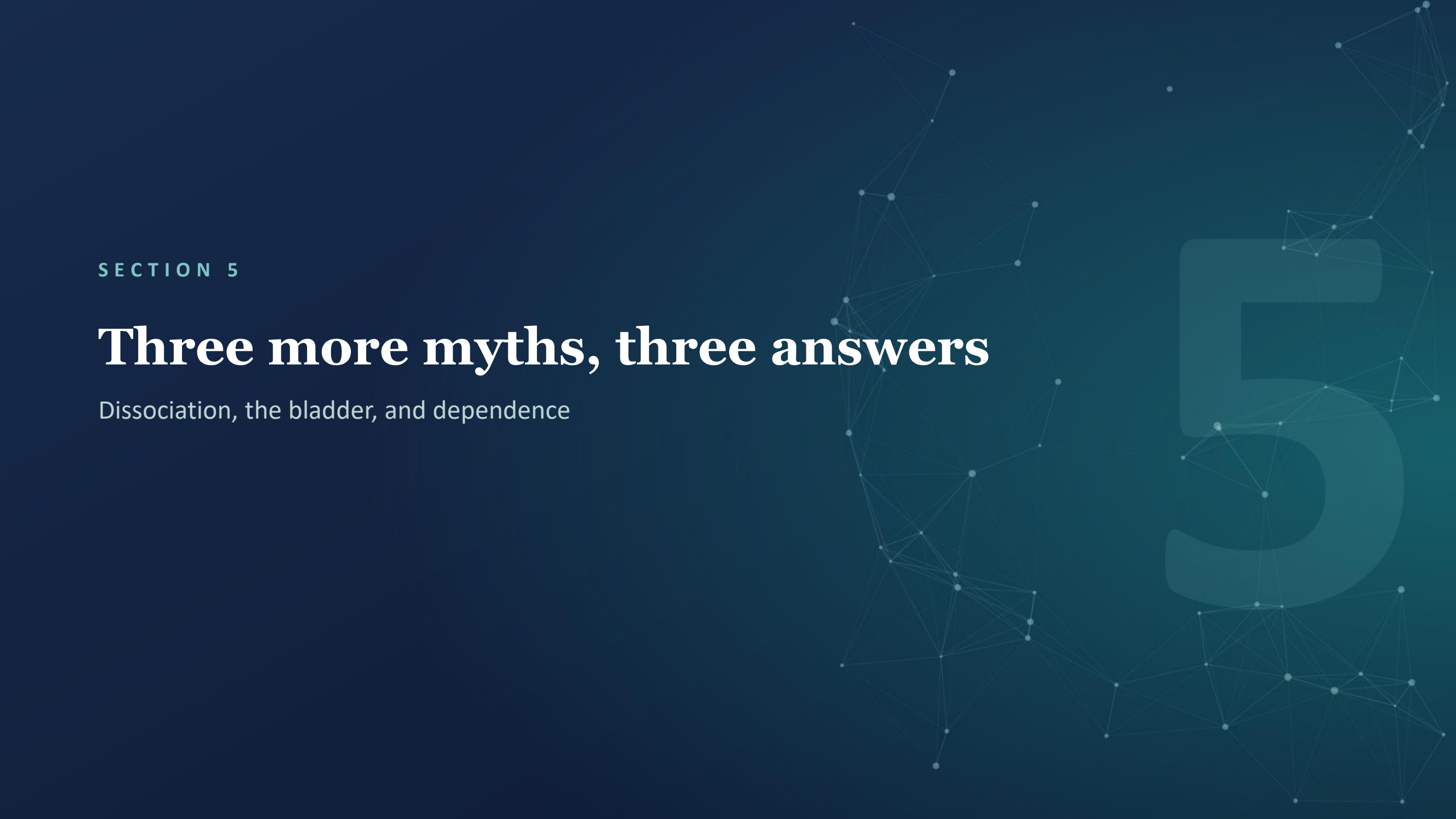
Ketamine lowers the symptom burden. Therapy does the lasting work.

Shiroma PR, et al. J Clin Psychiatry. 2020. | Feder A, et al. J Clin Psychiatry. 2025. | Price RB, et al. Am J Psychiatry. 2022 (depression).

SECTION 5

Three more myths, three answers

Dissociation, the bladder, and dependence



MYTH 2

They gave ketamine under general anesthesia.

Nobody felt a thing. Both groups improved anyway.

40

surgical patients with depression, ketamine or saline under anesthesia

36.8%

guessed their assignment correctly. The masking held

60% / 50%

day 1 response, ketamine vs placebo

Dissociation is a side effect to monitor, not a marker of response.

Lii TR, et al. Nat Ment Health. 2023 (n = 40, single dose). | Ballard ED, Zarate CA. Nat Commun. 2020.

MYTH 3

The bladder question

Recreational use

44–77%

with urinary symptoms, after about five years of use

Therapeutic use

0–24%

across 27 studies; little difference from comparison arms in RCTs

Absent signal is not established safety. Oral dosing carries the highest metabolite load.

Hydrate on treatment days, void hourly, ask about symptoms, check urine.

Andrade C. J Clin Psychiatry. 2025. | Kerr-Gaffney J, et al. J Psychopharmacol. 2025.

MYTH 4

Abuse liability follows the delivery model

Under supervision

0.3%

of sessions in one supervised clinic series involved misuse. Low abuse liability across 30 studies.

Take-home dosing

~10%

took more than prescribed. Dependence cases cluster in unsupervised access.

Supervision lowers risk. It does not eliminate it.

Wanting more of a treatment that worked is not drug seeking.

Vasudeva S, et al. J Psychopharmacol. 2026. Thirty studies, searched through August 2025.

The harm does not concentrate in the drug.
It concentrates in the delivery model.

Bladder

Oral dosing: highest metabolite exposure

Dependence

Nearly every case involves unsupervised access

Monitoring

Exists only where a clinician is present

FOR ADMINISTRATORS, REFERRAL STAFF, AND CLINICIANS

Ten questions to ask any ketamine program

1. Psychiatric prescriber evaluates first?
2. Validated measures at every visit?
3. Prescriber on site for every dose?
4. Blood pressure and oxygen monitored?
5. **Nothing ever sent home?**
6. A real emergency plan?
7. Coordinates with the care team?
8. Defined course and stopping rule?
9. Therapy built in or encouraged?
10. Shares records and outcomes?

If you ask only one: "What happens when a patient gets worse?"

FDA alert on compounded ketamine, Oct 10, 2023. | ASKP3 IV ketamine consensus guidelines, 2026.

PRACTICAL TAKEAWAYS

What to carry back

1. Off label is a regulatory status, not an evidence rating.
2. PTSD symptoms can drop within days. Lasting gains need therapy alongside.
3. Comorbid PTSD cuts conventional remission by about 43%.
4. Relief opens a window. Pair ketamine with trauma focused therapy.
5. Veteran data are promising and still developing. Measure PCL-5 and PHQ-9.
6. Dissociation is a side effect. Screen the bladder.
7. Harm follows the delivery model. Vet the program.

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Questions

Dr. Lisa Parker, DNP, APRN, NP · Parker Neuroscience, LLC

Route selection framing: NEI PsychopharmaPearls, episode 276, “Choosing Ketamine Treatment,” Andrew J. Cutler, MD and Lisa Harding, MD, February 2026.

VA/DoD guidelines: healthquality.va.gov · National Center for PTSD: ptsd.va.gov