What else does an opioid drug bind at the dose that works?

Measured off-target profiles for four opioid drugs at 10 nM free concentration: 6 to 13 targets each, every value traced to its studies.

Fatou Kineh Ndow, Ph.D. · **Babajide Kolade, Ph.D.** — Fitila Labs · **curasynth@fitila.ai**

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PDF of this poster

Background

Opioid use disorder is treated through the μ receptor, but relapse is often stress-driven, and stress signals substantially through κ [1,2]. Opioid drugs are not selective: the same molecule reaches κ, δ, NOP and non-opioid targets clinically.

A comparison restricted to the receptors you thought to check cannot find what you did not anticipate.

Objective

Build the complete measured occupancy profile of four opioid drugs at one exposure, and ask which secondary engagements are real enough to design against.

Approach

We researched this in **Curasynth** [3], a drug-discovery evidence platform that reconciles measurements across public sources and keeps the assay, endpoint and source publication attached to every value.

$$f = C / (C + K_i) \quad \text{at } C = 10\ \text{nM}$$

Nominal free concentration at the site of action, not a measured PK value. Target abundance is not modeled, so ligand depletion is ~0.

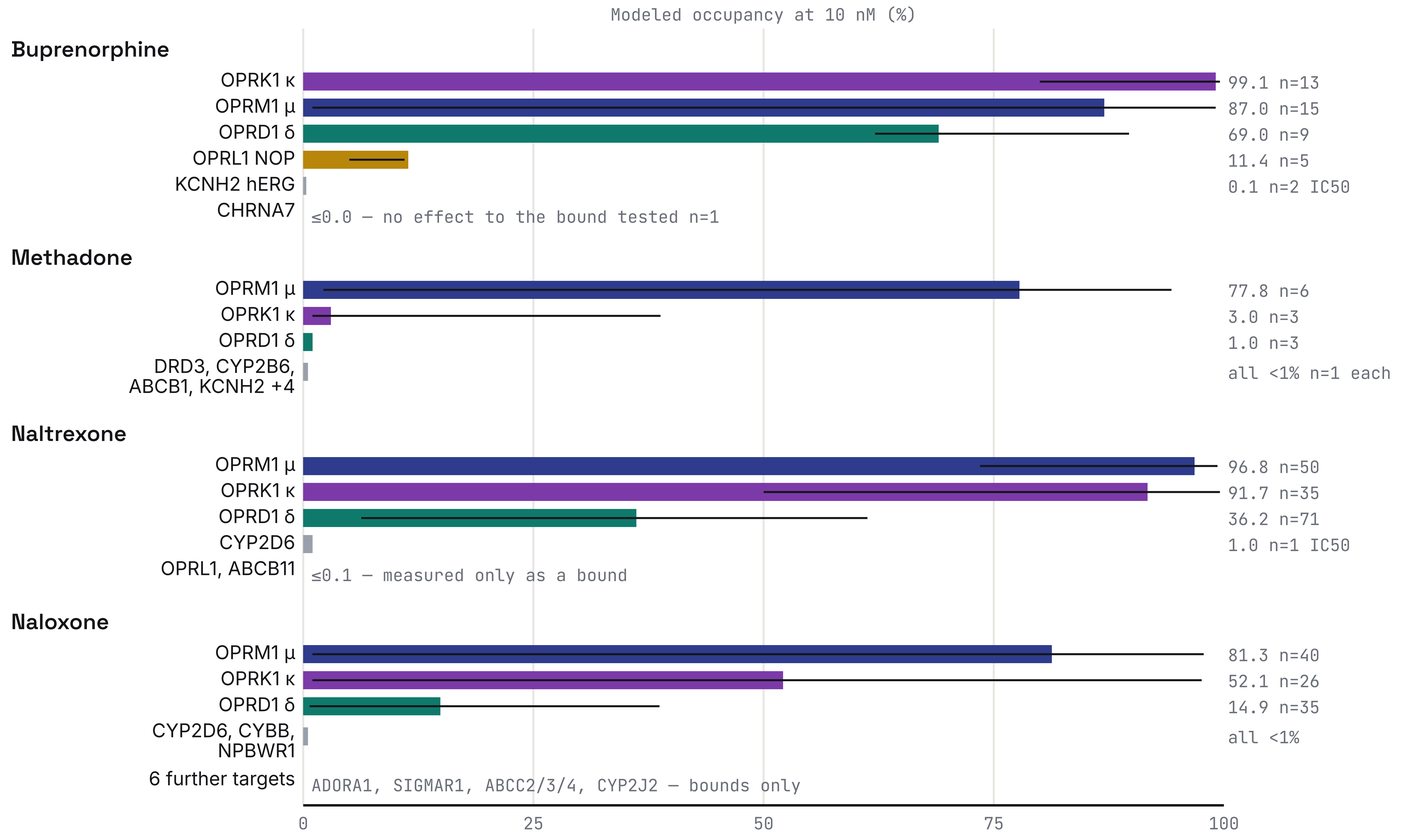
Reading the profiles

- **Bar** = modeled occupancy; **whisker** = weakest to strongest measured affinity for that pair.
- **≤** = measured only as a bound: no effect up to a concentration tested.
- **n** = distinct measurements, one published value counting once.

Scope

- Human targets; assay system not recorded upstream.
- Binding endpoints preferred; one published value counts once.

Measured occupancy at 10 nM: every target, every drug



Every target with a measurement, solved together at one free concentration [3]. Grey = non-opioid. A wide whisker is a thinly-measured pair. **Buprenorphine alone reaches NOP**; naloxone's record is the broadest, at 13 targets, most of them bounds saying where it does *not* act.

What the profile implies clinically

DRUG	STRONGEST OFF-TARGET	OCC.
Buprenorphine	κ — dysphoria, sedation	99%
Naltrexone	κ — dysphoria, sedation	92%
Naloxone	κ — dysphoria, sedation	52%
Methadone	μ — respiratory depression	78%

From the off-target liability screen [3], which scores safety-relevant targets at each exposure and names the manifestation of the strongest engagement. It reaches the same κ conclusion by a different route.

One number, opened

Buprenorphine · NOP · 77.6 nM · 5 measurements · 3 papers

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77.0 bindingdb PMID 21866885
77.0 chembl PMID 24761755
77.4 chembl PMID 21866885
212 chembl PMID 24761755
212 chembl PMID 25898137
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The receptor the comparison would have missed. All five measurements cite a publication.

Hypothesis for testing

At comparable μ engagement and partial-agonist signaling, additional verified κ antagonism may reduce stress-induced opioid seeking while preserving withdrawal suppression.

Rodent studies link κ signaling to stress-related reinstatement [1,2]. Human efficacy is not established. Occupancy is binding, not signaling.

Conclusion

Three of the four drugs engage κ substantially at the exposure where they act on μ, and buprenorphine alone reaches NOP. A profile restricted to the receptors chosen in advance would have reported neither.

Every value resolves to its source rows.

[1] Zhou et al. Synapse. 2013;67:358–361. PMID 23345075.
[2] Sedki et al. Addict Biol. 2015;20:423–432. PMID 24725195.
[3] Fitila Labs. Curasynth [software]. drug_target_occupancy and drug_target_affinity_rollup v2026-10-22; ChEMBL 35, BindingDB 202610. Accessed 24 Oct 2026.