

Terapia del disturbo da uso di oppiacei: Gold Standard e Linee Guida Internazionali

Epidemiology of Drug Use in USA

Table 1. Epidemiology of drug use. Prevalence of specific drug abuse and vulnerability to develop addictions. SAMHSA National Survey on Drug Use and Health, 2017; others 2007–2018.

National household survey and related surveys (2007–2016)

Heroin use—ever	~5.2 million
Heroin addiction	~652,000
Illicit use of opiate medication—ever	~37.1 million (i.e., 14.2% of the population 12 and over)
Dependence on such medication use	~2.1 million
Opiate (heroin, fentanyl, and other) overdose deaths	~72,3000 (in 2017)*
Cocaine use—ever	~40.5 million
Cocaine addiction	~966,000
Alcohol use—ever	~216 million
Alcoholism	~14.5 million
Marijuana use—ever	~123 million
Marijuana daily use	~4 million

Development of addiction after self-exposure

Opiate addiction	~1 in 5 to 1 in 15 (20 to 6.5%)
Alcoholism, marijuana, and cocaine dependency	~1 in 8 to 1 in 15 (12.5 to 6.5%)

*National Center for Health Statistics (U.S. Centers for Disease Control and Prevention), 2019.

Treatment for Opioid Addiction in USA

Table 2. Status of methadone, buprenorphine, and extended-release naltrexone treatments for opioid addiction in the United States: Decrease and then increase in numbers in treatment 2015–2017 (SAMHSA, 2018).

Treatment	U.S. patients in treatment		
	2015	2016	2017
Methadone maintenance	356,843	345,443 (−11,400; −3.2%)	382,867 (+37,424; +10.8%)
Buprenorphine maintenance	75,723	61,486 (−14,237; −18.8%)	112,223 (+50,737; +82.5%)
Extended-release naltrexone	7035	10,128 (+3093; +44.0%)	23,065 (+12,937; +128.7%)

Vulnerability to develop opioid use disorders (OUDs): A general working model

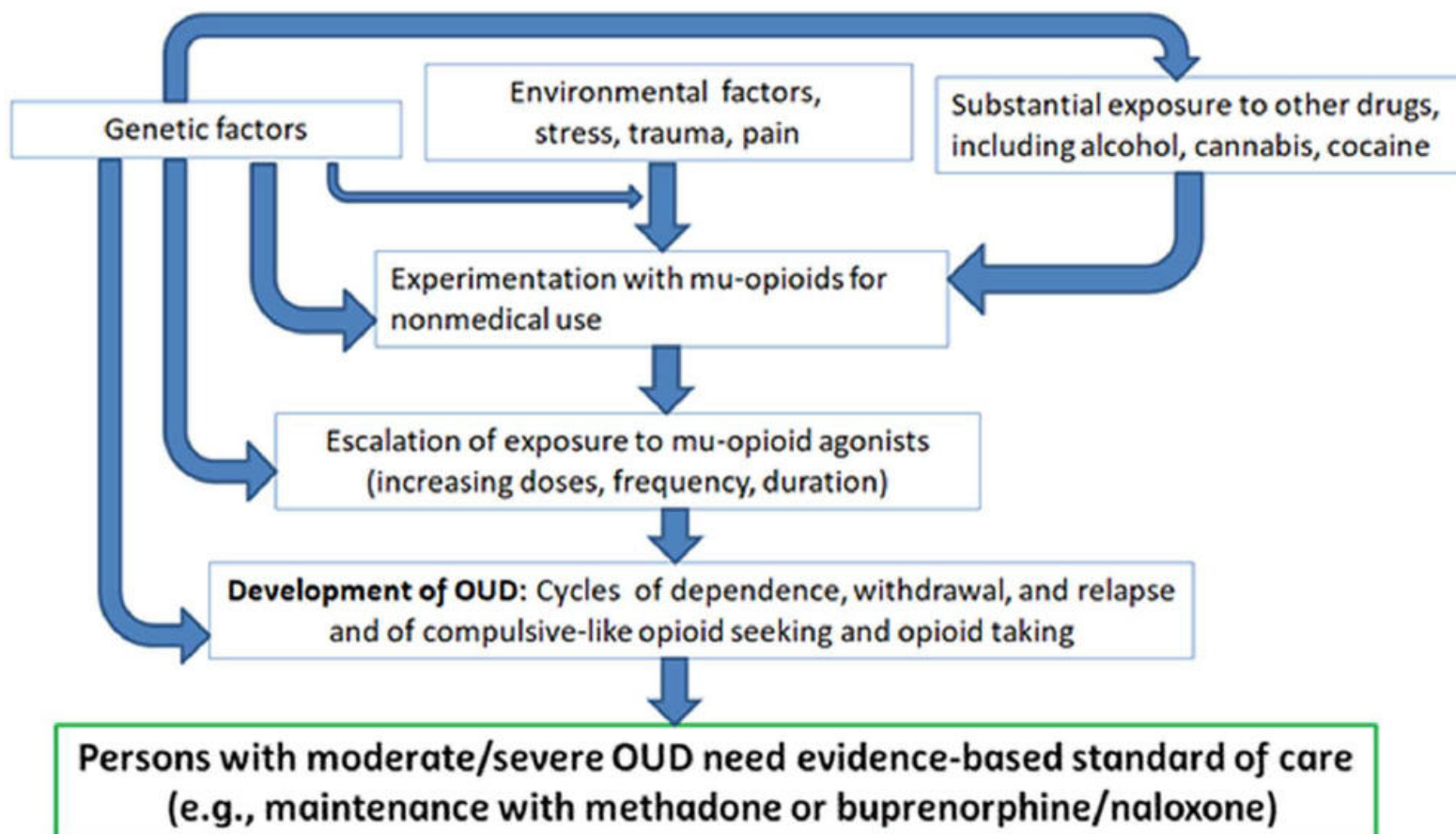
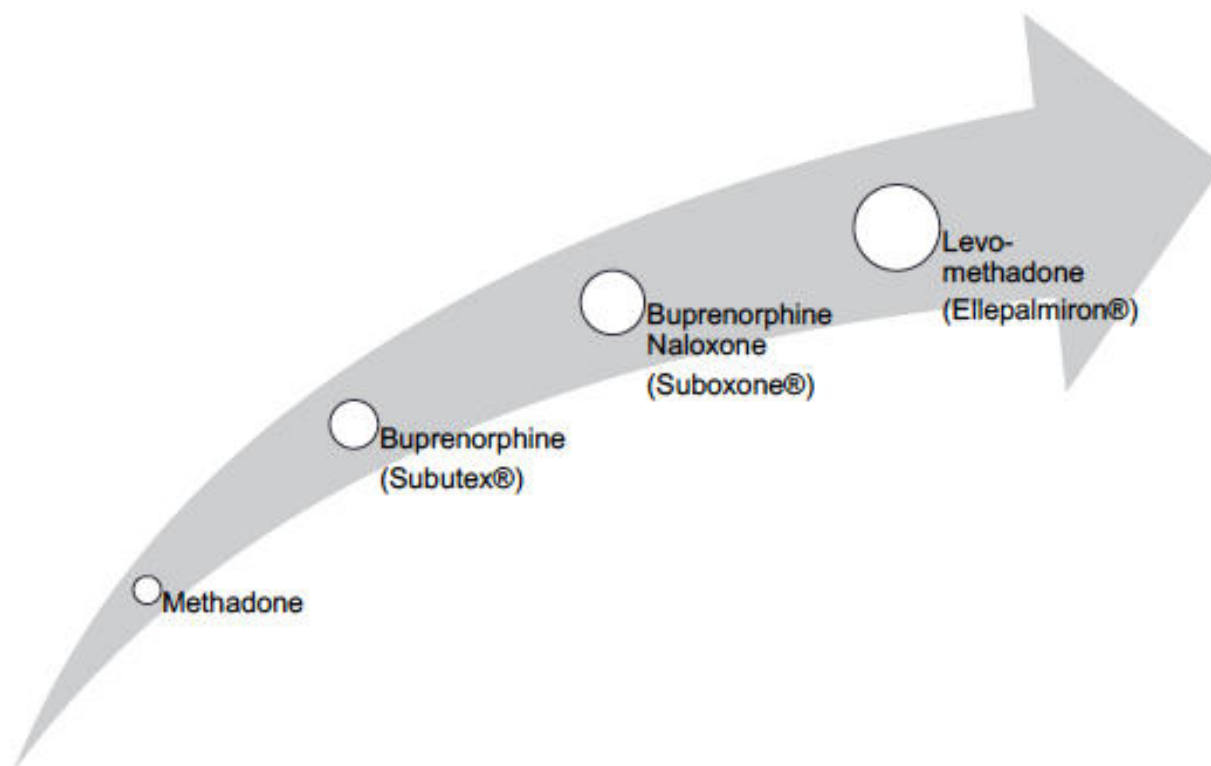


Table 3. FDA-approved medications for OUD, with typical dosing paradigms for each of the approved formulations. PO, per os (oral); SL, sublingual; BUC, buccal; SQ, subcutaneous; IM, intramuscular.

Treatment	Dose range	Considerations
Methadone (PO)	80–150 mg/day (typical range)	Maintenance dosing is determined during the early weeks of treatment following upward titration. Individual genetic and drug history differences may lead to requirement of higher doses than the typical range. FDA approved in 1972.
Buprenorphine-naloxone (SL or BUC)	8–24 mg/day buprenorphine (1–6 mg/day naltrexone) (typical range)	4:1 ratio (w/w) of buprenorphine-naloxone. Because of partial agonist nature of buprenorphine, no further treatment effect to be gained by doses greater than 24 mg/day. FDA approved in 2002.
Buprenorphine extended-release formulation (SQ)	80–300 mg/monthly injection	Two formulations available. FDA approved in 2016 and 2017.
Naltrexone tablets (PO)/extended-release formulation (IM)	50 or 100 mg/day orally; 380 mg/monthly IM injection	Requires a patient to be opioid free for 7–10 days before administration. FDA approved in 1984 (tablets, no longer marketed); 2010 (extended release).

Treatment	Dosage range	Consideration
Buprenorphine Implant (26 mm in length and 2.5 mm in diameter)	74.2 mg (equivalent to 80 mg of buprenorphine hydrochloride)	Maintenance treatment of opioid addiction that provides non-fluctuating blood levels of buprenorphine around the clock for a period of six months following a single treatment procedure
Buprenorphine long-acting (SQ) (CAM2038)	8-32 mg (one weekly q1w) 64-160 mg (once-monthly q4w)	Maintenance treatment of opioid addiction, intended for administration one weekly (q1w) and once monthly monthly (q4w)
Buprenorphine and naloxone sublingual film	2 mg/0.5mg – 12 mg/3 mg	Maintenance treatment of opioid addiction
Levo-methadone	1:2 vs. methadone typical range	Maintenance treatment of opioid addiction



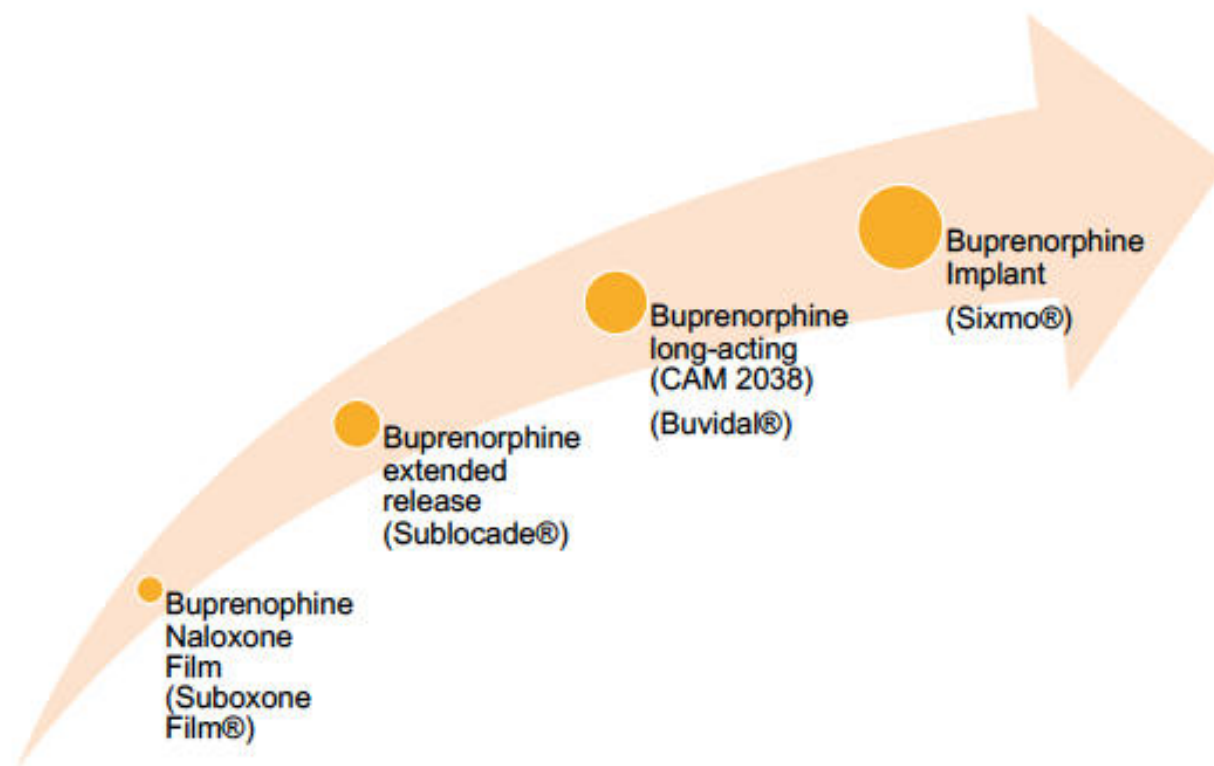


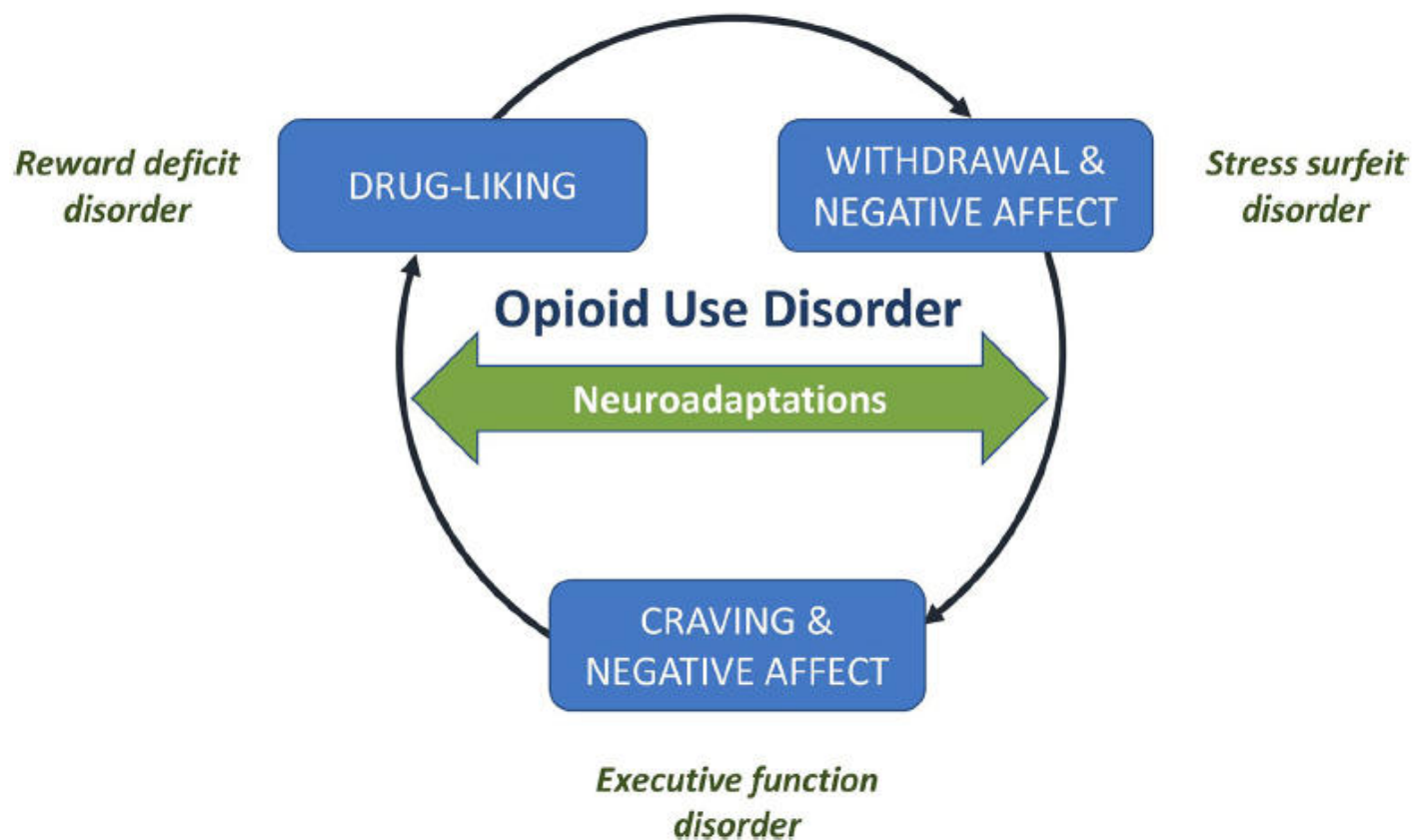
Table 1 Comparison of commonly available products to treat opioid dependence

Drugs	Active ingredients	Administration	Average dosage/target range	Half-life
Revia®, Depade®	Naltrexone	Oral (tablet)	50 mg, 1×/day	13 hours ⁴⁵
Vivitrol® XR	Naltrexone	IM	380 mg, 1×/month	5–10 days ⁵⁹
Methadose®, Diskets®, Dolophine®	Methadone HCl	Oral (dispersible tablet in liquid), IM	2:1 (parental-to-oral ratio), 80–120 mg oral ⁶⁰	8–59 hours ⁶¹
Xtampza® ER	Oxycodone HCl	Oral (capsule)	9–36 mg, 2×/day ⁶²	5.6 hours ⁶³
Narcan®	Naloxone HCl	Nasal spray	4 mg, 1 spray ³³	0.5–1.35 hours ⁶⁴
Suboxone®	Buprenorphine/naloxone	Oral (SL) tablet, buccal (film)	4/1 mg, 8/2 mg, 12/3 mg ⁶²	24–42 hours/2–12 hours ⁶⁵
Bunavail®	Buprenorphine/naloxone	Buccal (film)	2.1/0.3 mg, 4.2/0.7 mg, 6.3/1 mg ⁶⁶	16.4–27.5 hours/1.9–2.4 hours ⁶⁷
Zubsolv®	Buprenorphine/naloxone	Oral (SL) tablet	Two 5.7 mg/1.4 mg tablets 1×/day (11.4 mg/2.8 mg) ⁶⁸	24–48 hours/2–12 hours ⁶⁵
Probuphine®	Buprenorphine HCl	Subdermal implant	Four implants deliver equivalent to daily doses <8 mg suboxone ⁵⁵	24–48 hours ⁵⁵

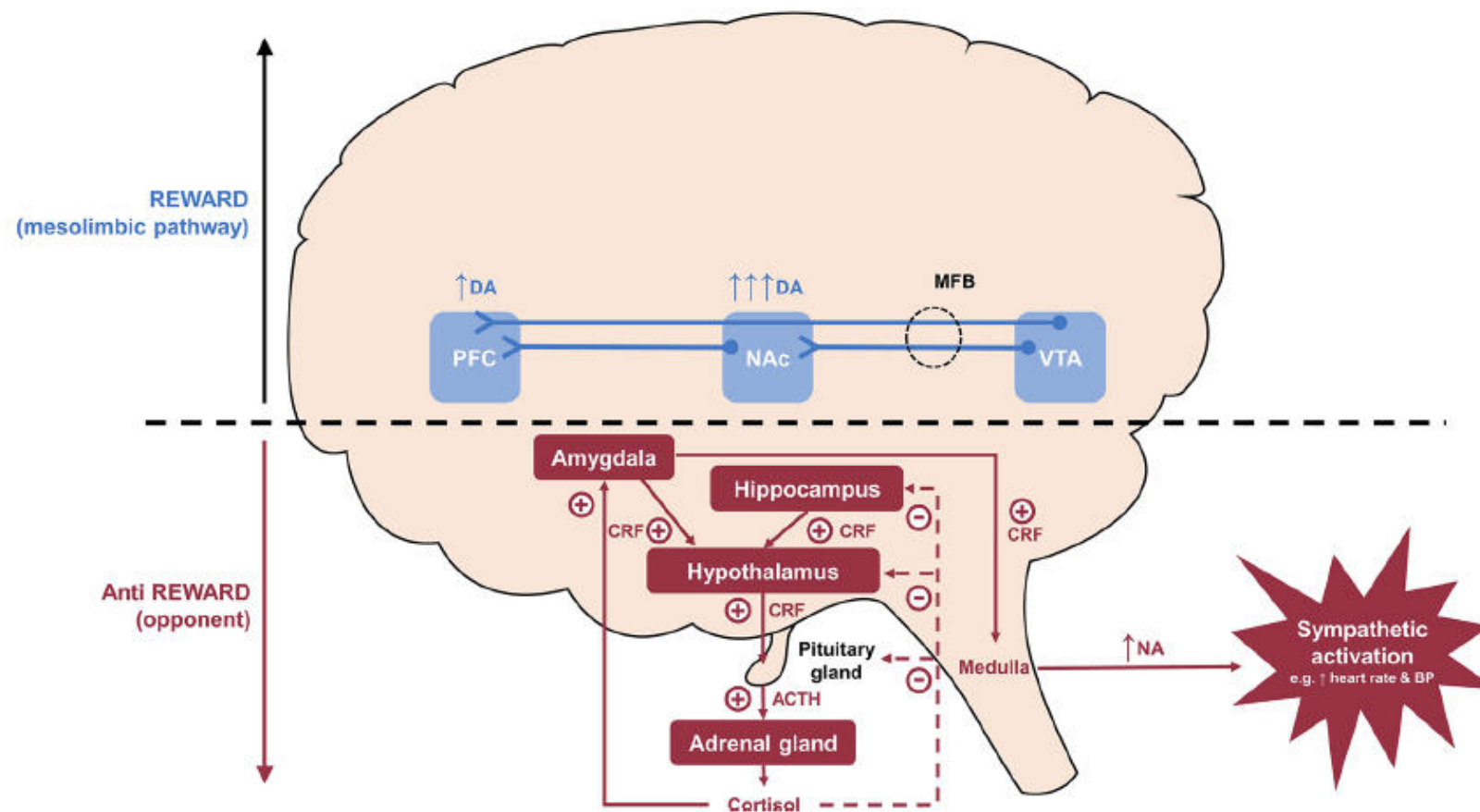
Abbreviations: IM, intramuscular; IV, intravenous; SL, sublingual.

Why searching for new treatments for opioid addiction?

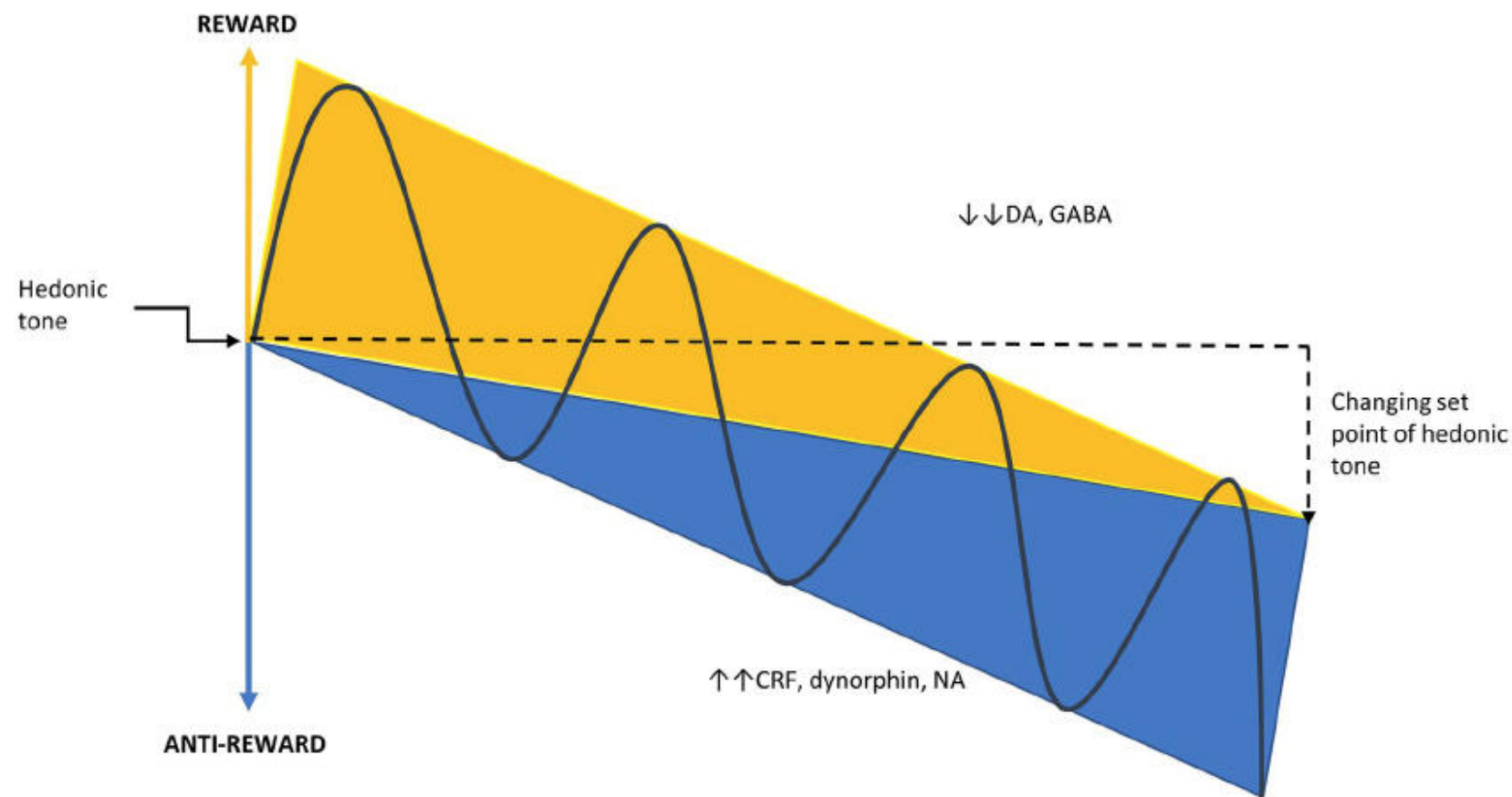
Drivers in the cycle of addiction



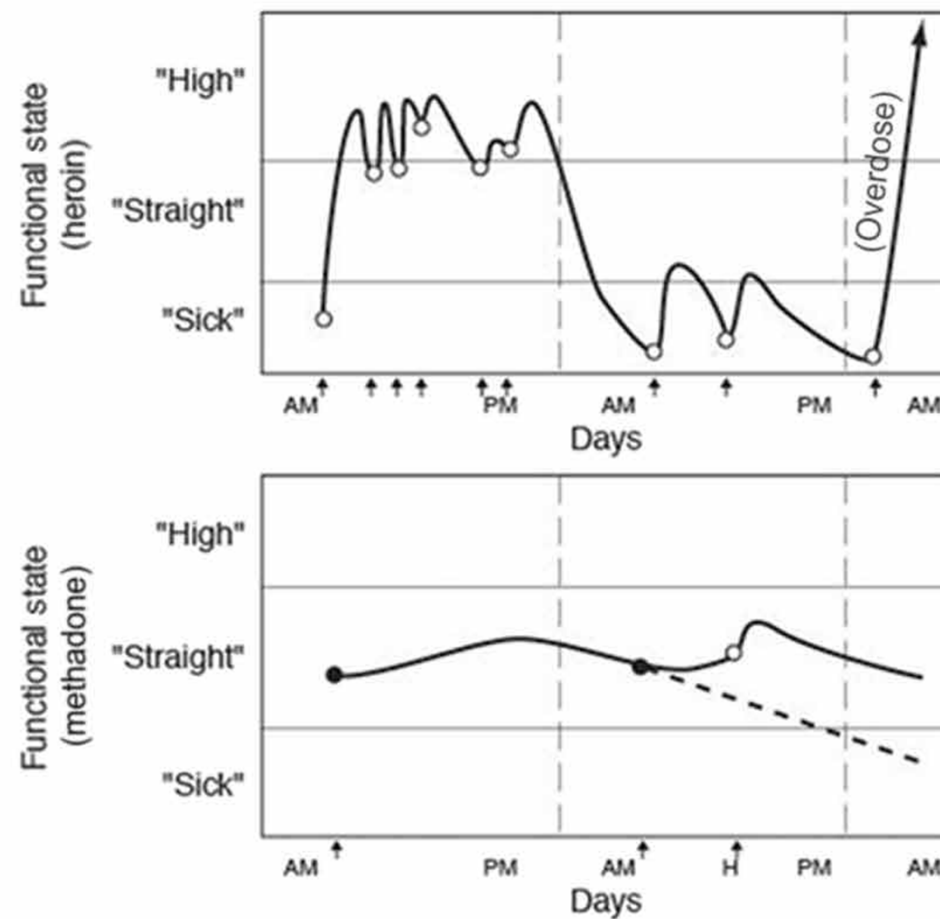
Reward vs anti-reward

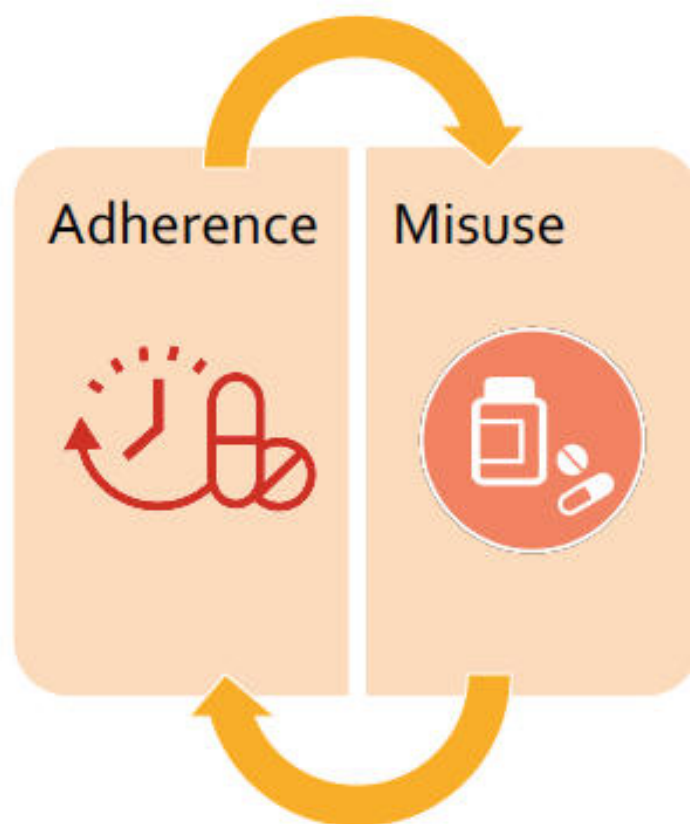


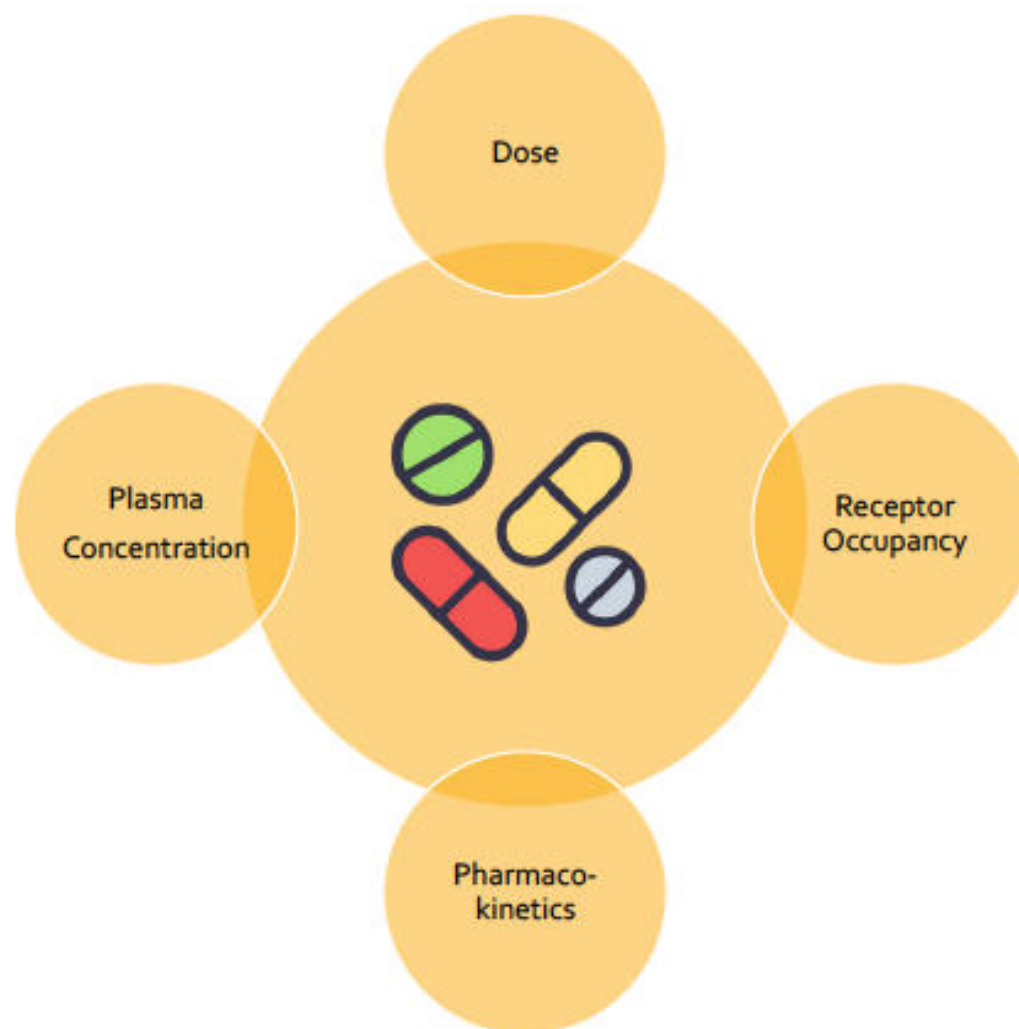
Homeostatic set-point in reward and anti-reward



Heroin addiction contrasted with methadone maintenance









Opioid overdose death in USA

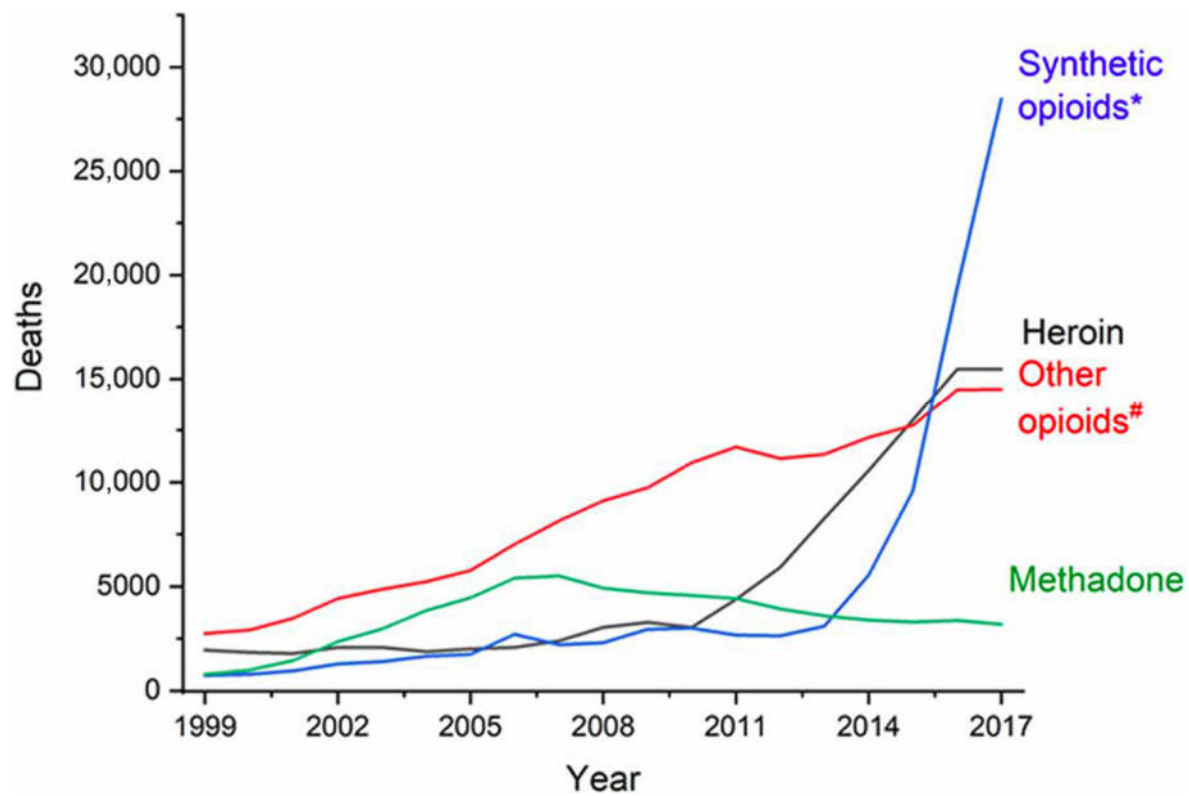
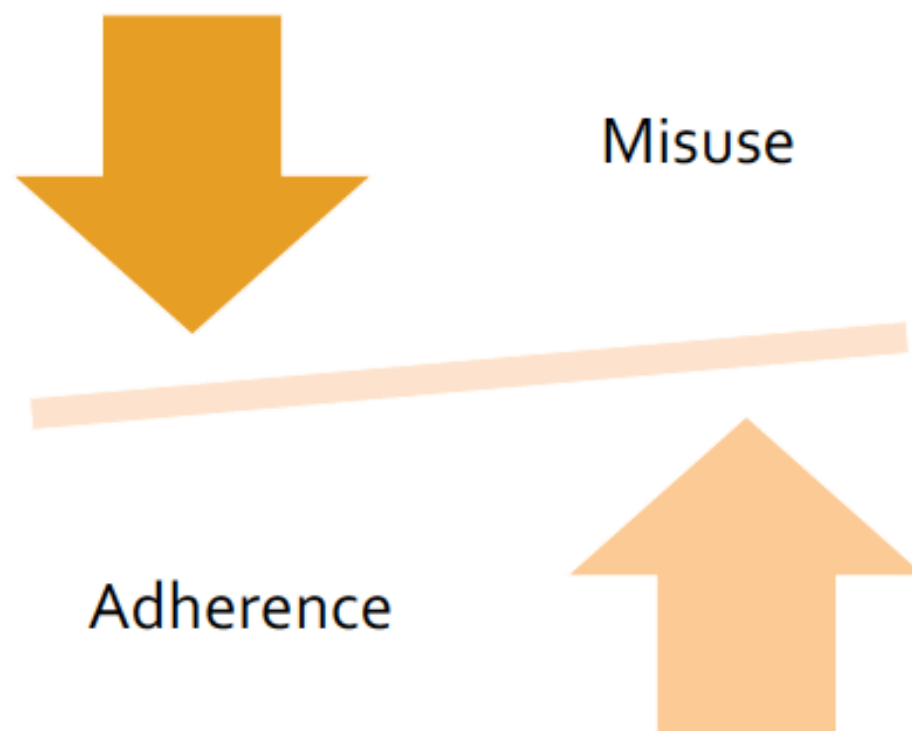


Table 2. Median retention rates across included studies.

	Retention 6 months % (range)	Retention 12 months % (range)	Retention 2 years % (range)	Retention 3 years % (range)
MMT	67.0% (46.8%–86.0%)	60.7% (20.3%–94.0%)	49.8% (29.5%–76.0%)	54.0% (20.0%–82.0%)
	[n = 9] (63, 65, 66, 74, 75, 78, 79, 81, 83)	[n = 24] (35–37, 46, 48, 54, 55, 59–63, 65, 66, 73–75, 77, 79, 81, 85, 91, 92, 94)	[n = 7] (42, 48, 63, 74, 89, 92, 94)	[n = 6] (37, 46, 59, 91, 92, 94)
BUP	56.8% (19.1%–64.0%)	45.4% (11.7%–61.6%)	-	-
	[n = 5] (49, 58, 70, 82, 88)	[n = 6] (49, 68, 69, 72, 84, 93)		
Mixed OST	54.0% (52.6%–75.8%)	40.4% (33.0%–65.8%)	-	-
	[n = 5] (44, 47, 51, 86, 87)	[n = 7] (41, 44, 51–53, 86, 87)		
Overall	58.0% (19.1%–86.0%)	57.0% (11.7%–94.0%)	49.8% (29.5%–76.0%)	38.4% (13.7%–82.0%)
	[N = 19] (44, 47, 49, 51, 58, 63, 65, 66, 70, 74, 75, 78, 79, 81–83, 86–88)	[N = 37] (35–37, 41, 44, 46, 48, 49, 51–55, 59–63, 65, 66, 68, 69, 72–75, 77, 79, 81, 84–87, 91–94)	[N = 9] (42, 48, 51, 63, 72, 74, 89, 92, 94)	[N = 8] (37, 46, 59, 68, 69, 91, 92, 94)

Median retention rates for buprenorphine and mixed OST are not reported at 2 and 3 years follow-up due to small study numbers (buprenorphine at 2-years (n = 1); buprenorphine at 3 years (n = 2); mixed OST at 2 years (n = 1); mixed OST at 3 years (n = 0))

<https://doi.org/10.1371/journal.pone.0232086.t002>



Treatment period completion (CAM2038)

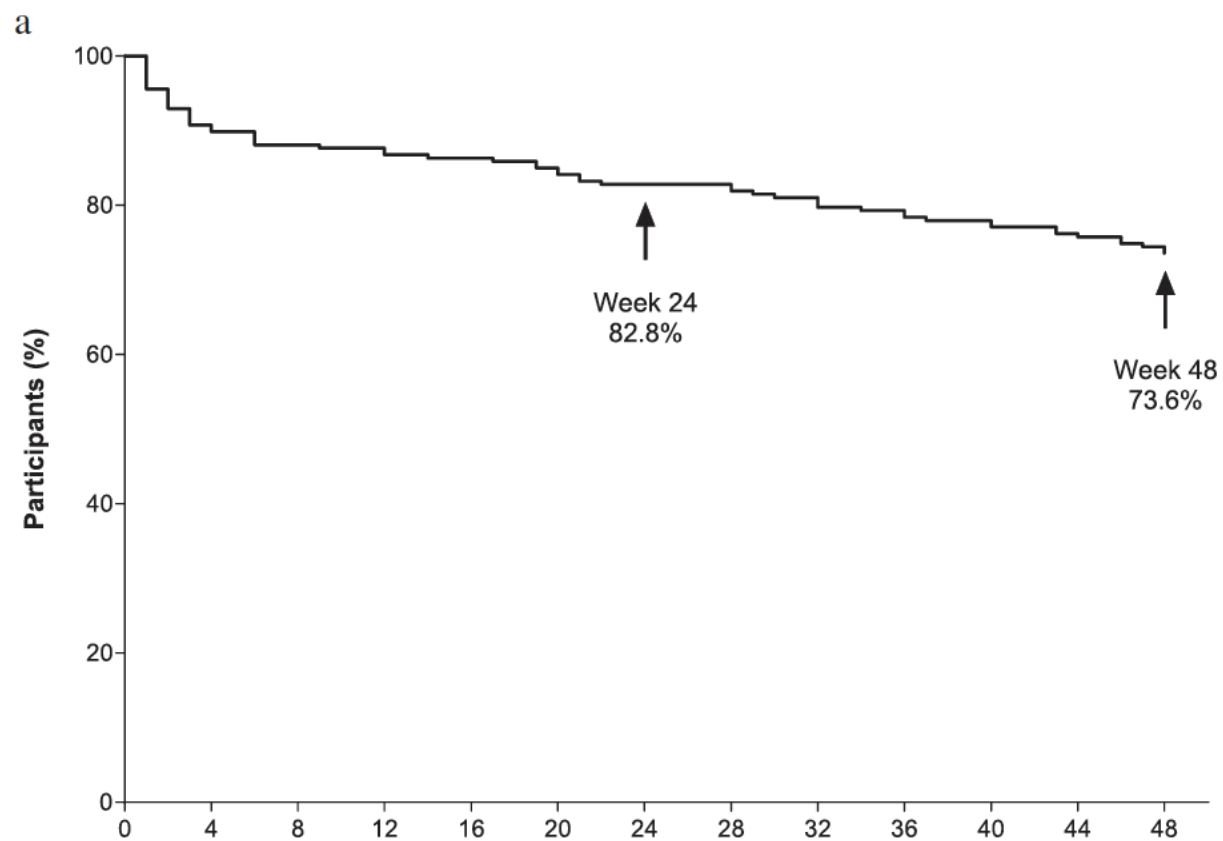
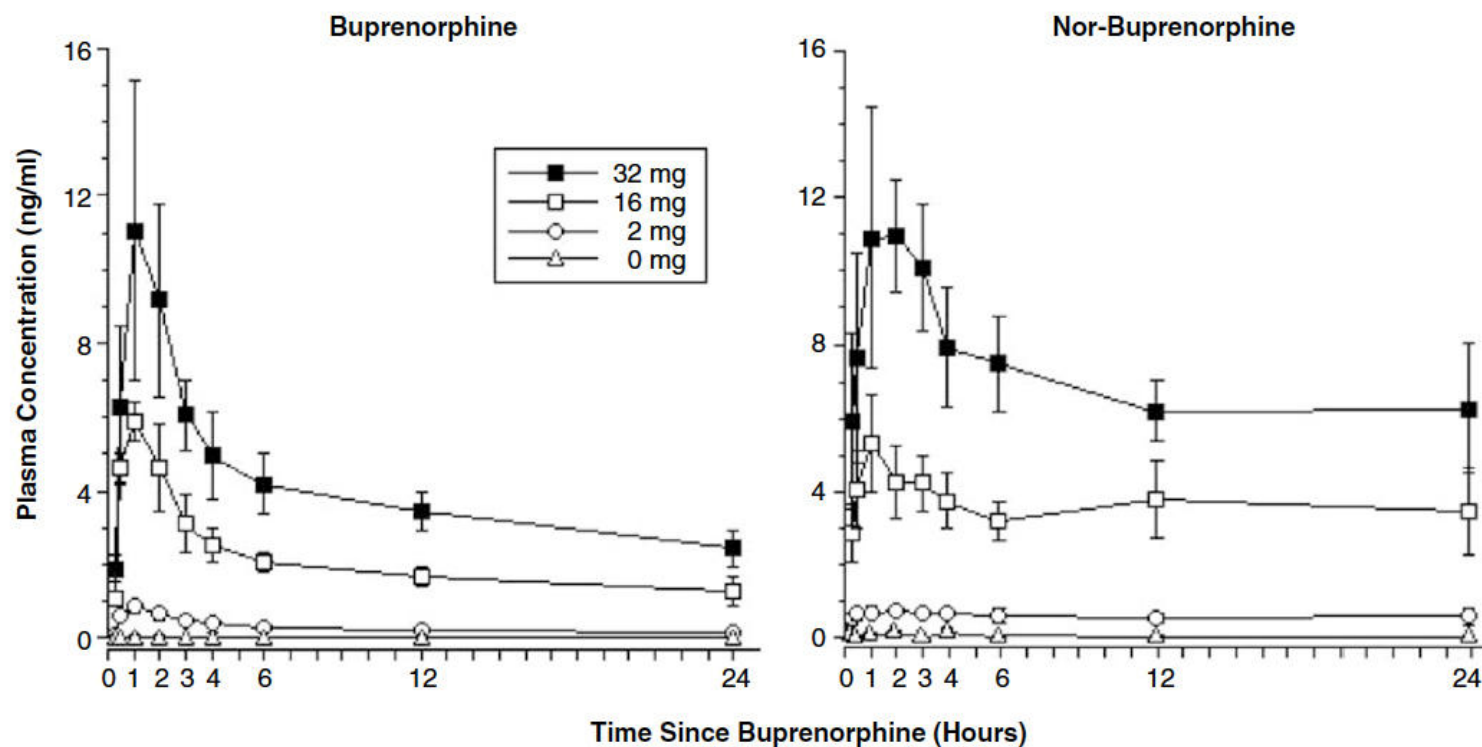
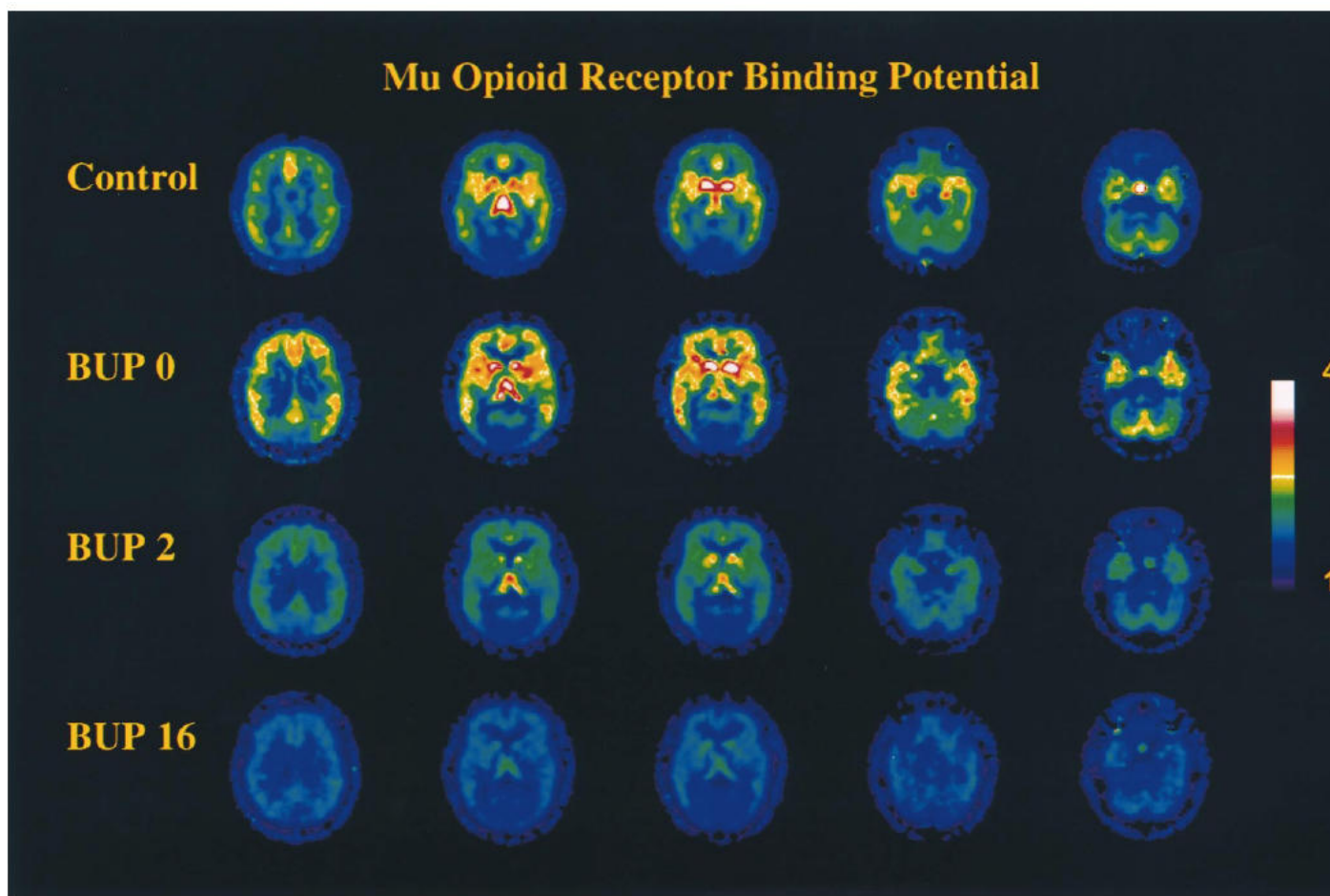


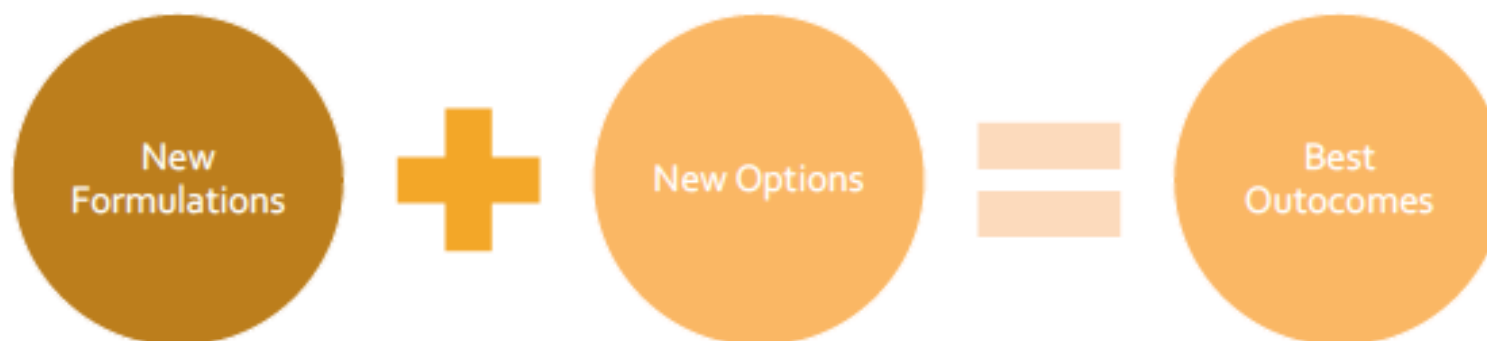
Table 1 Comparison Of Long-Acting Formulations Of Buprenorphine FDA-Approved For Treatment Of Opioid Use Disorder

Brand name	Probuphine	Sublocade	Brixadi (US) or buvidal (Europe/Australia)
Molecular name		RBP-6000	CAM2038
Pharmaceutical	Previously Braeburn, currently Titan	Indivior	Braeburn Pharmaceuticals/Camurus
Indicated population	Stable transmucosal buprenorphine dose of 8 mg or less for three months or longer	Initiated transmucosal buprenorphine (8–24 mg) for a minimum of 7 days.	Initiation of treatment in patients not already receiving buprenorphine or switching from transmucosal buprenorphine
Route of administration	Subcutaneous implant	Subcutaneous injection	Subcutaneous injection
Duration of effect	6 months	1 month	1 week or 1 month
Dosage	320 mg (Four 80 mg implants)	100 and 300 mg	8, 16, 24 and 32 mg (weekly) or 64, 96 and 128 mg (monthly)
Long-acting technology	Ethylene vinyl acetate (EVA) polymer	18% (weight/weight) buprenorphine base in the ATRIGEL Delivery System	Prolonged release FluidCrystal injection depot technology
Location	Upper arm	Abdomen	Buttock, thigh, stomach (abdomen) or upper arm
FDA-approval	2016	2017	2018 (tentative)
Plasma concentrations (ng/mL)	C_{max} 3.23 C_{trough} 0.72	C_{max} 4.88 (100 mg) 10.12 (300 mg) C_{trough} 2.48 (100 mg) 5.01 (300 mg)	C_{max} Weekly 4.35–8.23 Monthly 3.81–6.59 C_{trough} Weekly 0.26–0.54 Monthly 0.45–0.93
Provider burden	+++ Live training program Procedural competency	++ Supervised injection Monthly injections	++ Supervised injection Weekly or monthly injections
Special Handling Requirements	Requires implant procedure Need for removal or replacement every 6 months	Needs Refrigeration Injection only under skin around umbilicus	No special requirements

BUPRENORPHINE				NOR-BUPRENORPHINE		
BUP Dose	Tmax (hr)	Cmax (ng/ml)	AUC (ng/ml * hr)	Tmax (hr)	Cmax (ng/ml)	AUC (ng/ml * hr)
2 mg	0.9 + 0.1	0.3 + 0.1	6.5 + 1.6	1.6 + 0.4	0.7 + 0.2	14.0 + 8.8
16 mg	1.2 + 0.2	6.3 + 0.9	48.6 + 8.0	1.4 + 0.4	5.4 + 1.3	87.3 + 23.1
32 mg	1.2 + 0.2	13.2 + 4.2	96.0 + 16.1	1.6 + 0.2	14.2 + 2.9	168.0 + 31.0











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