Sustained-Release of a Novel Therapy for Treating Opioid Use Disorder (OUD)

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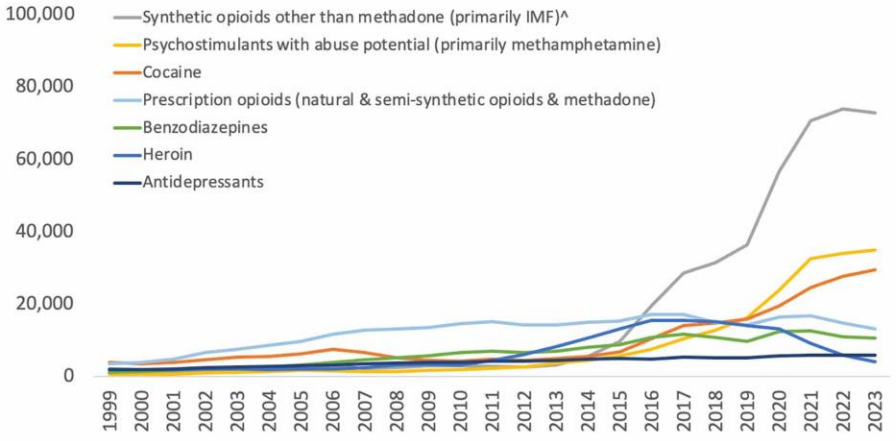
NEXT-GENERATION DELIVERY INNOVATIONS

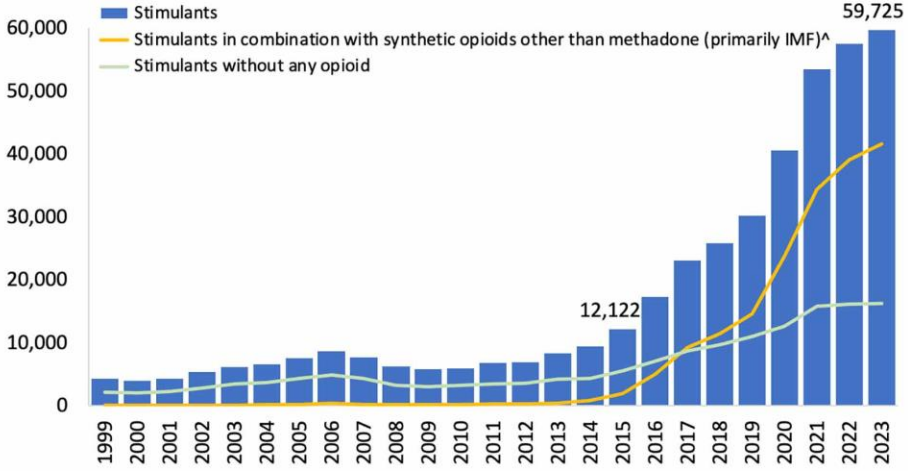
Why should we care about expanding OUD treatment?

Figure 2. U.S. Overdose Deaths*, Select Drugs or Drug Categories, 1999-2023



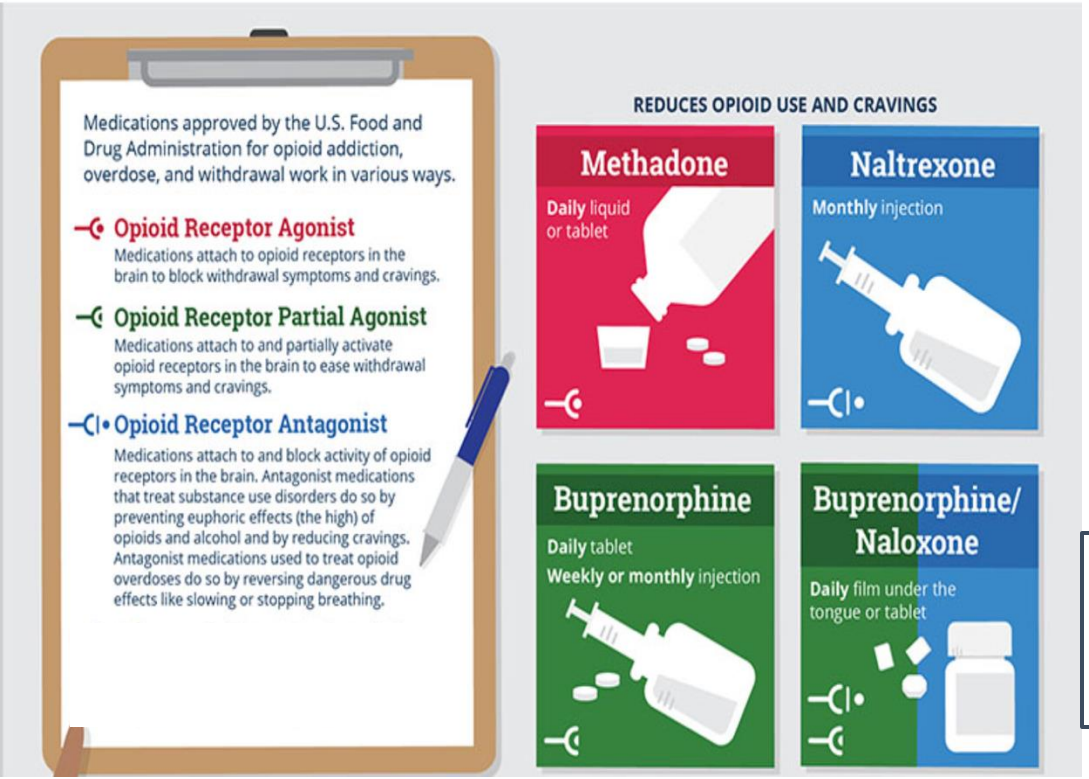
*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. ^Illicitly manufactured fentanyl. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2023 on CDC WONDER Online Database, released 1/2025.

Figure 6. U.S. Overdose Deaths Involving Stimulants (Cocaine or Psychostimulants with Abuse Potential), 1999-2023



*Among deaths with drug overdose as the underlying cause, the stimulants category included cocaine and psychostimulants with abuse potential (primarily methamphetamine) determined by the T40.5 and the T43.6 ICD-10 multiple cause-of-death codes, respectively. ^Illicitly manufactured fentanyl. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2023 on CDC WONDER Online Database, released 1/2025.

Current OUD Treatment



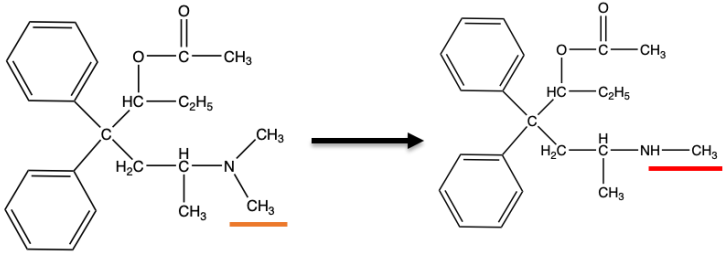
Treatment Limitations

- Frequent clinic visits
- Treatment retention
- Side effects due to regular administration
- Inadequate alleviation of withdrawal symptoms

Our research aims to address the unmet therapeutic needs in the treatment of opioid use disorder.

Potential Novel Therapy: nor-Levo-α-acetylmethadol (nor-LAAM)

N-demethylation of LAAM by CYP450 3A4



LAAM Nor-LAAM

Monkey brain amygdala tissue (Walczac et al., 1981)

Drug	K_i (nM)	IC_{50} (nM)
LAAM	740	100,000
Nor-LAAM	5.6	1.2
Dinor-LAAM	1140	800

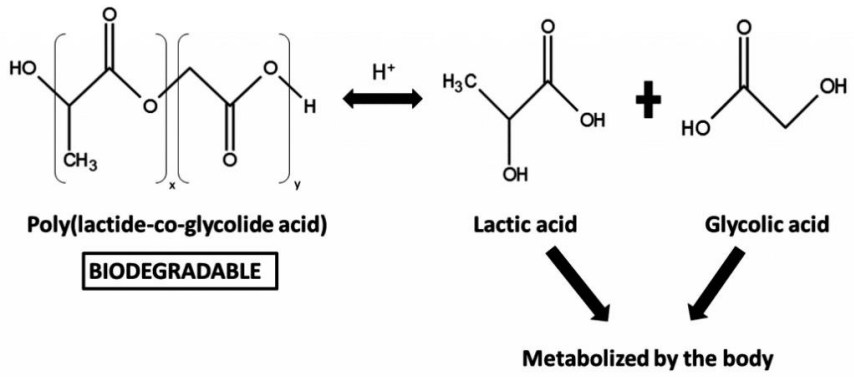
Rat brain homogenates (David A L Newcombe,2006, pg.296)

Drug	K_i (nM)	IC_{50} (nM)
LAAM	5.61	19.65
Nor-LAAM	0.19	0.67
Dinor-LAAM	0.64	2.29
Methadone	1.41	4.94

- **In different binding assays, Nor-LAAM was found to be more potent on mu-opioid receptors than LAAM and Methadone.**

Sustained Drug Delivery for OUD

- **Injectable polymeric microparticles**, High drug loading, sustained drug release for ≥ 1 months, biodegradable, biocompatible, and safe.



Cochrane Database of Systematic reviews | Review - Intervention

New search

Sustained-release naltrexone for opioid dependence

Hege Kornør, Philipp Paul K Lobmaier, Nikolaj Kunøe Authors' declarations of interest

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Sustained-Release Buprenorphine (RBP-6000) Blocks the Effects of Opioid Challenge With Hydromorphone in Subjects With Opioid Use Disorder

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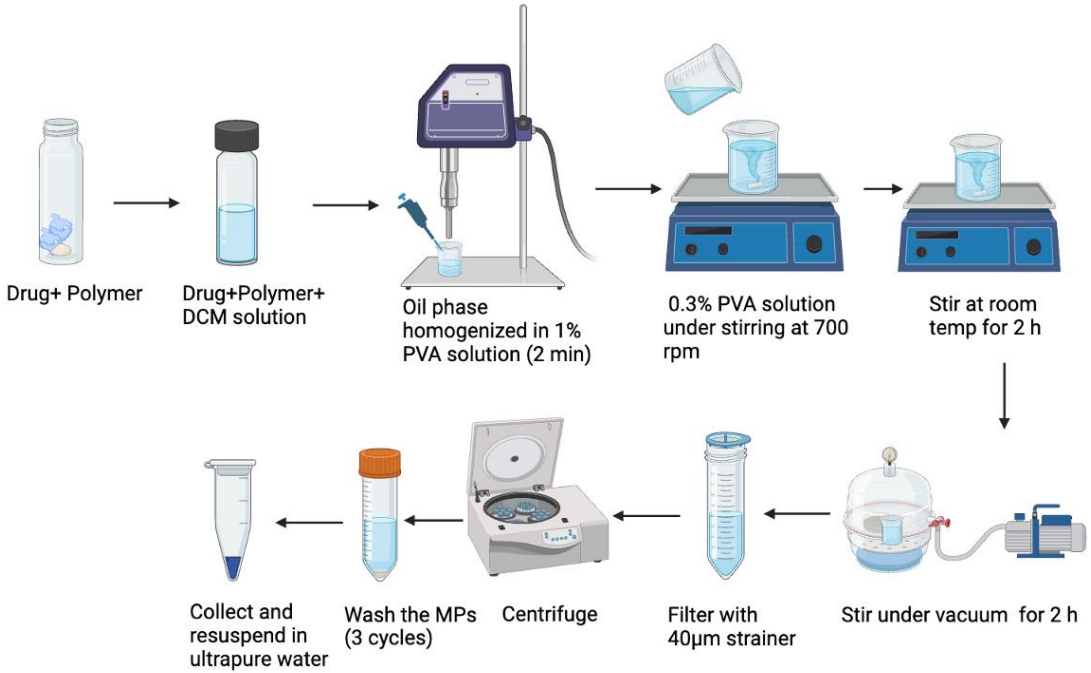
Formulation of nor-LAAM Microparticles (nor-LAAM-MP)

Nor-LAAM microparticles were prepared using an emulsion solvent evaporation method



Formulation characterizations

- Average size
- Drug loading
- *In-vitro* drug release
- Scanning electron microscopy (SEM)

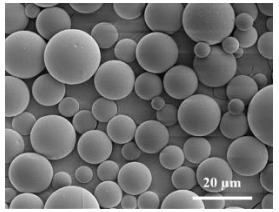
Table 1. Physicochemical Properties of Nor-LAAM-MP

Formulations	Polymer	Counterion	Particle size (nm)	Drug loading (wt. %)	EE (%)
F1	$PLGA_{18kDa}$	Pamoic acid	25.1± 1.1	13.0	65.0
F2		Oleic acid	18.8± 0.8	13.5	67.5
F3		Sodium docusate	20.4± 0.7	12.8	64.0
F4	PLGA-PEG/ $PLGA_{18kDa}$	Pamoic acid	15.8± 0.9	11.0	55.0
F5			24.5± 0.4	14.0	46.6
F6			26.5± 1.0	18.0	45.0

Abbreviations: PLGA: Poly (D, L-lactic-co-glycolic acid); PEG: Polyethylene glycol

Nor-LAAM-MP SEM Images

F4



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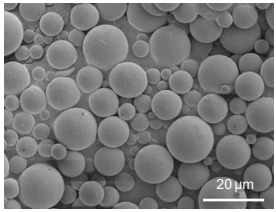

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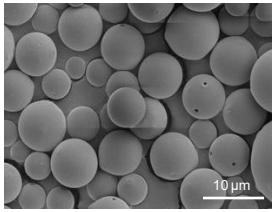
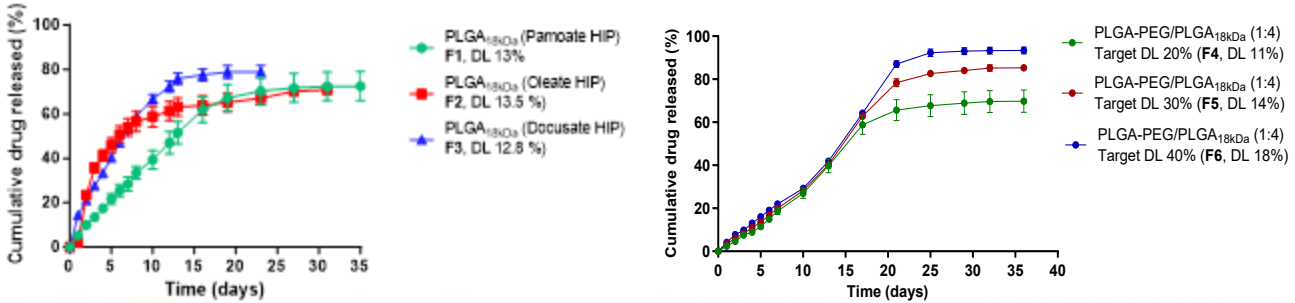
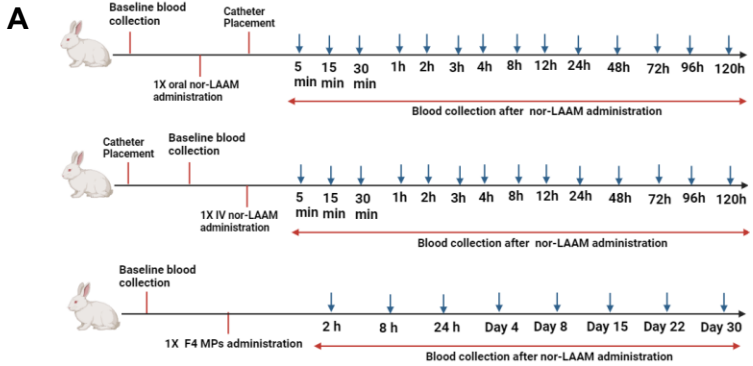
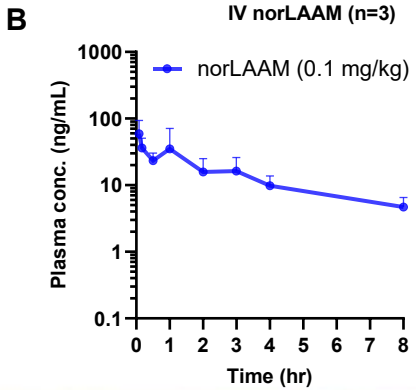


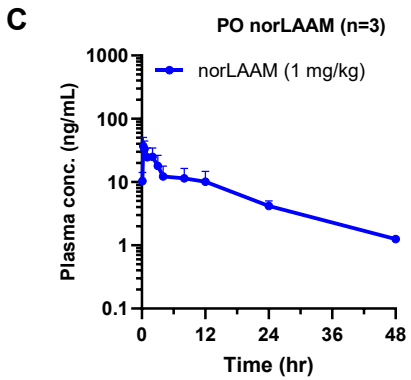
Nor-LAAM-MP in vitro Drug Release Profiles



In vivo Pharmacokinetics of nor-LAAM-MP







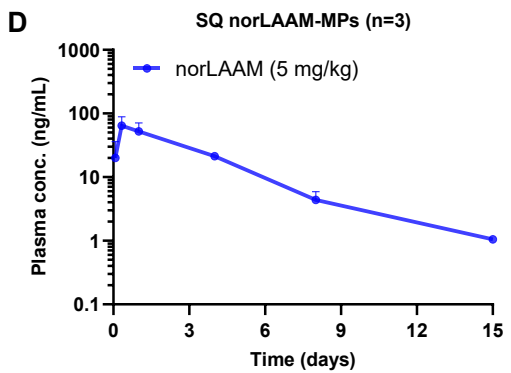
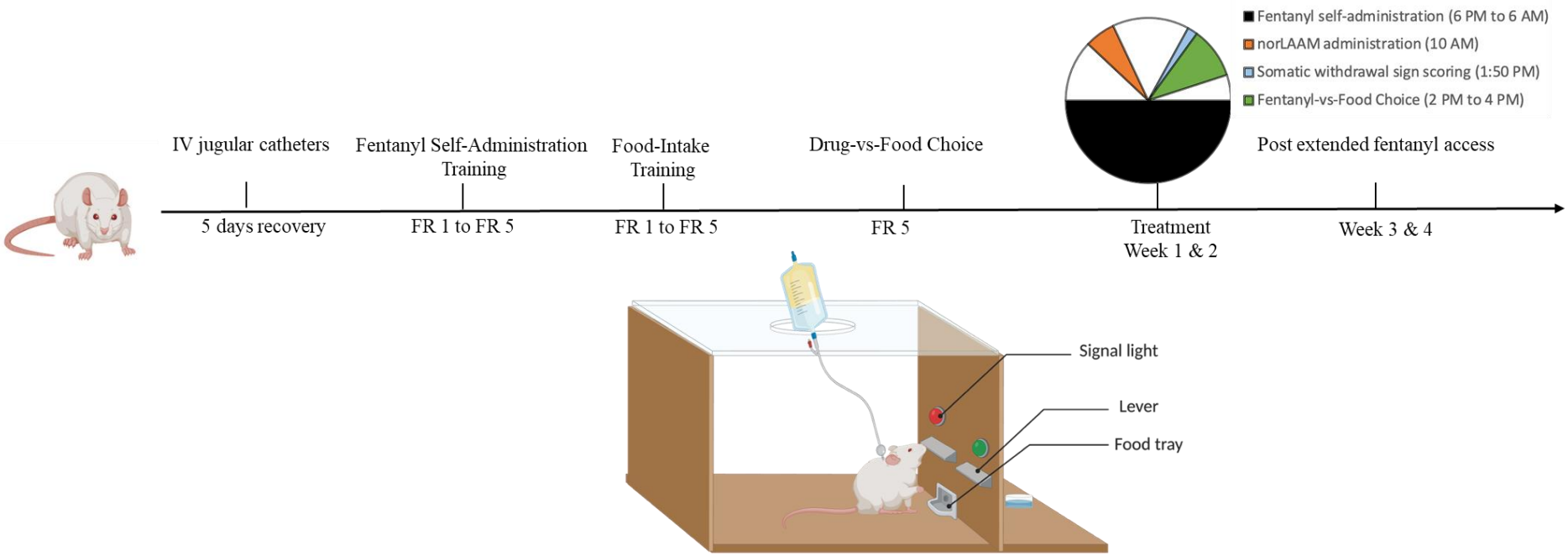


Table 2. Plasma pharmacokinetic parameters of norLAAM following administration of nor-LAAM to rabbits (mean ± SD, n = 3).

Formulation	Nor-LAAM solution	No-LAAM solution	Nor-LAAM-MP
Route of administration	**IV (0.1 mg/kg)**	**PO (1mg/kg)**	**SQ (5mg/kg)**
AUC_{inf} (h×ng/mL)	124.5 ± 39.6	**343.8 ± 90.7**	**5110.7 ± 1082.2**
$AUC_{0\rightarrow t}$ (h×ng/mL)	96.5 ± 17.0	299.7 ± 128.8	4932.5 ± 932.6
C_{max} or C_0 (ng/mL)	54.0 ± 26.2	37.0 ± 13.7	64.5 ± 24.3
t_{max} (h)	—	0.25	8.0
$t_{1/2}$ (h)	3.9 ± 1.7	**13.7 ± 3.6**	**55.3 ± 9.3**
CL (mL/h/kg)	866.5 ± 330.1	—	—
Vss (mL/kg)	4726.5 ± 18996.3	—	—
F (%)	—	**27.6 ± 22.9**	**82.1 ± 54.7 ***

AUCinf, area under the curve from time zero to infinity; AUC0→t, area under the curve from time zero to the last sampling time point; Cmax, maximum observed concentration; t1/2, half-life. Significant differences between PO and SQ: *p ≤0.05.

In vivo Efficacy of nor-LAAM-MP

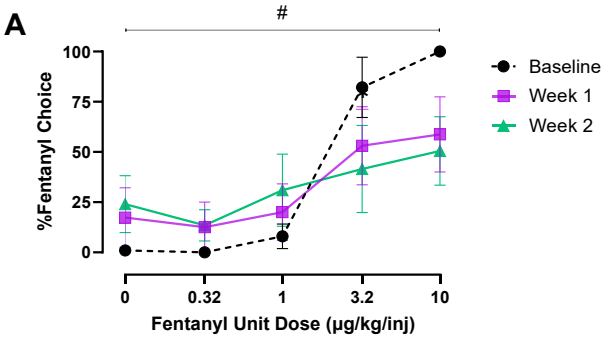


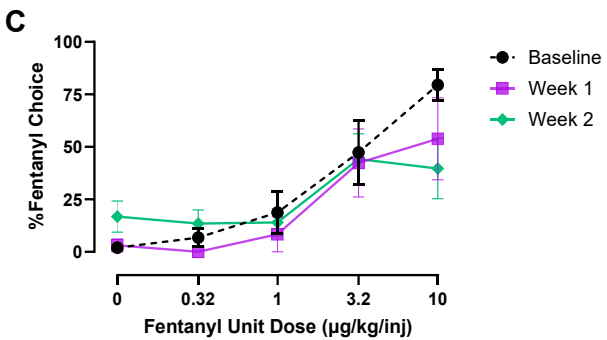
E. A. Townsend et al, j Neuropsychopharmacology, 2132–2139, 2022.

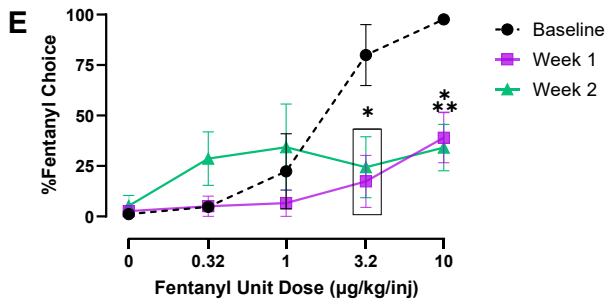
Vehicle (n=4)

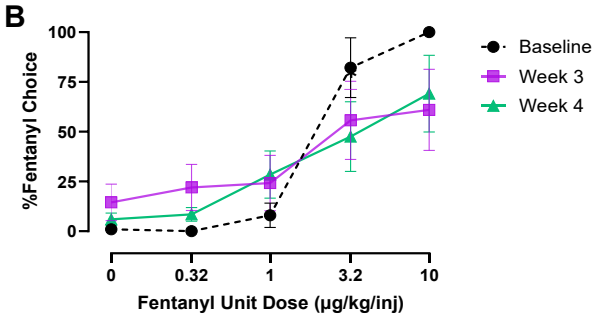
20 mg/kg nor-LAAM-MP (n=6)

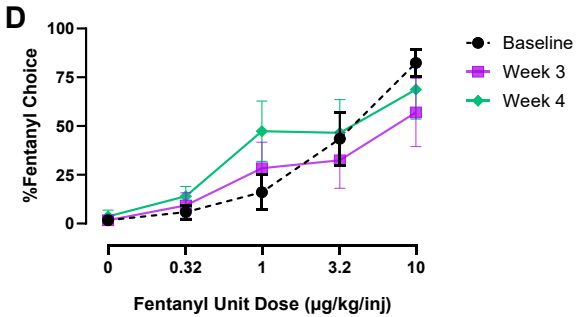
70 mg/kg nor-LAAM-MP (n=5)

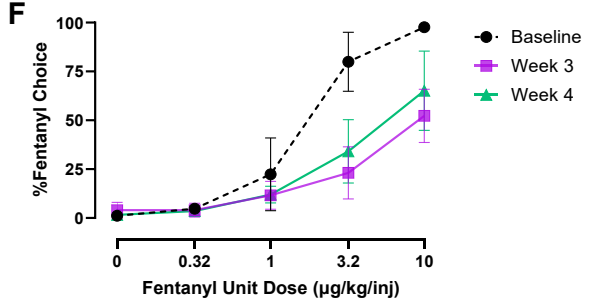












Two-Way ANOVA analysis

symbolizes a significant fentanyl unit dose and time interaction.

*symbolize significant difference relative to baseline, $p < 0.05$.

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