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This presentation is part of the Community Rounds Workshop Series

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Disclosures

There is nothing to disclose for this UVM CORA Community Rounds session.

Potential Conflicts of Interest (*if applicable*):

- Dr. John Brooklyn is a medical advisor to OpiRescue, part of OpiSafe.
- All Potential Conflicts of Interest have been resolved prior to the start of this program.

All recommendations involving clinical medicine made during this talk were based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in the care of patients.

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Use of Sustained Release Buprenorphine (SRB) in the Outpatient Setting

John Brooklyn, MD

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Medical Director of Howard Center Chittenden Clinic and BAART St. Albans Hub

Community Health Center of Burlington

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Outline

- Neurobiology of Opioid Use Disorder (OUD)
- Rationale for use of buprenorphine to treat OUD
- Evidence for injectable buprenorphine ’s (IJB) efficacy
- Identification of patient characteristics for IJB
- Office management of IJB
- Rural considerations

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"Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."

Thomas Sydenham, 1680

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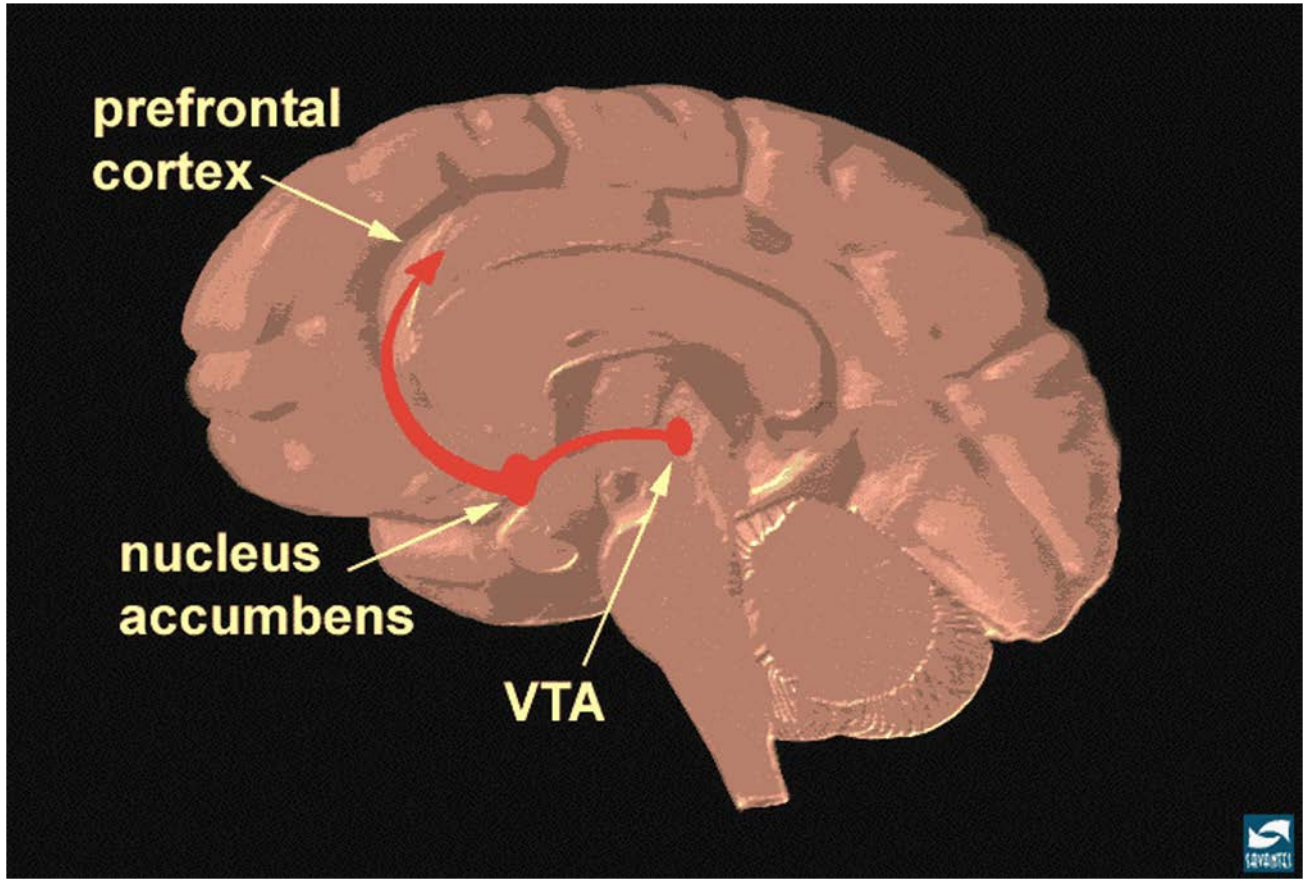
Neurobiology of Opioid Use

Reward pathway in brain

- Dopamine receptor activation in VTA
- Signal of reward sent to NA
- Reinforcement of reward signalled in PFC
- Drugs and alcohol have an effect on dopamine release at either VTA or NA



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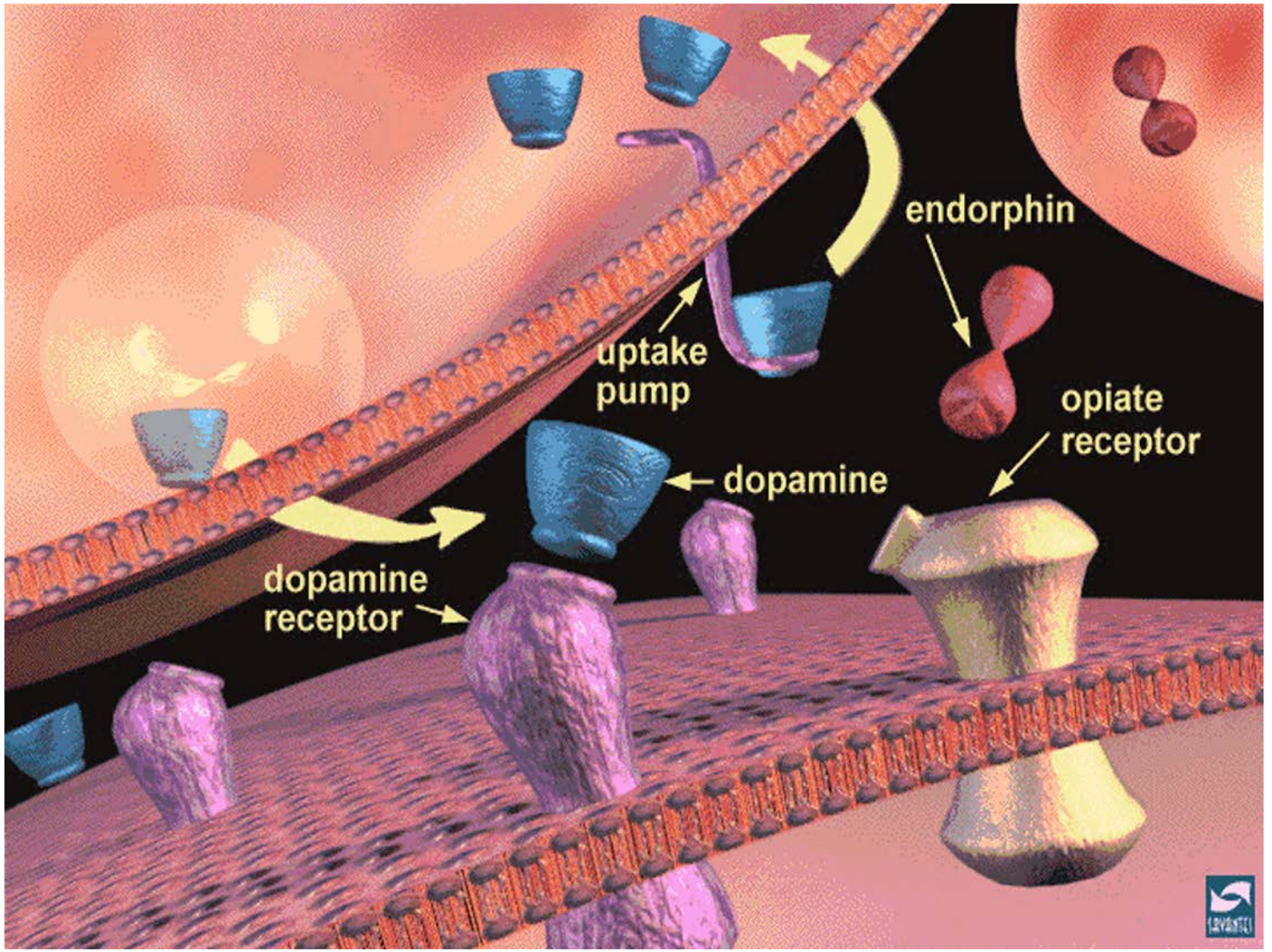
Neurobiology of Opioid Use



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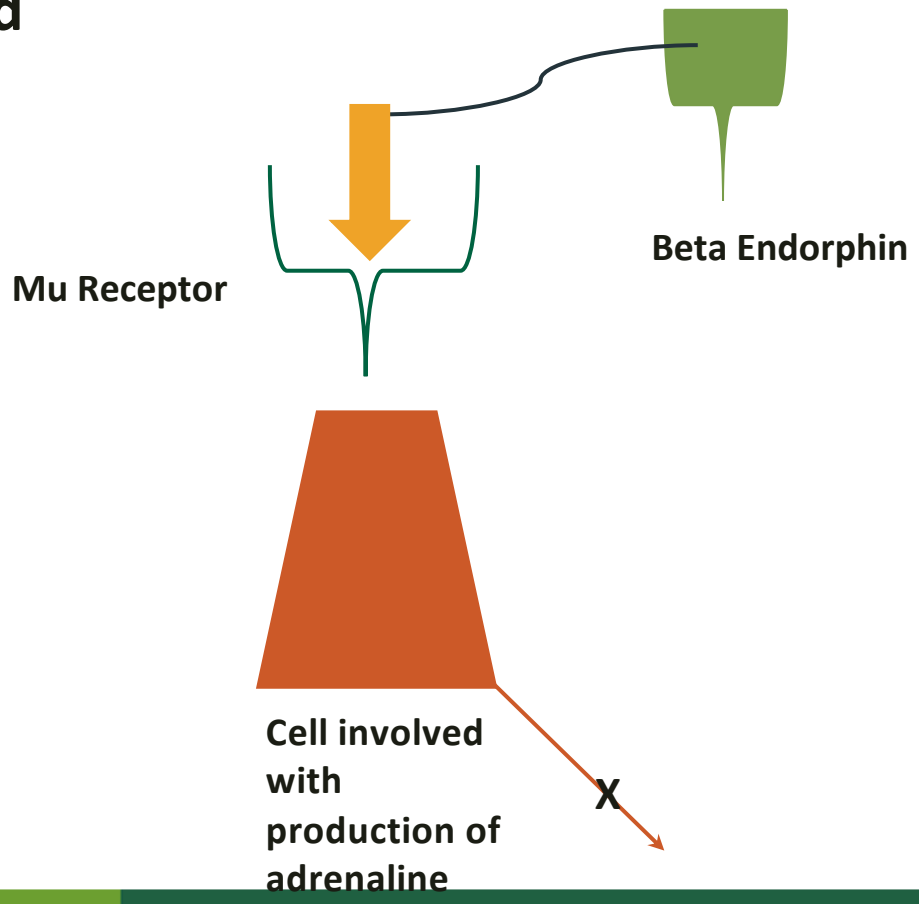
Receptor Modeling

Endogenous ligand



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Pro-opio-melano-cortin (POMC)

- Endorphin/enkephalin → opioid system
- Adrenocorticotropin → cortisol/stress system
- Melatonin → sleep-light/dark distinction

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Opioid Effects in the Brain

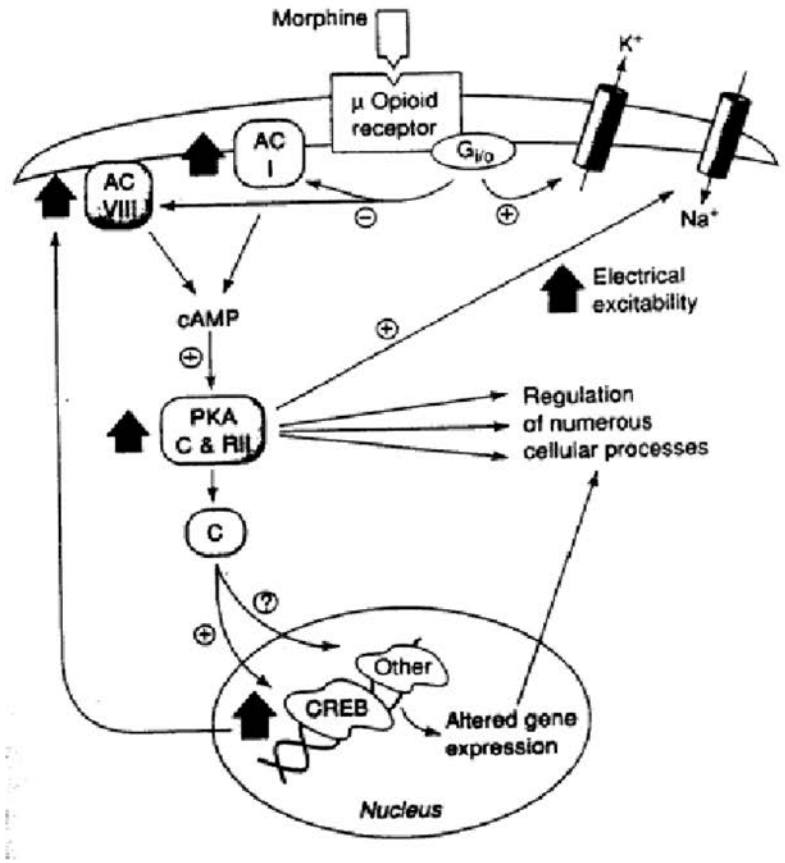

Figure 16–5. Opiate actions in the locus ceruleus. Opiates inhibit neurons of the locus ceruleus (LC) by increasing the conductance of an inwardly rectifying K^+ channel through coupling with subtypes of $G_{i/o}$, and by decreasing a Na^+-dependent inward current through coupling with $G_{i/o}$ and the consequent inhibition of adenylyl cyclase. Reduced levels of cAMP decrease protein kinase A (PKA) activity and the phosphorylation of the responsible channel or pump. Inhibition of the cAMP pathway also decreases the phosphorylation of numerous other proteins and thereby affects many additional processes in the neuron; for example, it reduces the phosphorylation state of CREB, which may initiate some of the longer-term changes in LC function. Upward bold arrows summarize the effects of prolonged exposure to morphine in the LC. Such long-term exposure increases levels of types I and VIII adenylyl cyclase, PKA catalytic (C) and regulatory type II (RII) subunits, and several phosphoproteins, including CREB. These changes contribute to the altered phenotype of the drug-addicted state. For example, the intrinsic excitability of LC neurons is increased by enhanced activity of the cAMP pathway and Na^+-dependent inward current, which contribute to the tolerance, dependence, and withdrawal exhibited by these neurons. Up-regulation of type VIII adenylyl cyclase is mediated by CREB, whereas up-regulation of type I adenylyl cyclase of the PKA subunits appears to occur through CREB-independent mechanisms. (Adapted with permission from Nestler EJ, Aghajanian EK. 1997. *Science* 278:58.)

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Heroin

- Short acting
- Highly reinforcing
- Chronic brain changes

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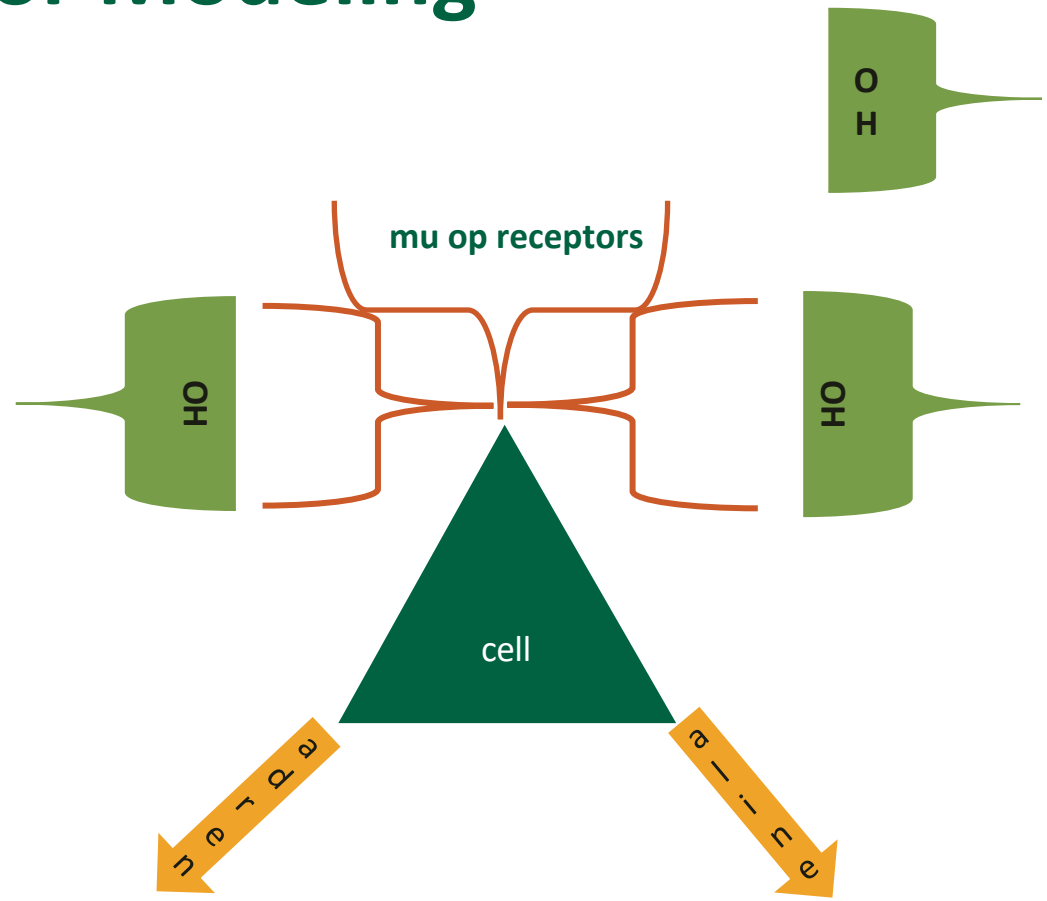
Heroin Receptor Modeling

Binding of heroin at mu recptors reduces adrenaline production



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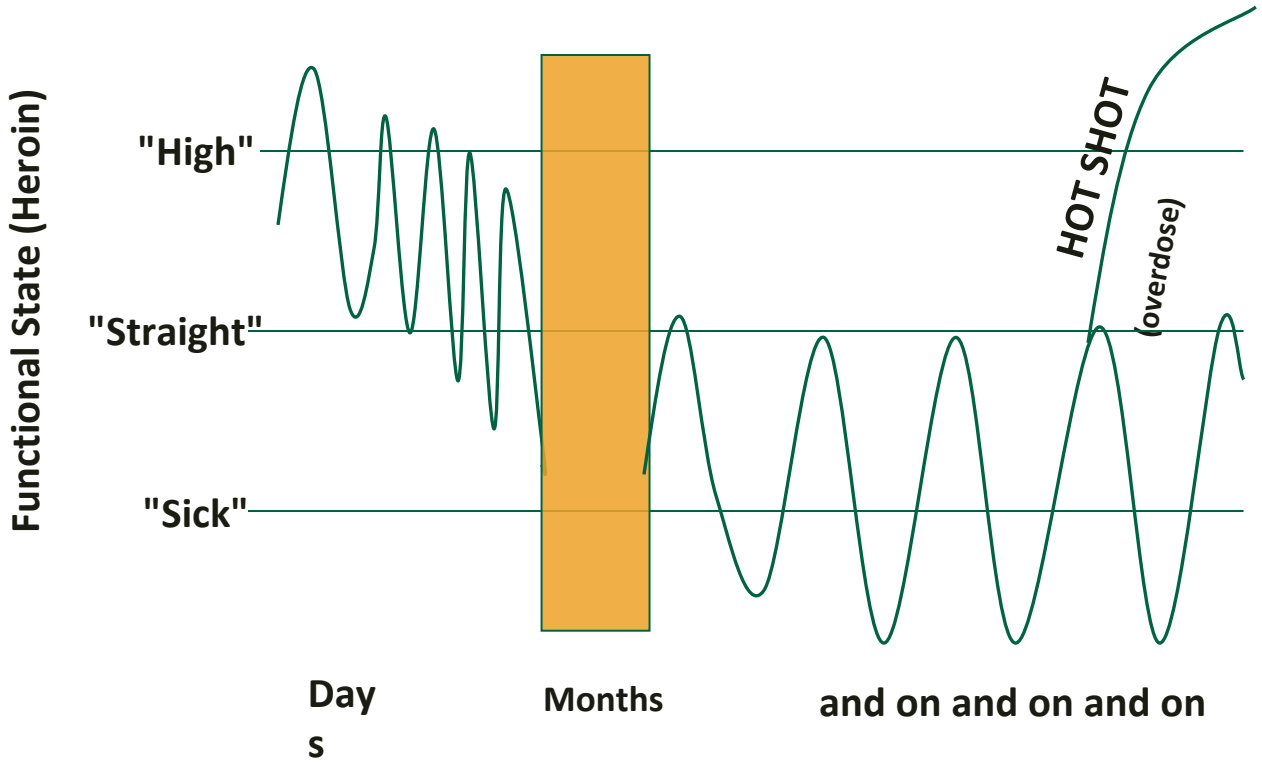
Impact of Short-Acting Heroin As Used on a Chronic Basis in Humans



JRB 2010

Modified from Dole, Nyswander and Kreek, 1966

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Heroin

- Withdrawal symptoms within 12 hours of stopping
- Permanently causing hyperexcitability and cravings
  - Release of adrenaline continues or patient feels uneasy and irritable until rebinding at the mu receptor recurs

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The final dried product is white heroin hydrochloride (powdered white heroin)

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DEA illustration of 2 milligrams of fentanyl, a lethal dose in most people

Fentanyl and Analogues

- Easier to smuggle than heroin
- Fraction of the amount needed
- More effect on user
- Often deadly

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Medications for Opioid Use Disorder (MOUD)

- Corrective NOT curative treatment for heroin users
- WHO list of most essential medications
- Long term treatment needed
- Methadone and buprenorphine most effective

SAMHSA, 2020

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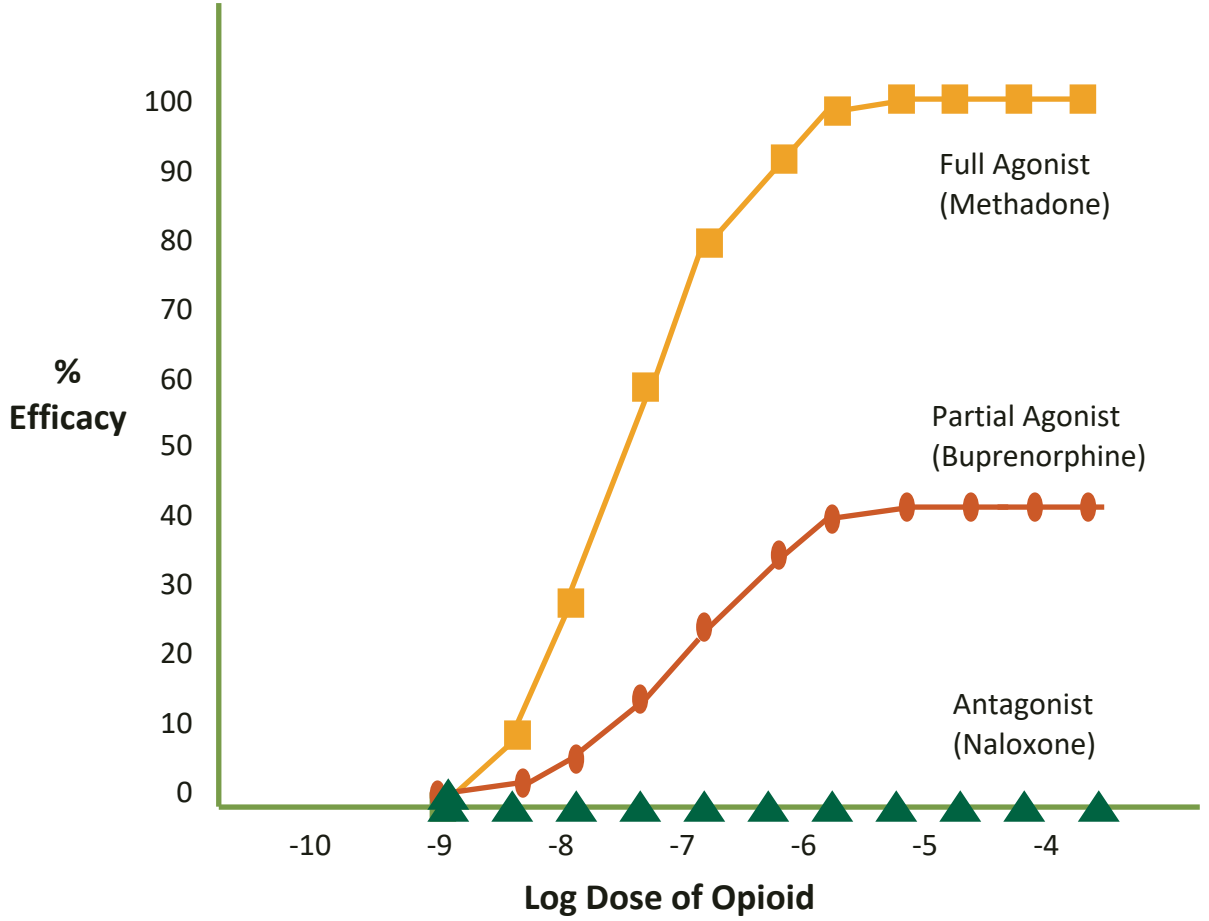
Efficacy: Full Agonist (Methadone) Partial Agonist (Buprenorphine), Antagonist (Naloxone)



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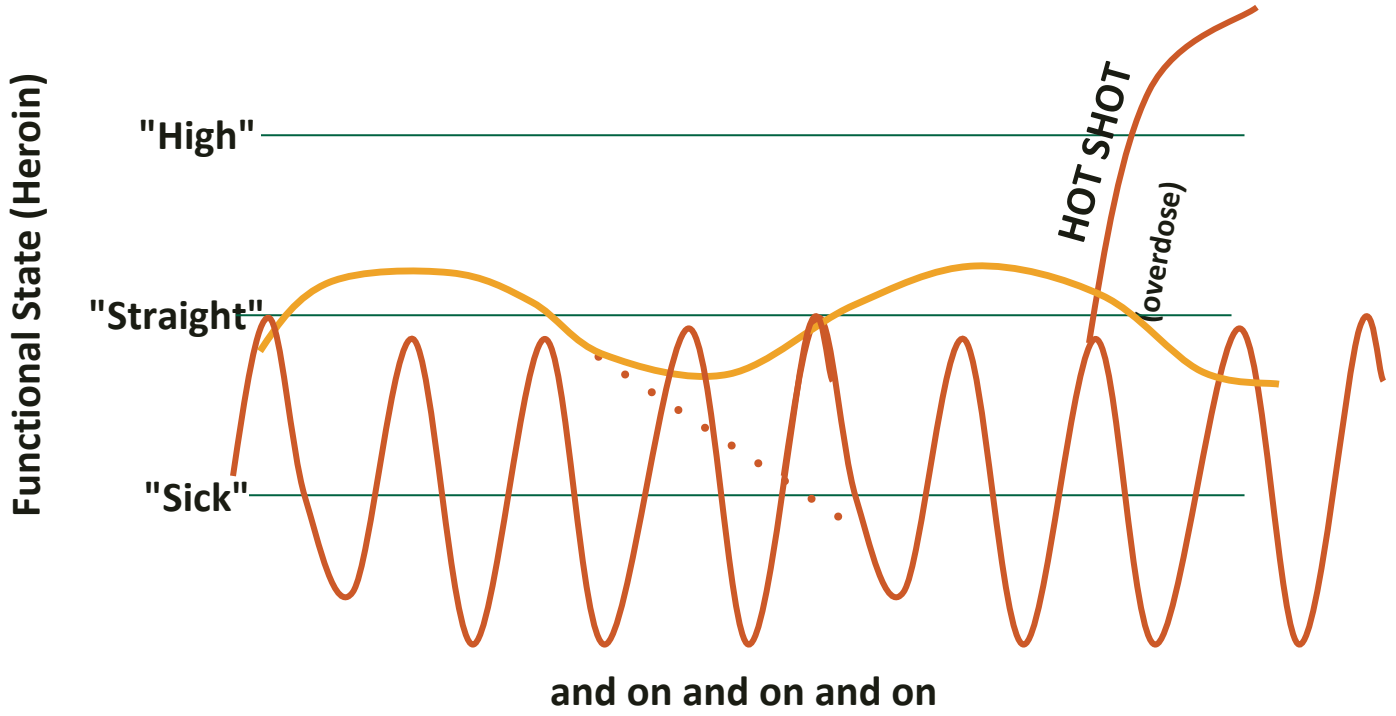
Now, add methadone



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Very modified, but indebted to Dole, Nyswander and Kreek, 1966

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Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder

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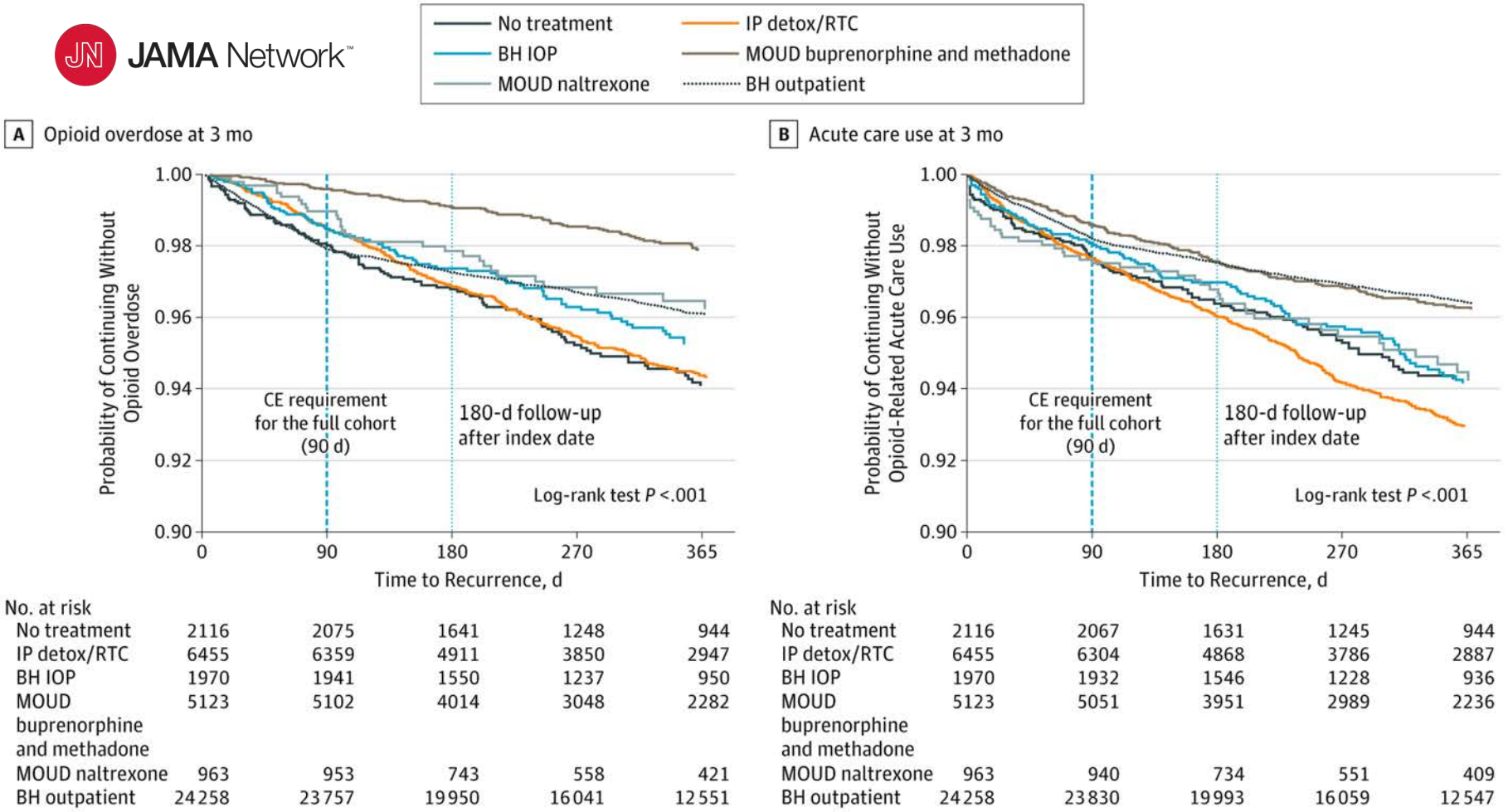

No. at risk

No treatment	2116	2075	1641	1248	944
IP detox/RTC	6455	6359	4911	3850	2947
BH IOP	1970	1941	1550	1237	950
MOUD buprenorphine and methadone	5123	5102	4014	3048	2282
MOUD naltrexone	963	953	743	558	421
BH outpatient	24258	23757	19950	16041	12551

No. at risk

No treatment	2116	2067	1631	1245	944
IP detox/RTC	6455	6304	4868	3786	2887
BH IOP	1970	1932	1546	1228	936
MOUD buprenorphine and methadone	5123	5051	3951	2989	2236
MOUD naltrexone	963	940	734	551	409
BH outpatient	24258	23830	19993	16059	12547

JAMA Netw Open. 2020;3(2):e1920622. doi:10.1001/jamanetworkopen.2019.20622

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Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder

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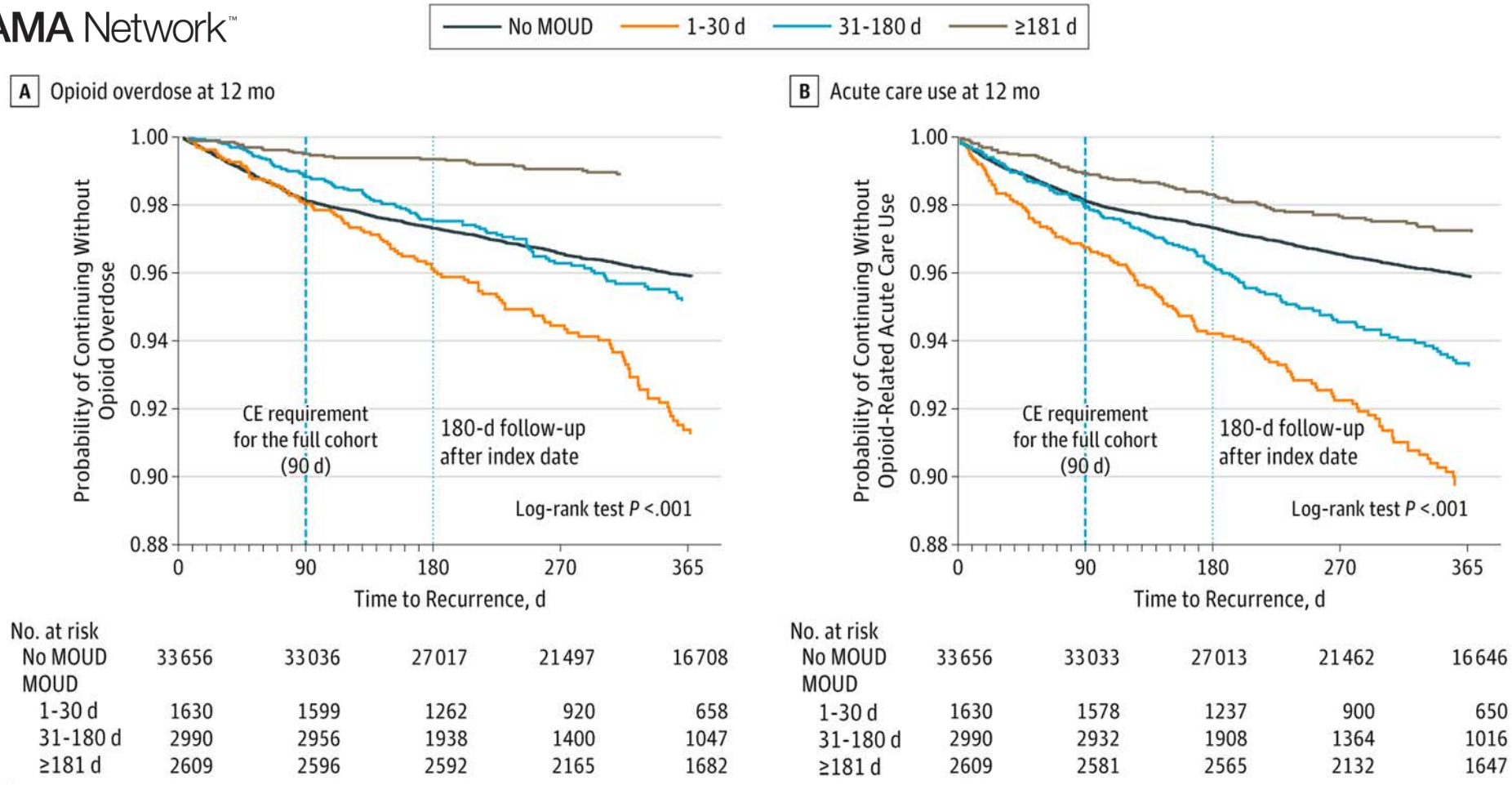

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Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder

Table 2. Adjusted Hazard Ratios for Overdose and Serious Opioid-Related Acute Care Use by Initial Treatment Group Compared With No Treatment[a]

Variable	Adjusted Hazard Ratio (95% CI)	
	3 Months	12 Months
Overdose		
No treatment	1 [Reference]	1 [Reference]
Inpatient detoxification or residential services	0.82 (0.57-1.19)	1 (0.79-1.25)
BH IOP	0.81 (0.50-1.32)	0.75 (0.56-1.02)
MOUD treatment with buprenorphine or methadone	0.24 (0.14-0.41)	0.41 (0.31-0.55)
MOUD treatment with naltrexone	0.59 (0.29-1.20)	0.73 (0.48-1.11)
BH other	0.92 (0.67-1.27)	0.69 (0.56-0.85)
ED or inpatient stay		
No treatment	1 [Reference]	1 [Reference]
Inpatient detoxification or residential services	1.05 (0.76-1.45)	1.20 (0.96-1.50)
BH IOP	0.84 (0.54-1.30)	0.90 (0.67-1.20)
MOUD treatment with buprenorphine or methadone	0.68 (0.47-0.99)	0.74 (0.58-0.95)
MOUD treatment with naltrexone	1.15 (0.69-1.92)	1.07 (0.75-1.54)
BH other	0.59 (0.44-0.80)	0.60 (0.48-0.74)

Abbreviations: BH IOP, intensive behavioral health (intensive outpatient or partial hospitalization); BH other, only nonintensive behavioral health (outpatient counseling); ED, emergency department; MOUD, medication for opioid use disorder.

[a] The hazard ratios were adjusted for age, sex, race/ethnicity, insurance type, baseline medical (modified Elixhauser index score) and mental health comorbidities (depression, anxiety, posttraumatic stress disorder, and attention-deficit/hyperactivity disorder), evidence of overdose or infections related to intravenous drug use, and cost rank.

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Buprenorphine Pharmacodynamics

High affinity for the mu opioid receptor

- Competes with other opioids and blocks their effects

Slow dissociation from the mu opioid receptor

- Prolonged therapeutic effect for opioid dependence treatment

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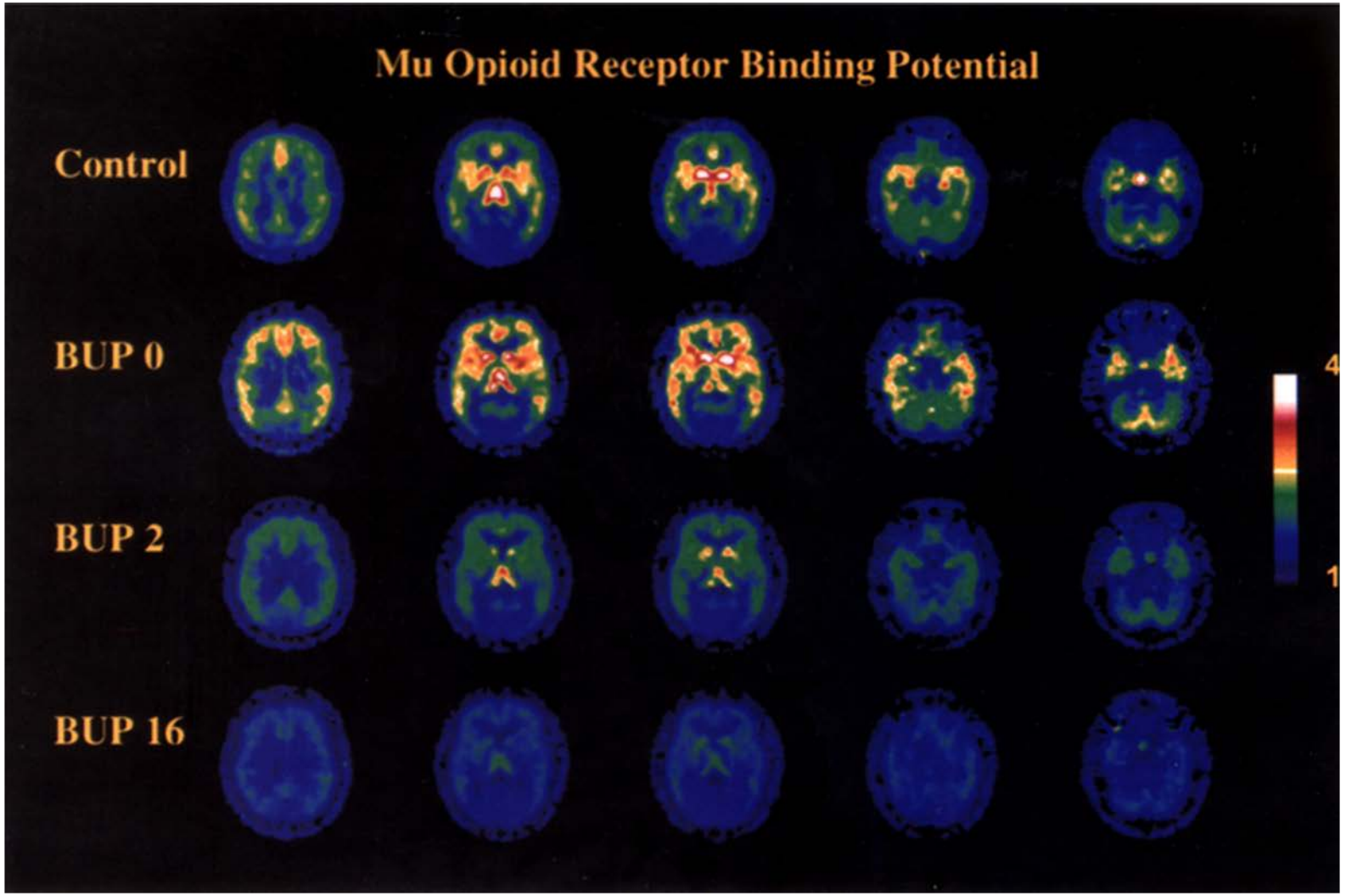

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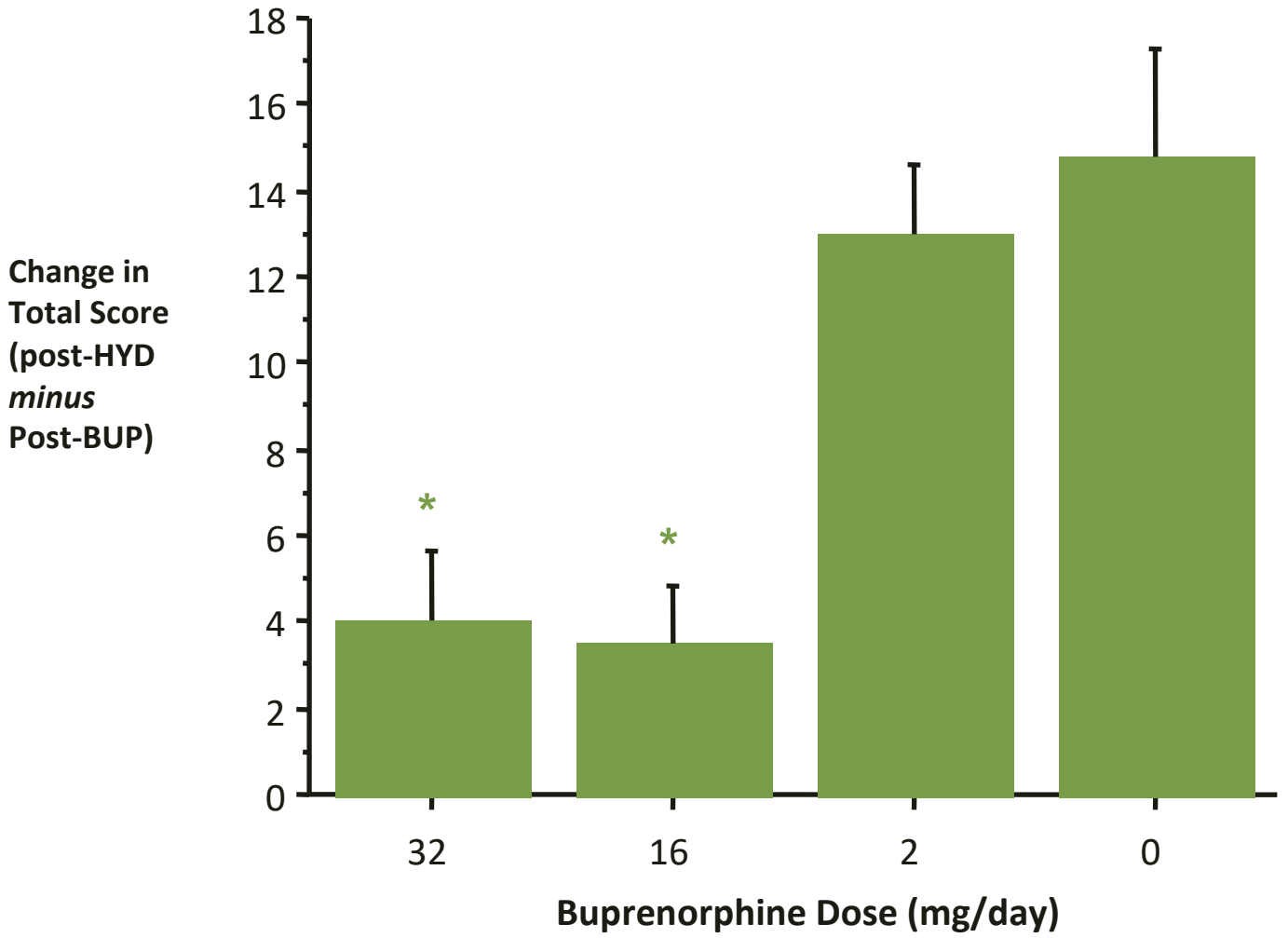
Buprenorphine Blockade of Hydromorphone Opiate Effects



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Buprenorphine Tablet Safety and Efficacy Trial

Fudala et al. (2003):

- Buprenorphine, buprenorphine plus naloxone vs. placebo
  - 4-week efficacy study, 48-week open label
  - Buprenorphine 16mg
  - Buprenorphine groups exhibit less craving, less illicit opiate use on Utox testing
  - Rates of adverse events similar with placebo

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Maintenance Treatment Using Buprenorphine

To summarize efficacy of maintenance buprenorphine:

- Studies show buprenorphine more effective than placebo, similarly effective as moderate doses of methadone and LAAM on primary outcomes of:
    1. Treatment retention
    2. Rates of opioid-positive urines
    3. Self-reports of craving and illicit-opioid use

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Comparison of Buprenorphine: Maintenance vs. Detoxification

- Double-blind, placebo-controlled RCT (n=20 per group)
  - 16 mg/day SL tablets, or 6-day taper
- Psychosocial treatments:
  - Group and individual counseling
  - Assistance with social service agencies (e.g., for housing and employment)

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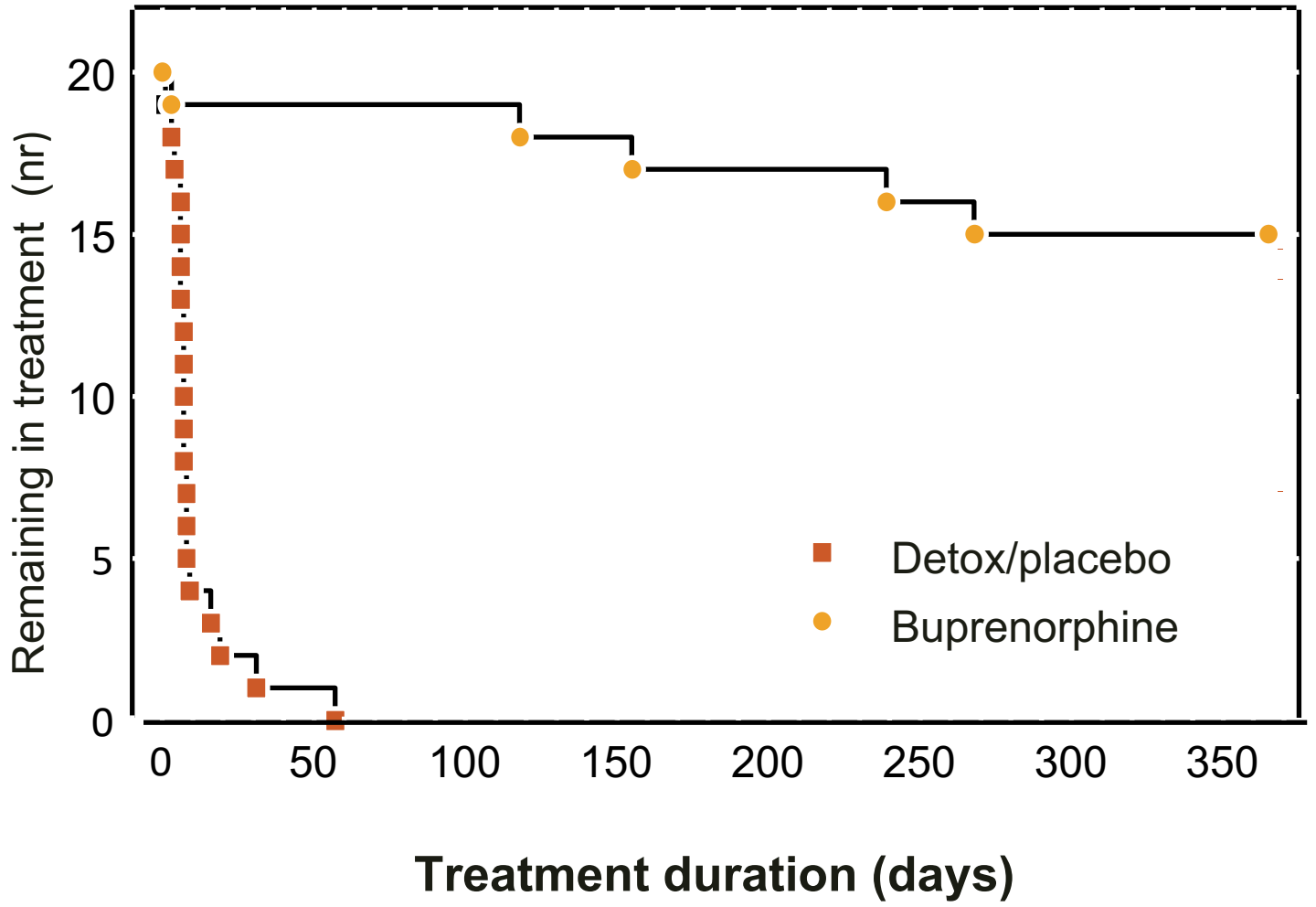
Buprenorphine Maintenance and Detoxification: Retention



(Kakko et al., 2003)

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Buprenorphine Detox vs. Maintenance: Mortality

	Detox/Placebo	Buprenorphine	Cox regression
Mortality	4/20 (20%)	0/20 (0%)	c^2=5.9; p=0.015

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Limitations of Sublingual Buprenorphine

- Daily
- Pharmacy
- Stigma
- Office visits
- Inconvenience
- Compliance

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Sustained-Release Opioid Formulations

- Prolonged release of BUP into bloodstream with a single administration
- Suppress withdrawal and block exogenously-administered opioids for extended durations
- Avoid the plasma peaks and troughs observed with SL administration

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Sustained Release Injectable Buprenorphine

- Retention rates are similar to SL dosing over 6 months in studies
- Similar in terms of opioid negative urines, cravings and withdrawals

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Formulations

Invidior

- “Sublocade”
- Available in 300 mg and 100 mg dosages

Braeburn

- “Brixadi” or “CAM-2028”
- Not yet available, anticipated launch date
- Will be available in 24 mg and 32 mg dosages

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Induction

- Must be stable on doses of SL buprenorphine 8-24 mg for 7 days
- Stability implies absence of withdrawal symptoms

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Dosing

- Recommendation is 300 mg/1.5 ml injection monthly for 2 months
- Then 100 mg/0.5 mg monthly thereafter

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Clinical monitoring

- SL BPN undergoes first pass metabolism and produces NBPN found in urine
- Presence of NBPN often used as marker of adherence
- Non-SL routes (IV,IN,SC) of BPN do not undergo first pass metabolism and will have much less NBPN in the urine.
- Minimal interaction with CYP450 inducers or inhibitors with SC route
- Potential for elevations in LFTS 3-5x/normal

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Side effects

- Most common are injection site concerns
- Ping pong size subcutaneous lump can persist for 8 weeks for 300 mg; 4 weeks for 100 mg
- Rotation across abdomen is needed
- Constipation
- Sedation
- Pain
- Allergic reaction

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Clinical settings

- Not for induction
- Leaving inpatient setting on SL BPN where treatment may not be readily available
- Intolerance to naloxone component of BPN/NLX
- Risk of injection of BPN
- Diversion or inability to keep SL BPN safe
- Transportation difficulties
- Workplace hours

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Monitoring

- How often to see in office?
- How often to get drug testing
- How often to check liver tests?
- How often to provide counseling?
- What to do about non-compliance?

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Rural Implications

- Travel to clinics and early hours for employment are barriers
- Lack of providers in most rural counties affects treatment access
- Having a regional program for injections allows more latitude in work, home and social life

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Questions?

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Our next session will be held on
Wednesday, March 24th 12-1pm ET

Acute Pain Management:
Safe Opioid Prescribing for Patients After Surgery

Marjorie Meyer, MD

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Vermont Center on Behavior and Health: http://www.med.uvm.edu/behaviorandhealth/

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