Beyond MOR: four opioid receptors at matched μ occupancy

Four opioid drugs on reconciled human binding affinities (κ, δ and the often-omitted NOP receptor), with the published spread carried through to every estimate.

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

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Background

Opioid use disorder is treated mainly through the μ receptor (MOR): agonists suppress withdrawal, antagonists block reward. Relapse is often stress-driven rather than reward-driven, and stress-related reinstatement signals substantially through κ [1,2].

Opioid drugs are rarely selective: the same molecule engages κ, δ and NOP at clinical concentrations, yet are usually described by their μ action alone. Those secondary profiles are where a polypharmacology hypothesis lives.

Objective

At matched modeled μ occupancy, compare κ, δ and NOP engagement across four opioid-receptor drugs, and ask what polypharmacology hypothesis the differences support.

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.

$$f = C / (C + K_i)$$

$$C = f/(1-f) \times K_i(\mu)$$

f fractional μ occupancy · **C** free concentration · K_i approximates K_d at equilibrium. At f = 0.8, C = 4 × K_i(μ).

At matched μ, secondary occupancy depends only on the affinity ratio, so varying the μ reference cannot reorder the drugs.

Scope

- **Human receptor** by UniProt accession; assay system not recorded upstream.
- **K_i only**; endpoints are never pooled.
- **One value counts once**, however many database rows carry it.
- **Stereoisomers** pooled and labelled.

Reconciled affinities

DRUG	RCP	K_i nM	RANGE	N	PUB
Buprenorphine	μ	1.50	0.09–1000	15	9
	κ	0.089	0.04–2.5	13	10
	δ	4.47	1.15–6.1	9	8
	NOP	77.6	77–212	5	3
Methadone	μ	2.85	0.6–447	6	6
	κ	324	15.8–1000	3	3
	δ	1000	132–1000	3	3
Naltrexone	μ	0.335	0.07–3.6	50	36
	κ	0.891	0.04–10	35	25
	δ	17.6	6.3–149	71	40
Naloxone	μ	2.30	0.23–1000	40	25
	κ	9.12	0.25–1000	26	17
	δ	57.0	15.9–1516	35	26

Median over distinct measurements [3]; range is the full measured spread. Flagged cells rest on three papers: a floor on the uncertainty, not an estimate of it. Only buprenorphine has a measured NOP affinity.

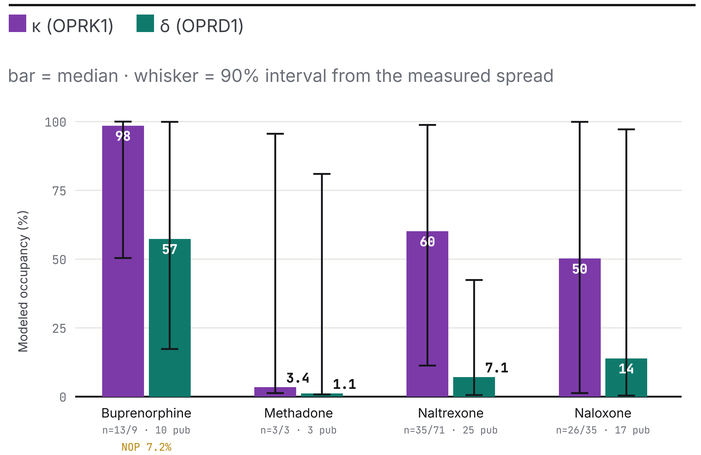
The evidence behind one number

Buprenorphine · κ · median 0.089 nM · 13 measurements · 10 papers

0.040 chembl — 0.040 bindingdb — 0.040 PMID 29107424
0.067 PMID 23438330 — 0.070 PMID 24933507
0.089 PMID 24761755 — 0.089 PMID 25898137
0.620 PMID 19027293 — 0.800 PMID 10649968
0.800 PMID 17887741 — 0.800 PMID 9686407
2.500 PMID 21866885 — 2.500 PMID 24761755

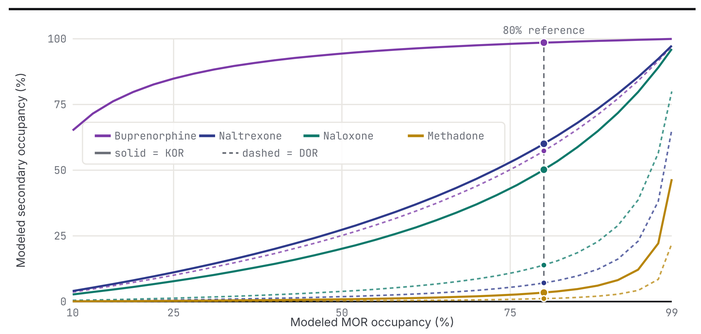
Every value on this poster opens like this. 11 of these 13 cite a publication; the 2009 [4] and 2011 [5] studies are both in here.

Secondary occupancy at 80% modeled μ



Intervals: 5th–95th percentile of 40,000 draws sampling each receptor's affinity log-uniformly across its measured range. Each drug uses its own free concentration; equal occupancy does not imply equal signaling.

Profiles across the modeled MOR reference



Solid = κ, dashed = δ; circles mark the 80% reference. With K_i fixed the ordering cannot change, because at matched μ, secondary occupancy depends only on the affinity ratio, so this shows the model's shape, not a test of the evidence. Gap sizes do vary.

Interpretation

A μ-only description omits engagement the binding record supports. At matched μ, buprenorphine's modeled κ occupancy is highest and methadone's lowest, and buprenorphine alone reaches a fourth receptor.

That ordering is not statistically separable: carried through its measured spread, the record does not rank these drugs. The ordering in any one source [4,5] is an artifact of that source.

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 of heroin seeking [1,2]. Human efficacy is not established. Occupancy is binding, not signaling: buprenorphine is a μ partial agonist and κ antagonist, so equal occupancy is not equal functional effect.

What separates, and what does not

COMPARISON	P(κ-PREF.)	VERDICT
Bupre > Methadone	0.93	overlaps
Bupre > Naltrexone	0.84	overlaps
Bupre > Naloxone	0.77	overlaps
Naltrexone > Naloxone	0.48	overlaps

Paired draws: how often one drug is more κ-preferring. None clears 95%.

Conclusion

Matched μ occupancy makes the κ, δ and NOP differences visible, and the affinity record is too dispersed to confirm a ranking among them. The spread is wider than every separation it is asked to support.

Every value resolves to its source rows; the same query regenerates this comparison for any drug set.

[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_affinity_rollup v2026-10-22; human μ/κ/δ/NOP K_i from ChEMBL 35 and BindingDB 202610. Accessed 24 Oct 2026.
[4] Wentland et al. Bioorg Med Chem Lett. 2009;19:203–208. PMID 19027293.
[5] Cami-Kobeci et al. J Med Chem. 2011;54:6531–6537.