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Psychiatry and Addictions Case Conference

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BEYOND "WAIT FOR WITHDRAWAL"

Ketamine-assisted and next-generation buprenorphine starts in the fentanyl era

DAVID VEITH, MD

ATTENDING, ACUTE CARE SERVICE, SEATTLE VA

ACTING ASSISTANT PROFESSOR, UNIVERSITY OF WASHINGTON DEPT OF PSYCHIATRY AND BEHAVIORAL SCIENCES

UW Medicine
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UW Psychiatry & Behavioral Sciences

project ECHO

SPEAKER DISCLOSURES

- ✓ No financial relationships
- ✓ Off-label: ketamine for opioid withdrawal
- ✓ Buprenorphine doses differing from approved FDA induction protocols
- ✓ Ketamine data are observational; nothing here is a standard of care yet

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

Mark Duncan MD
Rick Ries MD
Kari Stephens PhD
Barb McCann PhD
Anna Ratzliff MD PhD
Betsy Payn MA PMP
Esther Solano
Cara Towle MSN RN

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OBJECTIVES

By the end of this talk you should be able to:

1. Explain why fentanyl makes the traditional buprenorphine start unreliable
2. Compare overlapping, withdrawal-based and long-acting injectable starts
3. Describe the mechanism, protocols and evidence for ketamine-assisted starts
4. Choose a start strategy for a given patient and setting

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01

MEET MR. R

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MR. R, 41, ARMY VETERAN ADMITTED WITH CELLULITIS

Army veteran, two deployments

Chronic low back pain after an IED blast; PTSD

Prescribed oxycodone → heroin → fentanyl

Now smoking about 1 g of fentanyl a day

Admitted to medicine for cellulitis

Addiction psychiatry consulted on hospital day 1

Wants treatment for his opioid use

…but has a history with buprenorphine

> *"I'm never touching Suboxone again.*
>
> Mr. R, on admission

Composite teaching case.

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TWO YEARS AGO: HIS FIRST BUPRENORPHINE START

1

Day 0

Last fentanyl use

2

18 hours later

Feeling sick; takes buprenorphine 4 mg SL at a community clinic

3

+40 minutes

Drenching sweats, vomiting, cramping, agitation: worse than any withdrawal he'd had

4

Same day

Leaves, uses fentanyl to feel normal, never goes back

?

What happened? Why did 18 hours of waiting fail him?

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WHICH METHOD WOULD YOU OFFER MR. R?

A

Traditional start

Wait for COWS ≥ 8, then 2–4 mg SL

B

Overlapping start
Aka low-dose

Small, rising doses while he keeps getting opioids

C

Large-dose induction

Wait for COWS>12, then 16–32 mg on day 1

D

Ketamine-assisted start

Low-dose ketamine before buprenorphine

E

Long-acting injectable first

Get an injection on board before discharge

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02

WHY THE OLD PLAYBOOK FAILS: UNIQUE CHALLENGES IN THE AGE OF FENTANYL

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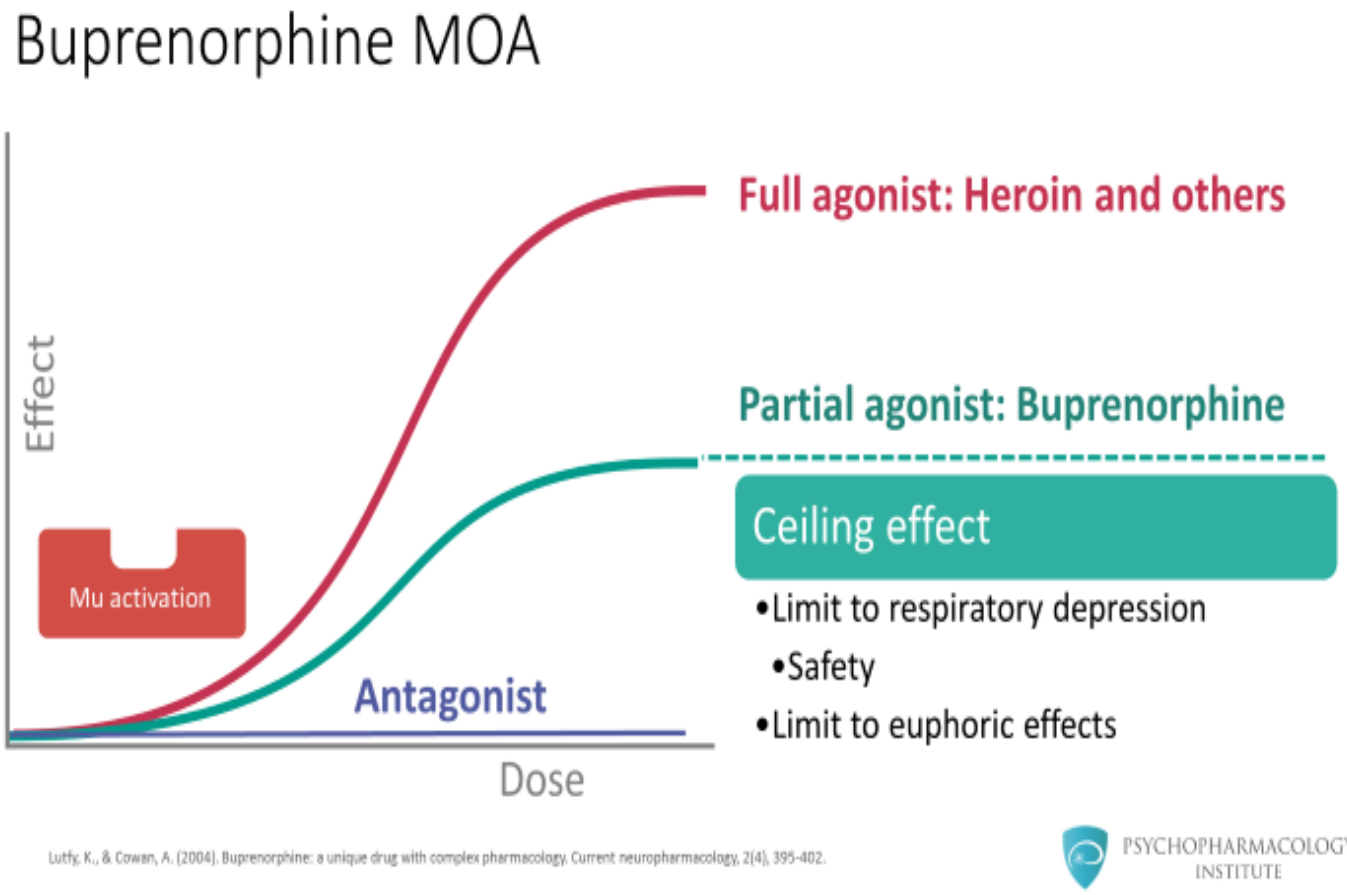
BUPRENORPHINE



Lutfy, K., & Cowan, A. (2004). Buprenorphine: a unique drug with complex pharmacology. Current neuropharmacology, 2(4), 395-402.

PSYCHOPHARMACOLOGY INSTITUTE

High affinity

Buprenorphine binds the mu receptor more tightly than fentanyl, heroin or morphine, so it pushes them off.

Partial agonist

It has a ceiling on effect, including a ceiling on respiratory depression.

Displacement plus a lower ceiling

Opioid effect falls abruptly from the full-agonist curve to the buprenorphine curve. That drop is precipitated withdrawal.

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FENTANYL: UNPREDICTABLY ALTERS THE “DANGER WINDOW”

12 hours

Traditional wait after short-acting opioids like heroin

48+ hours

Reports of precipitated withdrawal this long after last fentanyl use

5+ days

Spontaneous fentanyl withdrawal can still be severe

Fentanyl is lipophilic and accumulates in adipose tissue
From here it leaks out for days, so hours since last use and COWS score predict precipitated withdrawal poorly.

Two names used for the rest of this talk

Overlapping start

(“low-dose” or “micro”) Start buprenorphine while full agonists continue; no withdrawal needed

Withdrawal-based start

(“high-dose” or “macro”) Wait for withdrawal, then load buprenorphine quickly

Varshneya et al. J Addict Med 2022; Sharma et al. J Addict Med 2025; Greenwald et al. Ann Emerg Med 2022.

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03

THE ESTABLISHED FIXES

Overlapping and withdrawal-based starts

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OVERLAPPING STARTS: NO WITHDRAWAL REQUIRED (1 OF 3)

Day	Buprenorphine SL	Full agonist
1	0.5 mg once	Continue
2	0.5 mg twice	Continue
3	1 mg twice	Continue
4	2 mg twice	Continue
5	4 mg twice	Continue
6	8 mg + 4 mg	Continue
7	12–16 mg	**Stop**

Illustrative schedule. Buccal, transdermal patch and IV variants exist.

Best fit

- Inpatients already on full agonists
- Patients on methadone
- Patients who can't or won't tolerate withdrawal

Where it goes wrong

- Full agonist stopped or cut back too early
- Discharge in the middle of the schedule
- Small-dose logistics
- A week of ongoing fentanyl exposure outpatient

Hämmig et al. Subst Abuse Rehabil 2016 (Bernese method); Weimer et al. ASAM Clinical Considerations, J Addict Med 2023; Suen et al. JAMA Netw Open 2025.

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OVERLAPPING STARTS: NO WITHDRAWAL REQUIRED (2 OF 3)

Day	Bup
1	0.5
2	0.5
3	1 m
4	2 m
5	4 m
6	8 m
7	12–

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Illustrative schedule

Hämmig et al. Subst Abuse Rehabil 2016 (Bernese method); Weimer et al. ASAM Clinical Considerations, J Addict Med 2023; Suen et al. JAMA Netw Open 2025.

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OVERLAPPING STARTS: NO WITHDRAWAL REQUIRED (3 OF 3)

Day	Buprenorphi
1	0.5 mg once
2	0.5 mg twice
3	1 mg twice
4	2 mg twice
5	4 mg twice
6	8 mg + 4 mg
7	12–16 mg

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WITHDRAWAL-BASED STARTS

1. **Confirm moderate withdrawal (COWS ≥ 12)**
2. **Buprenorphine >16 mg SL**
3. **Reassess in 30–60 min; give 8 mg**
4. **Target 16–32 mg on day 1**

Herring et al., Highland Hospital ED (579 encounters)

0
Cases of respiratory depression or oversedation

0.8%
Precipitated withdrawal; not related to dose

138
Doses of 28 mg or more

2.4 h
Median ED length of stay

Precipitated withdrawal? The fix is usually more buprenorphine, not less.
The catch: the patient has to sit through **moderate withdrawal first**.

Herring AA et al. JAMA Netw Open 2021;4(7):e2117128.

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04

KETAMINE-ASSISTED STARTS

The promise of ketamine: Treat the withdrawal instead of waiting it out or avoiding it

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WHY KETAMINE? THREE MECHANISMS

NMDA antagonism

In animal models, NMDA blockade rapidly reverses the CNS adaptations behind opioid tolerance, dependence and withdrawal.

Mu-receptor resensitization

Restores receptors desensitized by fentanyl and boosts endogenous opioid signaling. Both papers call it a “proxy opioid agonist.”

Timing that matches

IM ketamine peaks in 15–30 min, half-life 2–3 h. Precipitated withdrawal peaks within 60 min in about 90% of people.

No respiratory depression outside anesthetic dosing. Schedule III: misuse and diversion still need a plan.

Engeriser et al. Addict Sci Clin Pract 2026; Grande et al. Addict Sci Clin Pract 2024; Dunn et al. Front Psychiatry 2023.

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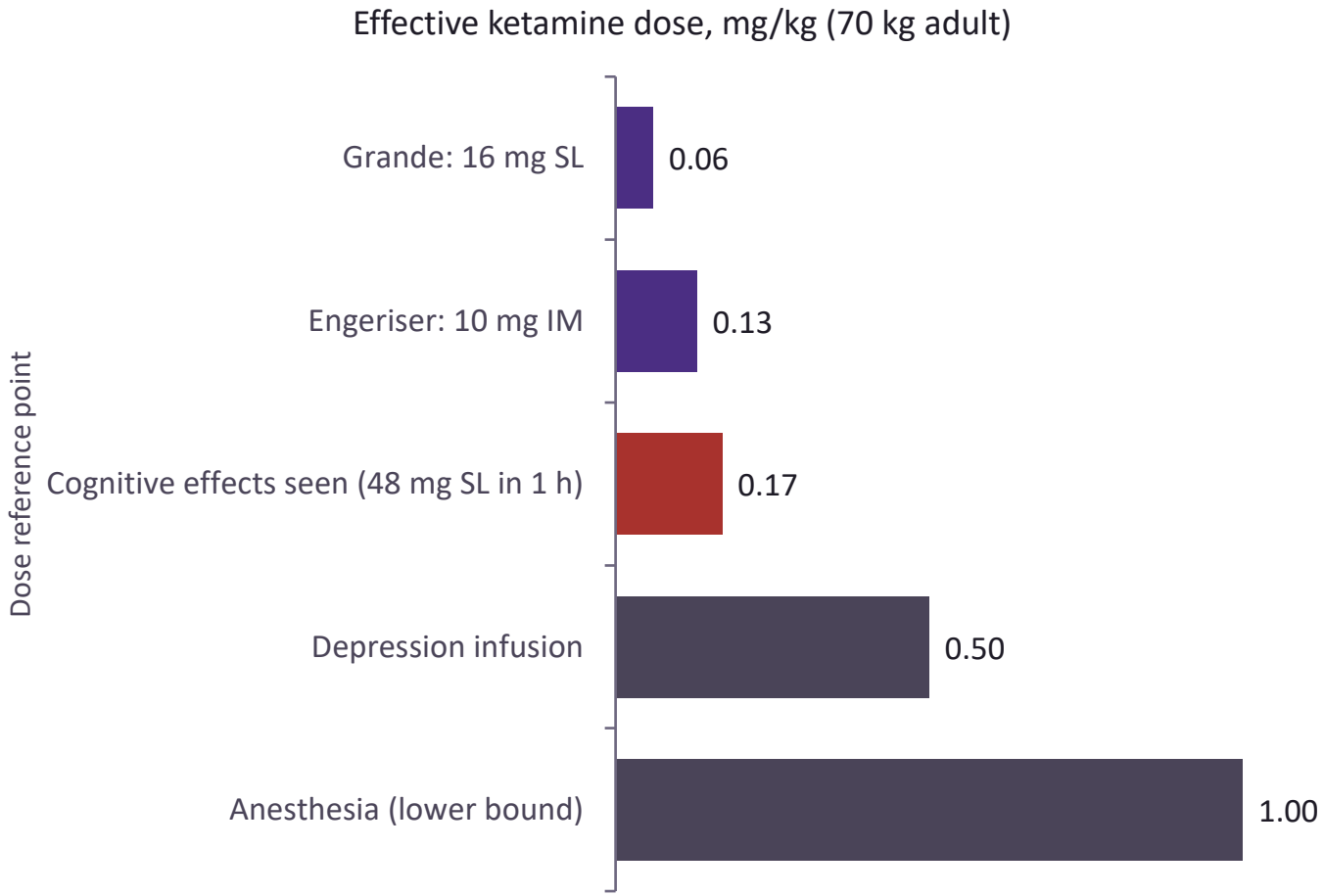
HOW LOW IS “LOW-DOSE” KETAMINE?



Both protocols sit far below the doses people associate with ketamine

- Grande 16 mg SL ≈ 3–6% of an anesthetic dose (SL bioavailability ~25%)
- Engeriser 10 mg IM ≈ 0.13 mg/kg (IM bioavailability ~93%)
- Perceptual changes appeared only at 48 mg within 1 hour, so Grande caps outpatient use at 16 mg TID, ≥ 3 h apart

Doses as reported in Grande et al. 2024 and Engeriser et al. 2026. Anesthesia 1–2 mg/kg; depression infusion 0.5 mg/kg.

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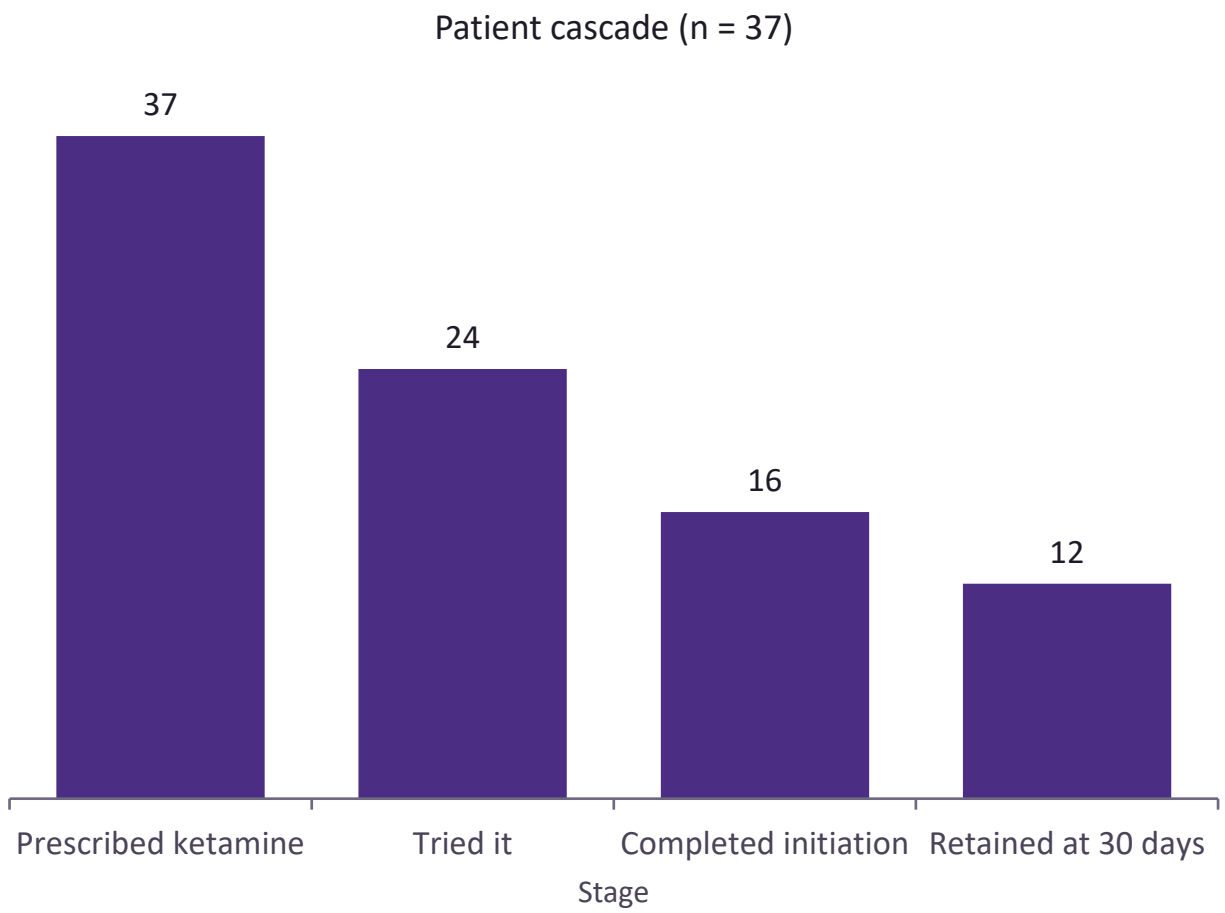
GRANDE 2024: OUTPATIENT SL KETAMINE BRIDGE



Washington State OTP and OBOT clinics, May 2022–July 2023

50% → 75%

Completion among those who tried ketamine, earlier vs. later patients as the protocol was refined

11 of 12

Later-group completers retained at 30 days

Completion = tolerating ≥ 8 mg in 24 h without worsening withdrawal.

Grande LA et al. Ketamine-assisted buprenorphine initiation: a pilot case series. Addict Sci Clin Pract 2024;19:60.

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GRANDE: THE 4-DAY PROTOCOL

Days 1–2

Stop fentanyl

Ketamine 16 mg SL as needed for withdrawal, 1–3 doses/day

→

Day 3

First buprenorphine

Ketamine 8–16 mg, then buprenorphine 2 mg; every 3 h × 4

→

Day 4

Build

Buprenorphine 4 mg every 3 h × 4; ketamine 8–16 mg premed optional

→

Day 5+

Consolidate

Buprenorphine 8 mg, repeat as needed up to 32 mg

Clonazepam 1 mg every morning, days 1–4. Given to every patient after some “precipitated withdrawal” turned out to be panic.

Grande et al. 2024, Table 4: allowed the final 4 patients to complete initiation with only mild withdrawal.

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GRANDE: FIVE LESSONS FROM REFINING THE PROTOCOL

1	**Premedicate, don't just rescue**	Ketamine before each buprenorphine dose worked better than ketamine after symptoms started.
2	**Keep it short**	A 10-day low-dose schedule lost patients to fading motivation and continued overdose risk.
3	**Stop fentanyl, bridge with ketamine**	Ongoing fentanyl use kept patients feeling “icky” and obscured whether the start was working.
4	**Treat the panic**	Abrupt distress after a dose was often panic, not withdrawal; clonazepam helped.
5	**Wait ≥ 48 h for buprenorphine**	Starting within 24 h of fentanyl, even with ketamine, caused severe withdrawal in two patients.

Grande et al. 2024, Treatment strategy evolution.

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GRANDE: SAFETY GUARDRAILS AND CAVEATS

Safety guardrails

- Cap at 8 doses (128 mg), below a typical recreational amount if taken at once
- Only side effect: about 45 min of perceptual change after 48 mg in 1 h (2 patients)
- Exclusions: age > 60, active cardiac disease, uncontrolled bipolar or psychotic disorder

Caveats

- 35% of patients had no outcome data
- One prescriber; no standardized withdrawal measure
- Compounded troches ($12–25 per course) are hard to get quickly
- First author is an educational consultant to a compounding pharmacy

Grande et al. 2024.

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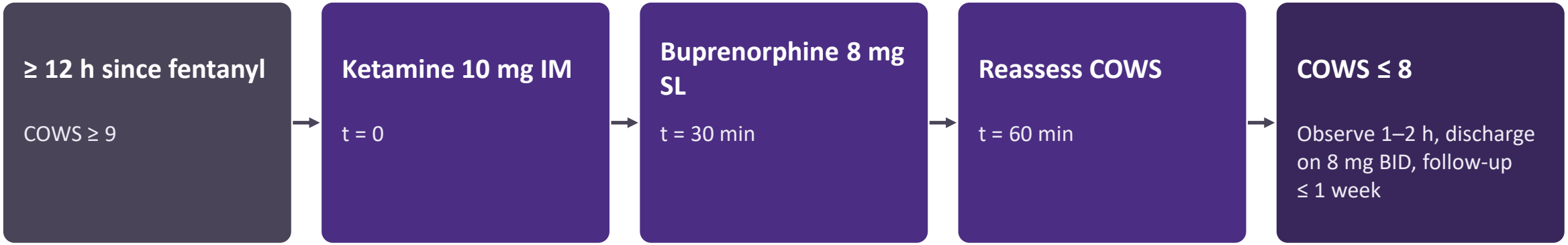
ENGERISER 2026: ONE IM DOSE, THEN A HIGH-DOSE START

AltaPointe 24-hour crisis center, Mobile, AL · 50 patients, June 2023–July 2024
Include: fentanyl within 24 h, COWS ≥ 9, wants buprenorphine. Exclude: active psychosis, severe cardiovascular disease.



Still COWS ≥ 9 at 60 min? More buprenorphine 8 mg, more ketamine (about 15 mg on average) or comfort meds. 7 of 50 needed extra medication.

Engeriser JL et al. Buprenorphine initiation from fentanyl using low-dose intramuscular ketamine: a pilot study. Addict Sci Clin Pract 2026;21:23.

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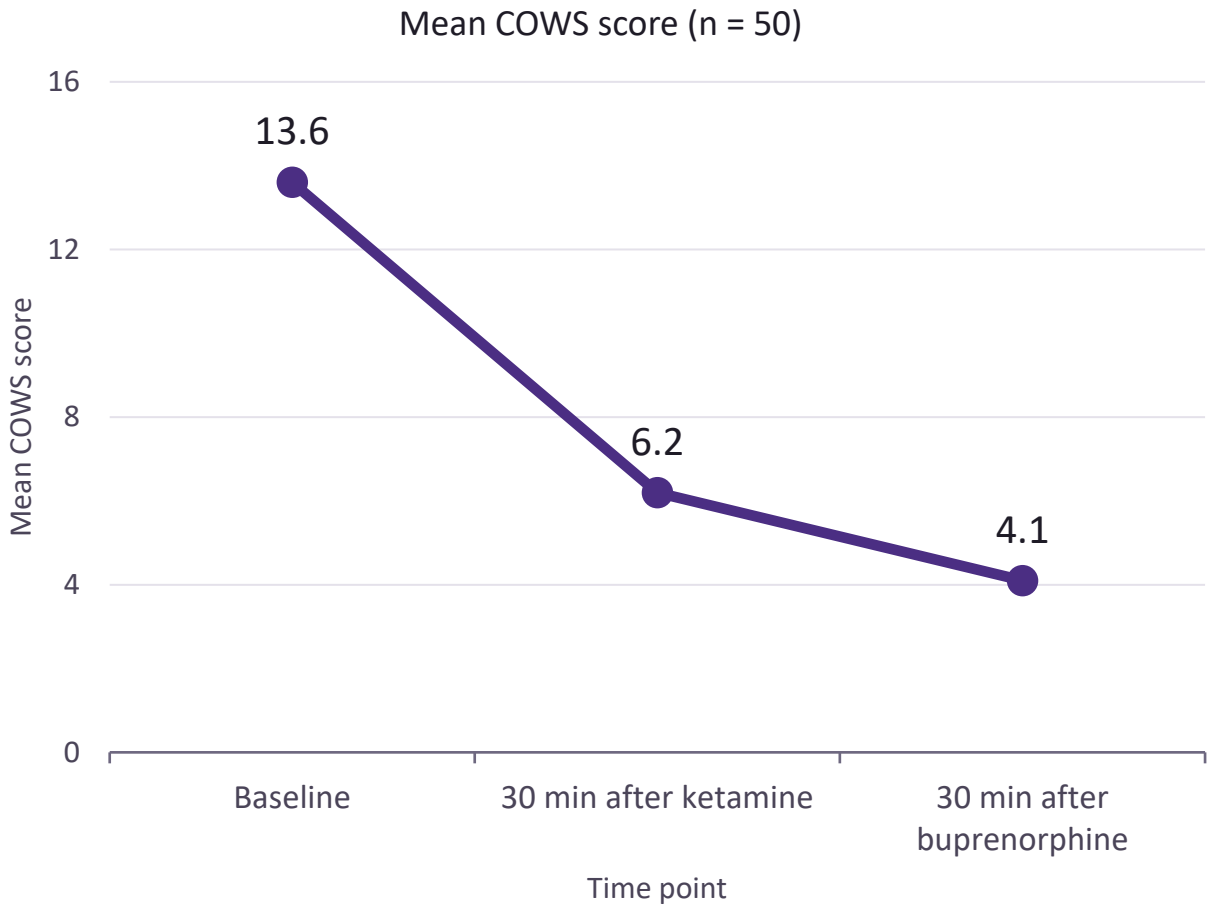
ENGERISER: WITHDRAWAL FELL BEFORE BUPRENORPHINE WAS GIVEN



54%

COWS 0–3 within 1 hour

66 → 7 h

Median length of stay

100%

Filled a buprenorphine prescription within 30 days

52%

Attended a follow-up visit within 30 days

$0.44 per dose. No patient reported an adverse effect of ketamine. 2 met criteria for precipitated withdrawal; 3 stayed overnight.

Engeriser et al. 2026. Effect sizes d = −1.91 (after ketamine) and −2.36 (after buprenorphine); both p < 0.001.

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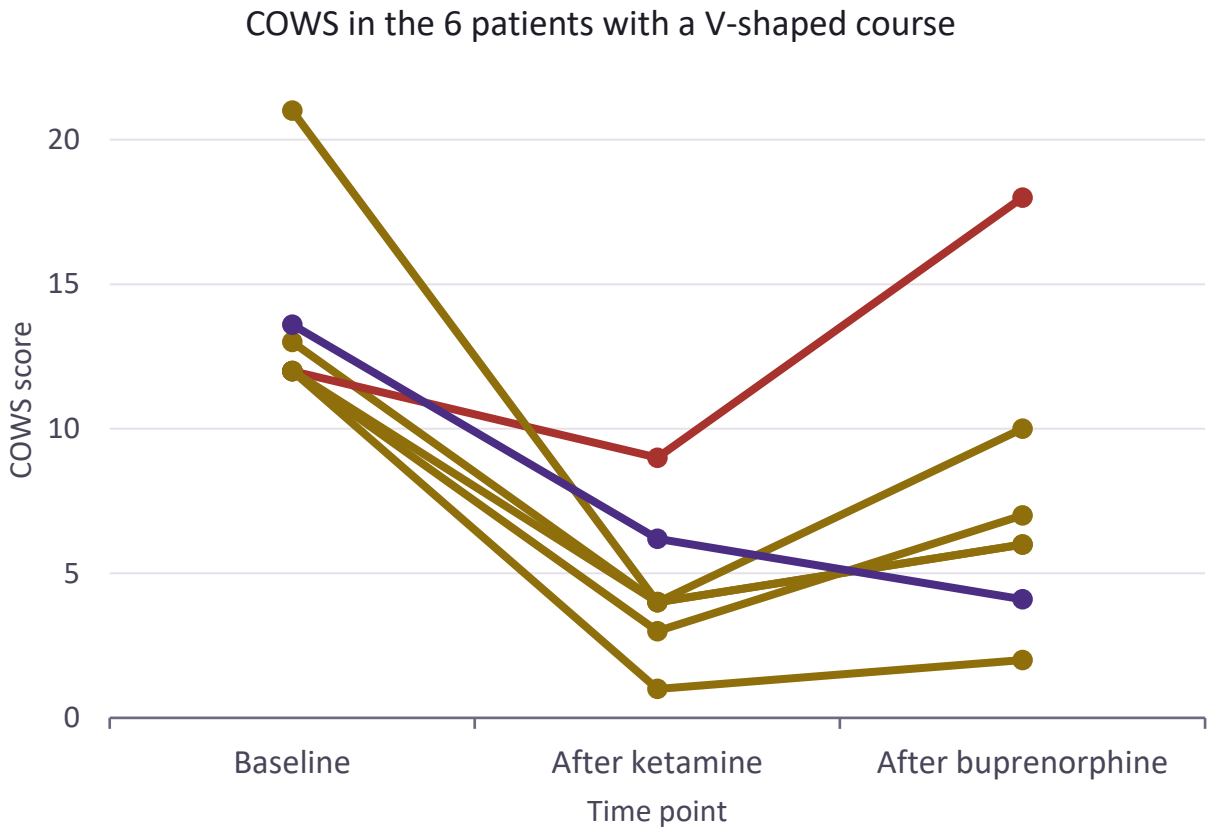
V-SHAPED RECOVERY: RELIEF, THEN A BRIEF REBOUND



Purple: cohort mean **Gold:** V-shaped patients **Red:** only patient above baseline

- 6 of 50 patients improved after ketamine, then worsened after buprenorphine
- They had the steepest ketamine response (77% drop vs. 54% overall)
- 5 of 6 still ended below baseline

What to do

- Warn the patient and nurse it may happen
- Give more buprenorphine (8 -16mg)
- Add ketamine or comfort meds if needed
- Continue the course!

Engeriser et al. 2026, Table 2 and Figure 2C (patients #3, 7, 12, 23, 32, 41).

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ENGERISER: SAFETY TIP AND CAVEATS

Prevent a dosing error

10 mg/mL

Use only the lowest-concentration vial

1 mL

Draw up in an insulin-size syringe

A 50 or 100 mg/mL vial makes an accidental dissociative or anesthetic dose possible with a small volume error.

Caveats

- Single-site QI project; unblinded; no concurrent control (all patients accepted ketamine)
- Length-of-stay comparison is a historical convenience sample
- Blood pressure not measured at set time points
- COWS not tracked beyond 60 minutes
- Fentanyl use self-reported for the first 20 patients
- Dissociation may have gone unreported

Engeriser et al. 2026, Discussion and Limitations.

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05

LONG-ACTING INJECTABLE PATHWAYS

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THREE WAYS TO GET AN INJECTION ON BOARD FAST

FDA-labeled rapid start

- Sublocade (2025 label): 4 mg TM buprenorphine, observe 1 h, then inject (300mg)
    - Trial, n = 729: retained at 2nd injection 66.4% vs. 54.5% with ≥ 7-day standard start
- Brixadi: 4 mg TM test dose, then 16 mg weekly; extra 8 mg within 3 days

Withdrawal-based direct-to-inject

- Weekly 24 mg injection with no SL buprenorphine first (ED trial)
- Precipitated withdrawal 3.2% at COWS 4–7
- 13.5% at COWS 0–3: some withdrawal still matters

Injectable-only overlapping

- Escalating weekly injections while fentanyl use continues
- No withdrawal and no SL doses needed
- Seattle protocol: next slide

Sublocade and Brixadi prescribing information; D'Onofrio et al. JAMA Netw Open 2024;7(7):e2420702.

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WATERS 2025: INJECTABLE-ONLY OVERLAPPING START

1

Day 1 *No SL buprenorphine first*

Brixadi 8 mg weekly

2

Day 2

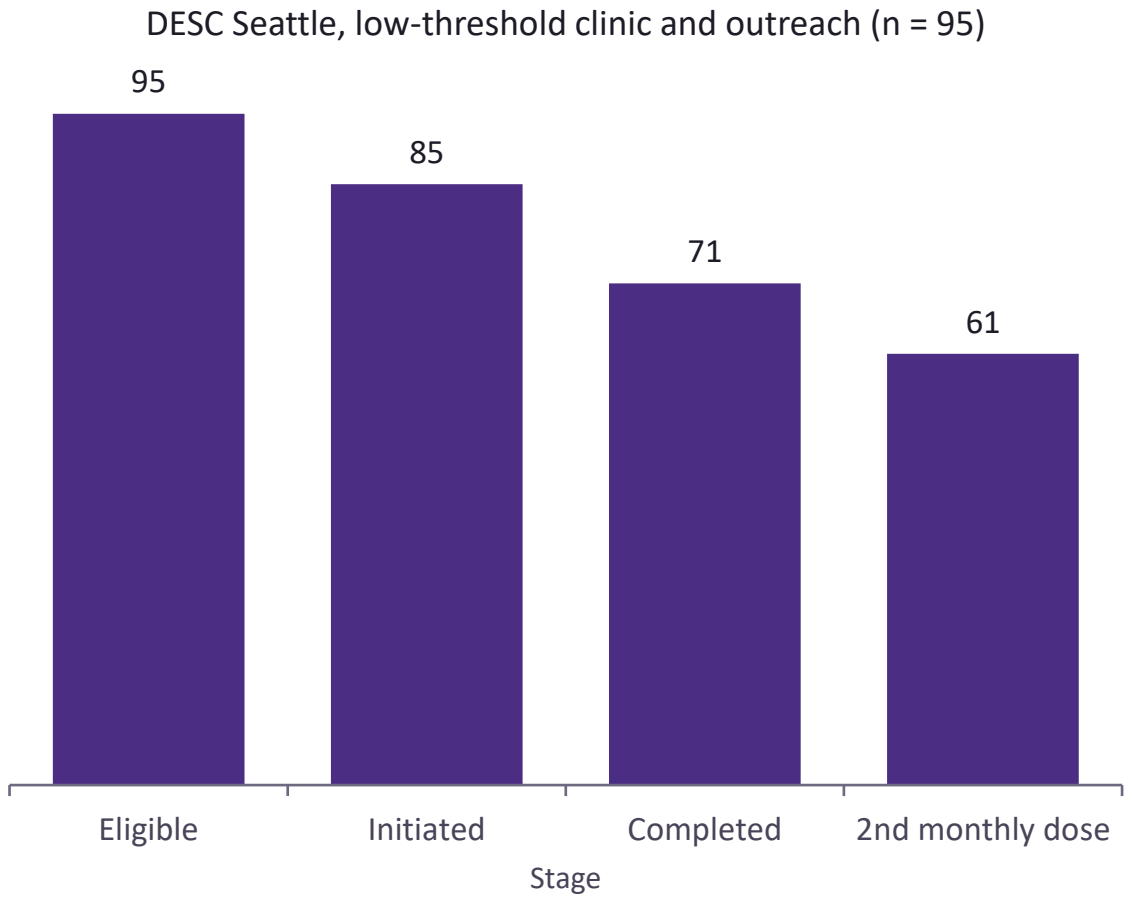
Brixadi 16 mg weekly

3

Day 3 *Sublocade 300 mg or Brixadi 128 mg*

Monthly injection

Fentanyl use continues throughout. Clonidine, hydroxyzine and ondansetron offered; SL buprenorphine PRN from 24 h after the monthly dose.



Waters RC et al. Injectable-only overlapping buprenorphine starting protocol in a low-threshold setting. JAMA Netw Open 2025;8(8):e2527016.

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06

PUTTING IT TOGETHER

Matching the start to the patient and the setting

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CHOOSING A START

Moderate withdrawal now, in an acute setting	**Withdrawal-based start, ± ketamine 10 mg IM first**
Prior precipitated withdrawal or high fear	**Ketamine-assisted start, or overlapping**
On full agonists or methadone; can't tolerate withdrawal	**Overlapping start**
Declines SL, uncertain follow up, cannot abstain from fentanyl	**Injectable only overlapping start**

**Patient preference is paramount.*

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MR. R: HOW IT WENT

1	**Hospital day 2**	About 18 h since fentanyl; COWS 12. Agrees to try ketamine after hearing the plan.
2	**t = 0**	Ketamine 10 mg IM. COWS 5 at 30 min: “first time I've felt normal in a day.”
3	**t = 30 min**	Buprenorphine 16 mg SL. COWS rises to 9: the V. Extra 8 mg bupe given. Diazepam for anxiety.
4	**Day 1 total**	24 mg. Comfortable by evening. COWS =2.
5	**Before discharge**	Long-acting injectable; VA SUD clinic within 1 week.

Re-poll

How would you start Mr. R now? Did your answer change?

Discussion: would an overlapping start have been just as good here?

Composite teaching case; course illustrative.

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TAKE-HOME POINTS

1	**Fentanyl changed the pharmacology**	So the start has to change with it. Time since last use is no longer as predictive.
2	**Precipitated withdrawal is treatable**	When in doubt, give more buprenorphine.
3	**Low-dose IM ketamine is the most promising new adjunct**	Cheap, fast and simple, but evidence is still just observational.
4	**Long-acting injectables: more flexibility than initially thought!**	Consider 3 injection overlap for patients who struggle abstaining or with adherence.
5	**Match the start to the patient**	Setting, current withdrawal symptoms, prior experience, and preference.

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Sublocade (buprenorphine extended-release) and Brixadi (buprenorphine) prescribing information, current labels.

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THANK YOU!

Questions?

David Veith, MD · Seattle VA

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