# OPIOIDS, BUPRENORPHINE AND REALITY

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# DISCLOSURES

- No support has been provided by:
  - Pharma
  - Device
  - Other conflicting investments

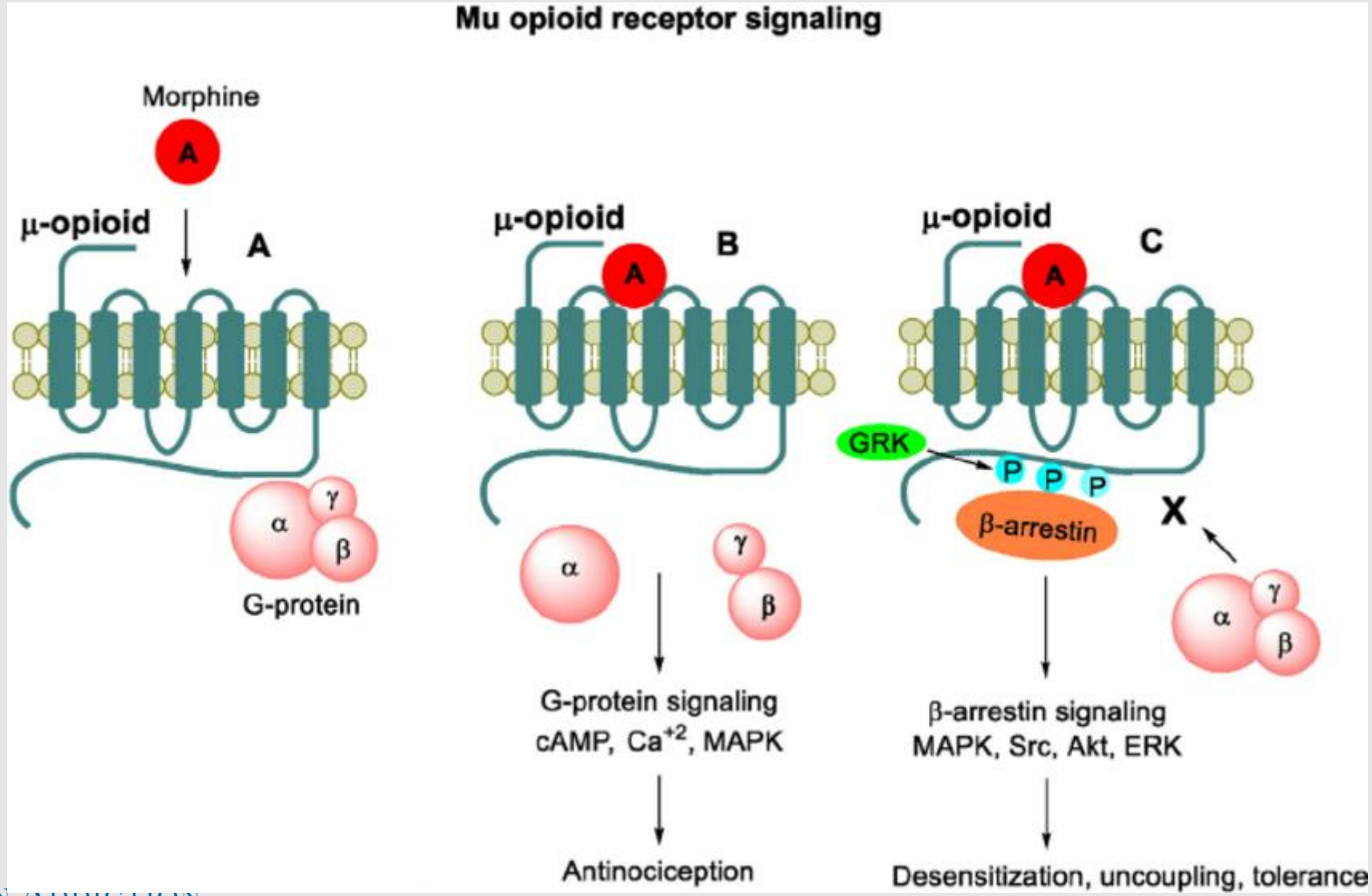
# SYNOPSIS

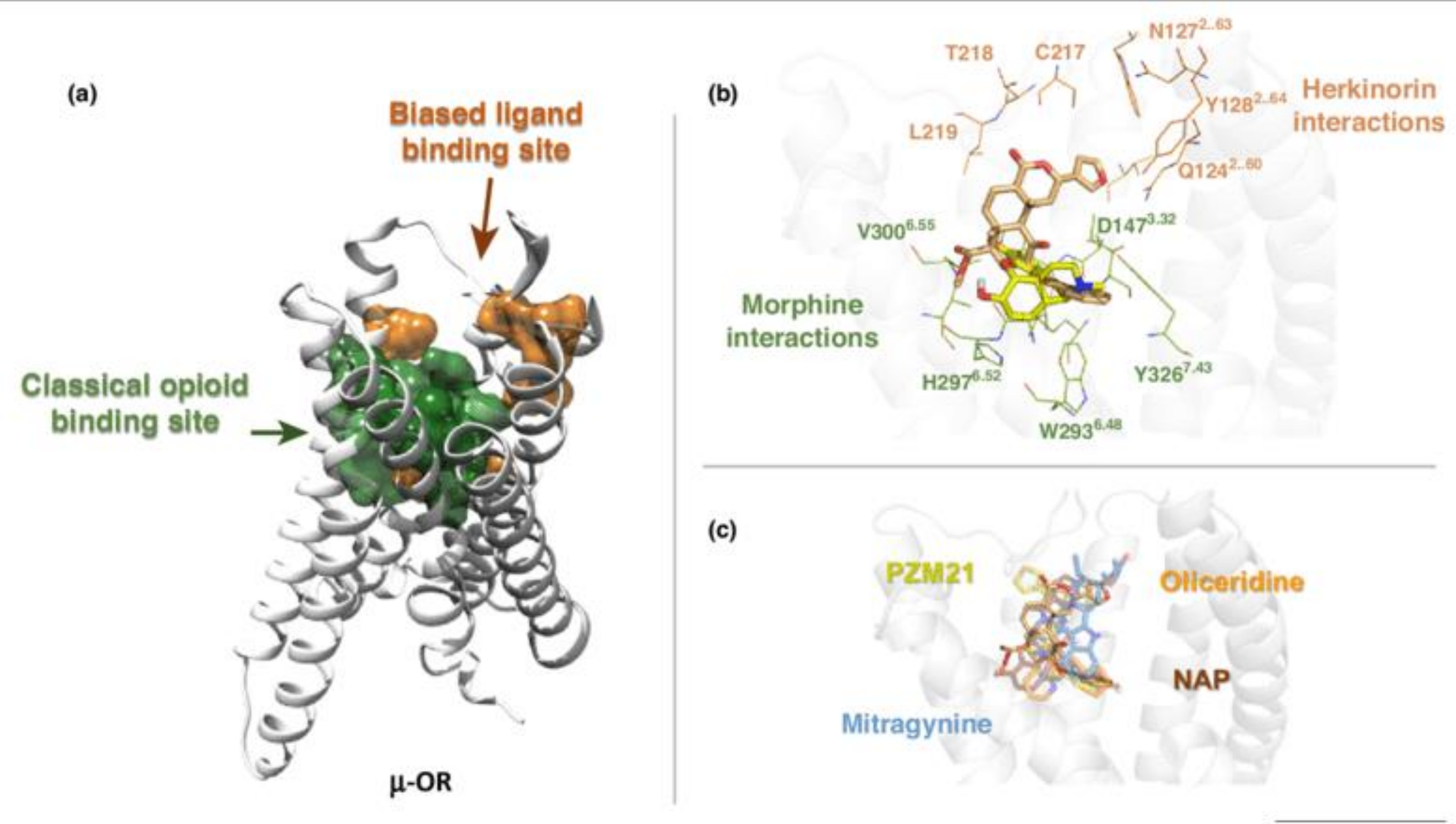
- In this lecture We will discuss the pharmacology and toxicology of opioids and how the body reacts to them. We will pay particular attention to buprenorphine's complex pharmacology and safety.

# OBJECTIVES

- The learner will be able to describe the body's natural opioids
- The learner will be able to describe the opioids core molecule and why it is important
- The learner will be able to describe the safety profile for buprenorphine
- The learner will apply this to their work and the instructions that are delivered to patients

# OPIOID RECEPTOR OVERVIEW



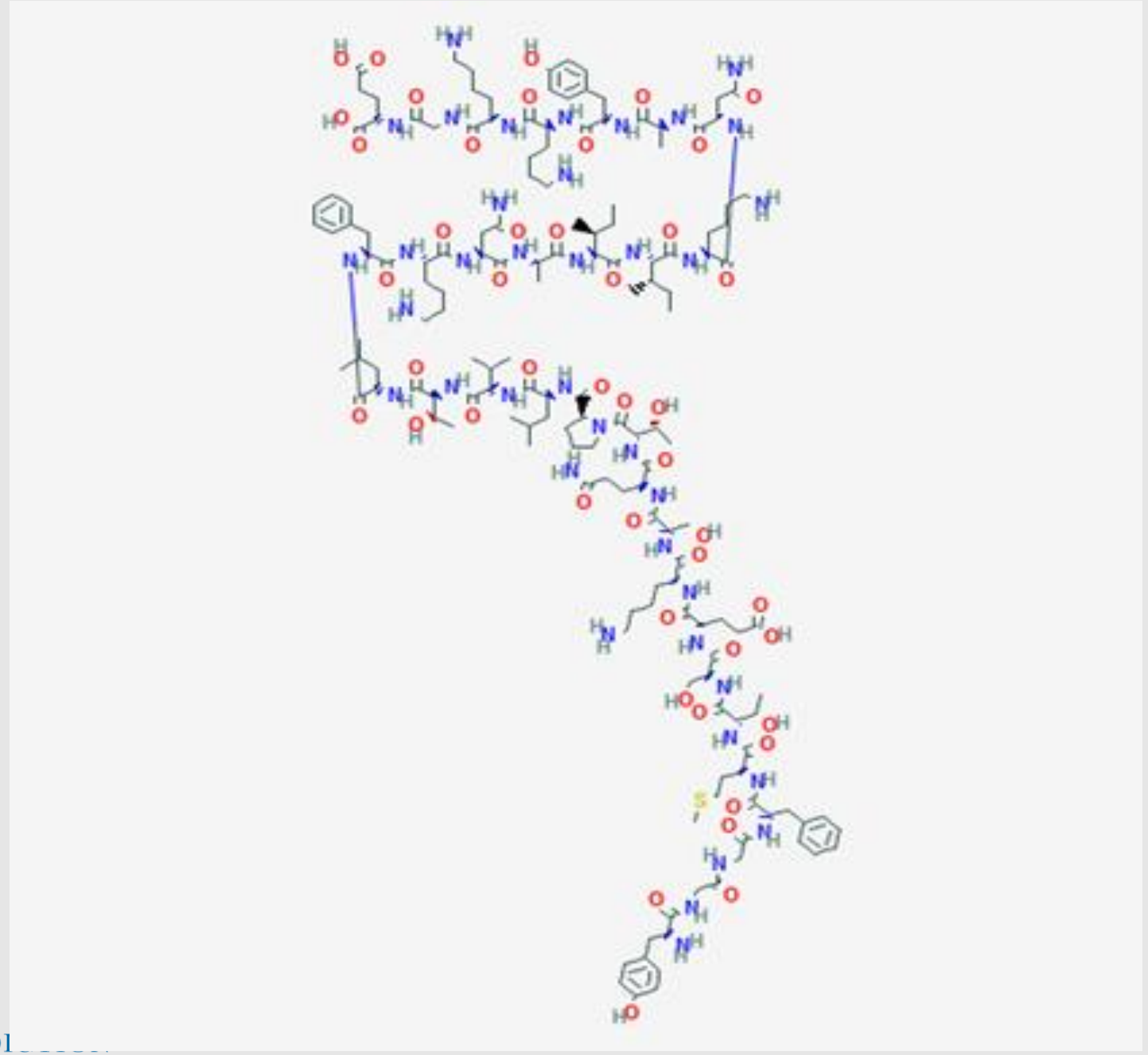

(a)
Biased ligand binding site
Classical opioid binding site
μ-OR
(b)
T218
C217
N127^2.63
Y128^2.64
L219
Q124^2.60
Herkinorin interactions
V300^6.55
D147^3.32
Morphine interactions
H297^6.52
Y326^7.43
W293^6.48
(c)
PZM21
Oliceridine
NAP
Mitragynine

# THE OPIOID CLASSES

- **Endogenous opioid peptides:** these are the bodies naturally produced opioids and include molecules such as endorphins, enkephalins, dynorphins and endomorphins.
- **Naturally occurring opiates and their esters:** These are the compounds that are directly linked to the opium poppy and include molecules such as morphine, codeine, thebaine and diacetylmorphine (heroin)
- **Semisynthetic opioids:** these are created from the naturally occurring opiates and their esters, and include oxycodone, hydromorphone and hydrocodone. These opioids contain the same basic chemical architecture is morphine and heroin
- **Synthetic opioids:** these are opioids which are fully laboratory derived, and while able to actively bind the opioid receptors, have a different core chemical structure than both naturally occurring and semisynthetic opioids, and include molecules such as fentanyl, methadone, and tramadol.

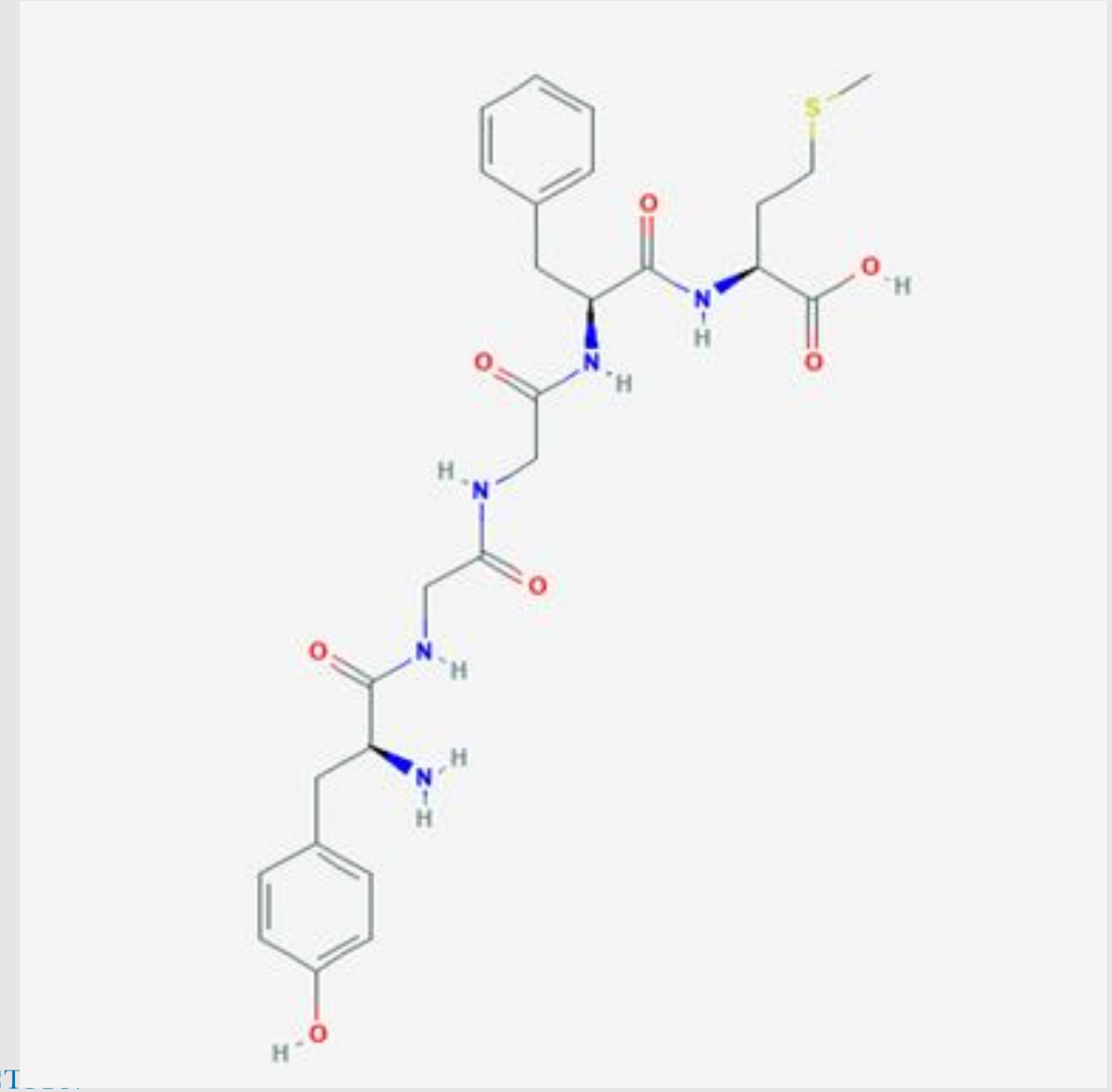
# ENDOGENOUS OPIOID PEPTIDES

- Derived from the hormone prepro-opiomelanocortin, ***endorphin*** was identified in the 1970s and has been found to be “the bodies morphine”.
- This molecule is released in times when the body is presented with physical or emotional challenge as well as significant pain or stress.
- When released it works in an area of the brain called the periaqueductal grey and is responsible for the ever fabled “runners high.”
- Its primary receptor is the mu-opioid receptor. Its structure is highly complex and the way in which it binds to the mu opioid receptor allows for predictable increase in pain control, mild euphoria and stress relief without impacting side effects such as respiratory suppression or dysphoria.



# ENDOGENOUS OPIOID PEPTIDES

- Enkephalin is derived from prepro-enkephalin, with a distribution of enkephalin into the brainstem and the spinal cord.
- It binds preferentially to the Delta opioid receptor but also to the mu opioid receptor. Like endorphin it has the capacity to produce analgesia, but also likely plays a significant role in mood stabilization and individuals response to pain.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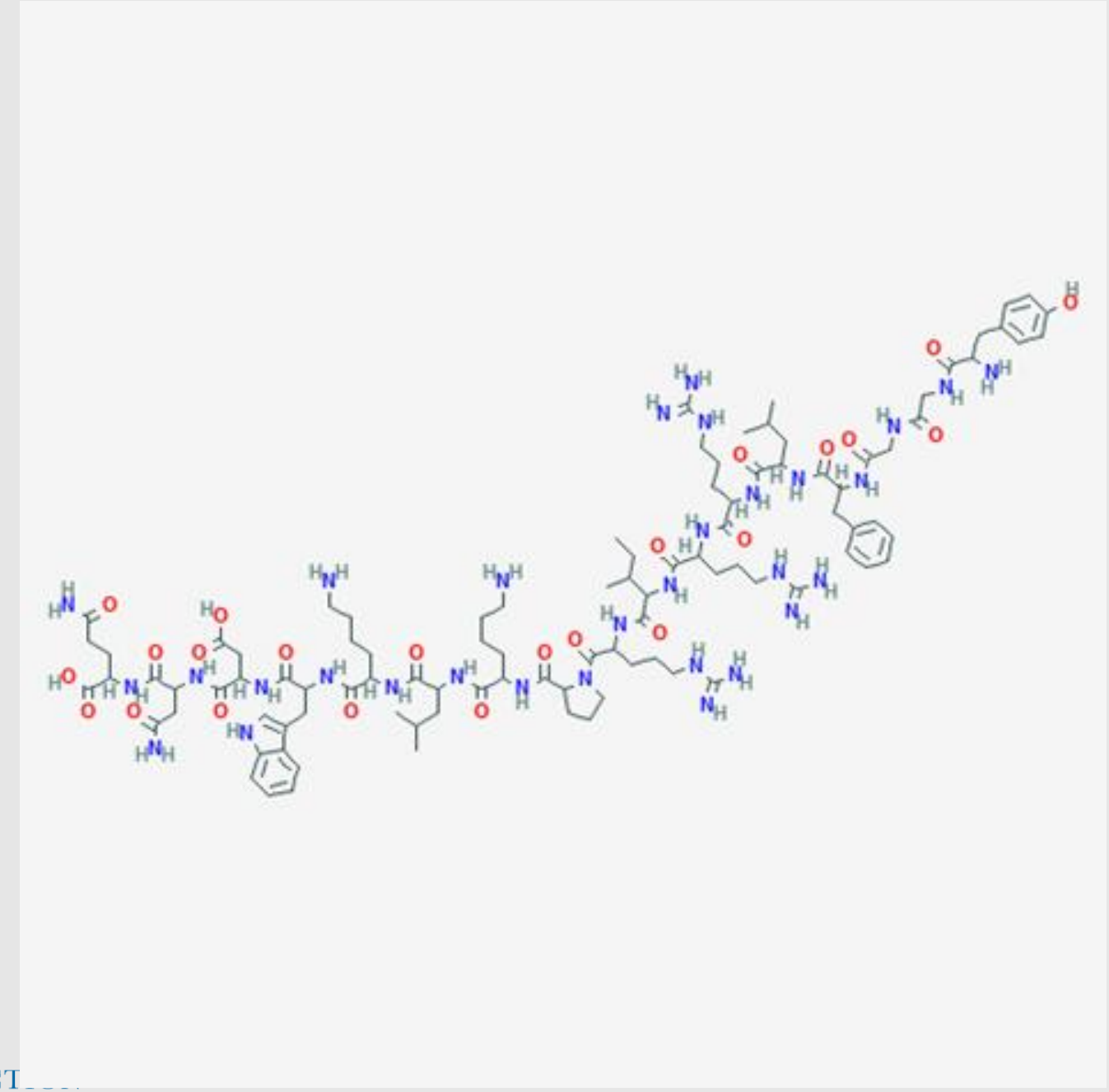
# ENDOGENOUS OPIOID PEPTIDES

- Dynorphins are derivatives of the hormone prepro-dynorphin and preferentially bind primarily to the Kappa-opioid receptor.
- Dynorphins play less of a role in the modulation of pain and instead focus on changes in learning and memory, emotional control and the stress response to pain.
- It may also play a role in the development or prevention of addiction-related behaviors.



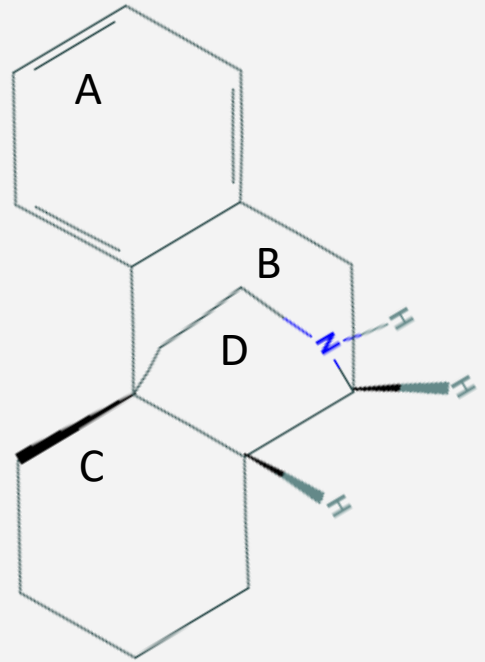
# THE HISTORY OF OPIOIDS

- 3400 B.C. opium was cultivated in lower Mesopotamia
- 460 B.C. Hippocrates recognized it a useful in treating pain
- 330 B.C. Alexander the Great introduced it to Persia and India
- 330 B.C. until 1839 the opium trade was thriving

- 1853 Dr. Alexander discovers Morphine
- 1870 C.R. Wright synthesized heroin
- 1895 Bayer begins mass production of Heroin

# THE CORE STRUCTURE

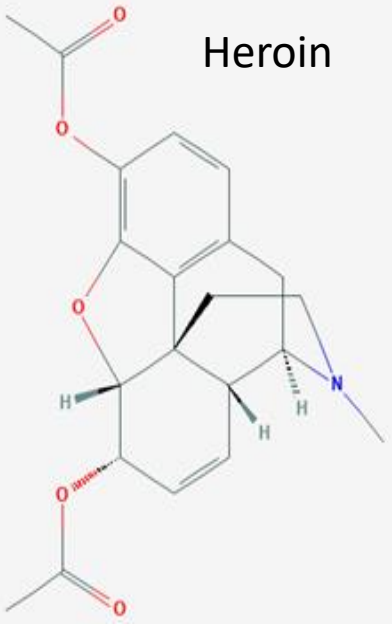
Morphinan has
a phenanthrene core structure
with the A ring remaining
aromatic and
the B and C rings being
saturated, and an additional
nitrogen-containing, six-
membered, saturated ring,
the D ring, being attached to
carbons 9 and 13 of the core,
and with the nitrogen being at
position 17 of the composite



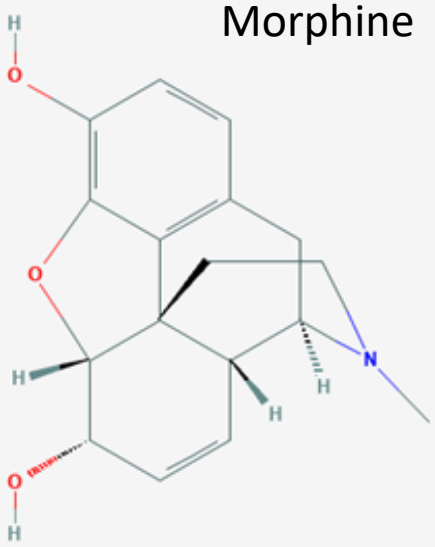
# NATURALLY OCCURRING OPIOIDS

- These opioids have the same Morpinan core structure with only small modifications
- 5 rings that form a “t” shaped structure which are the basis of the morphine ring (added a tetrahydrofuran ring, “E”)

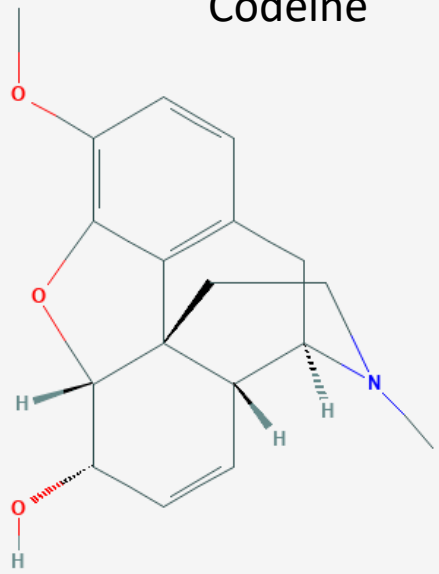
Heroin



Morphine



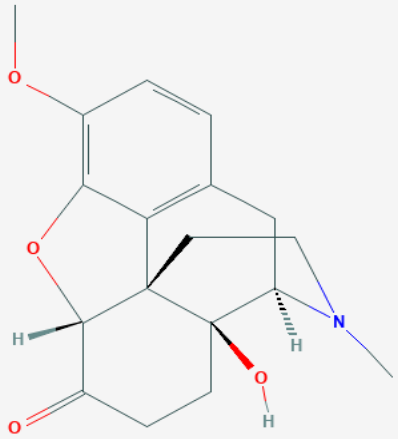
Codeine



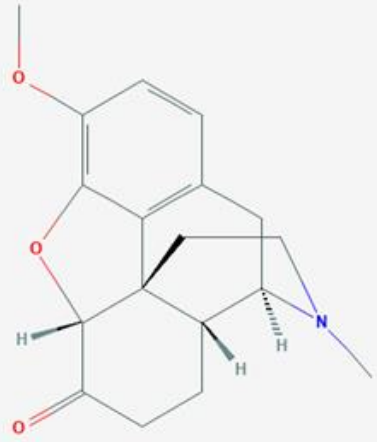
# SEMISYNTHETIC OPIOIDS

- Opioids produces from naturally occurring opioids and their esters

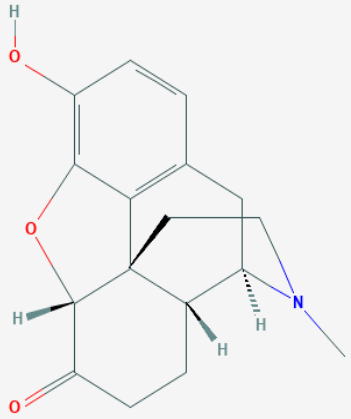
Oxycodone



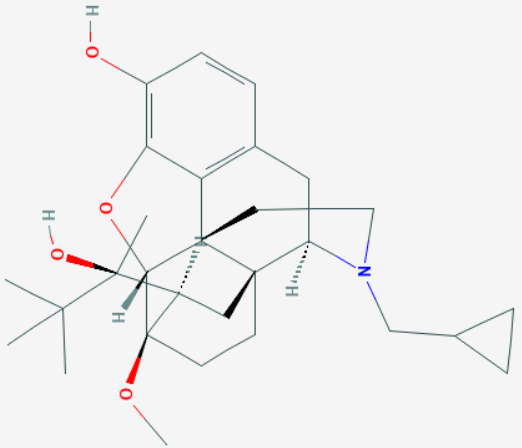
Hydrocodone



Hydromorphone



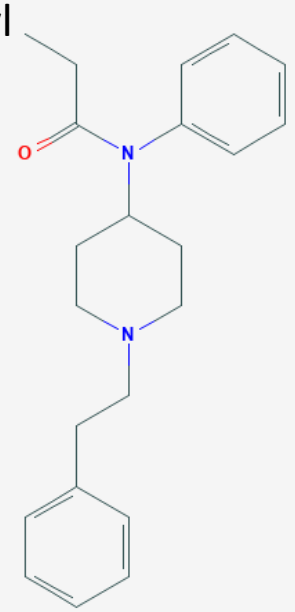
Buprenorphine



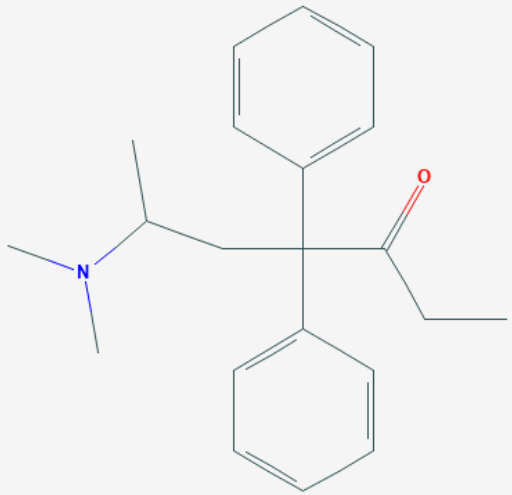
# SYNTHETIC OPIOIDS

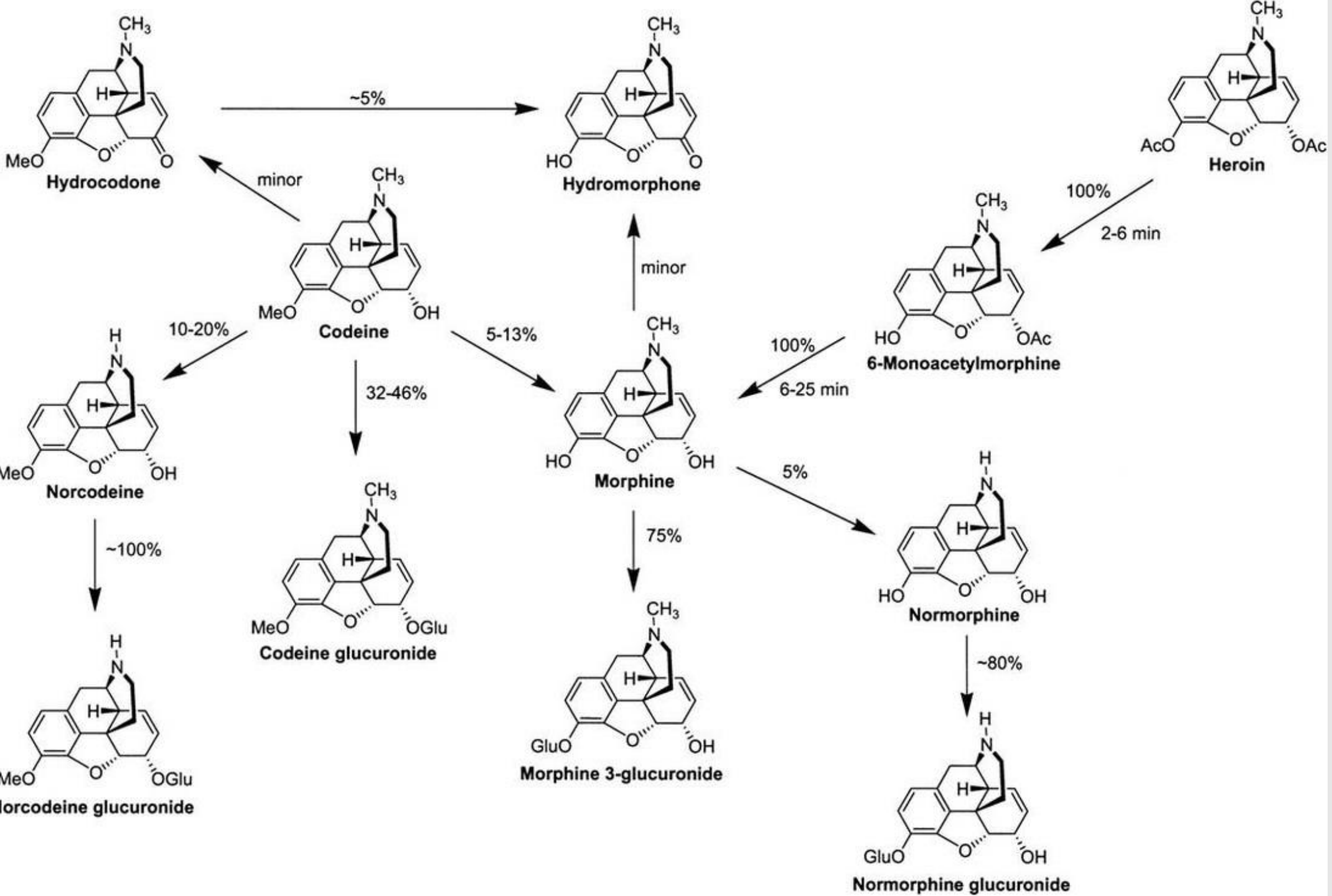
- Opioids fully derived from new structures

Fentanyl

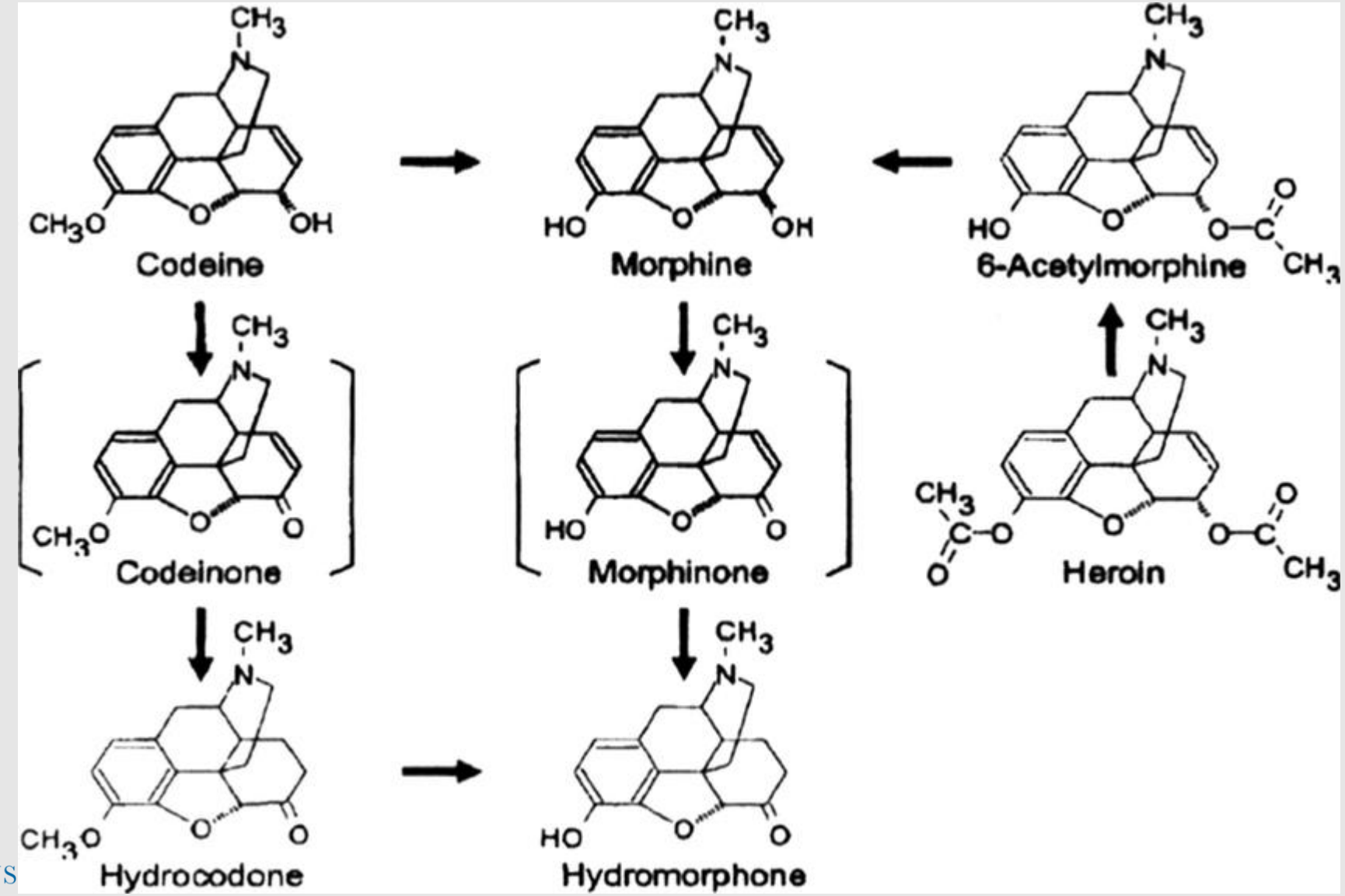



Methadone

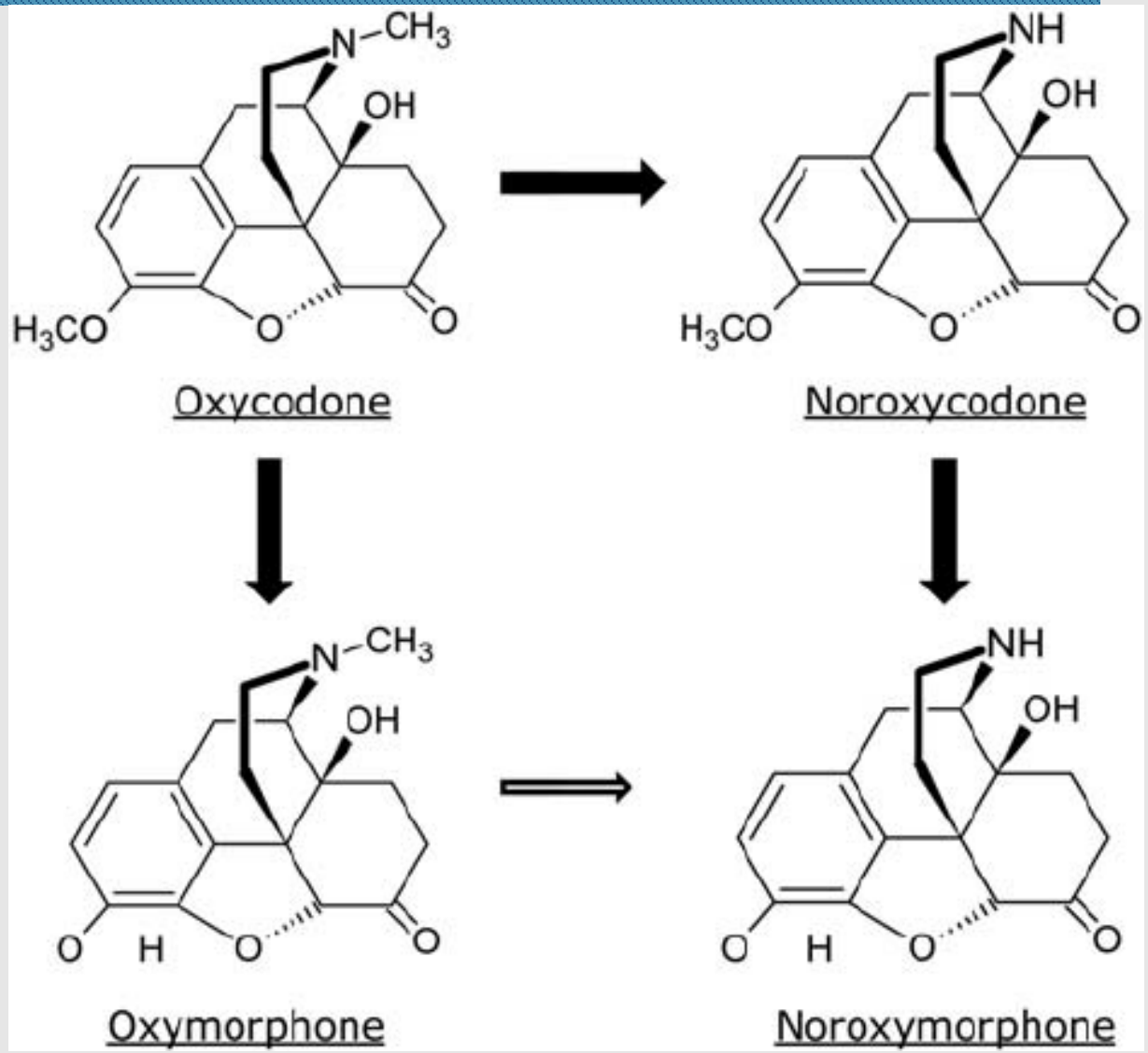


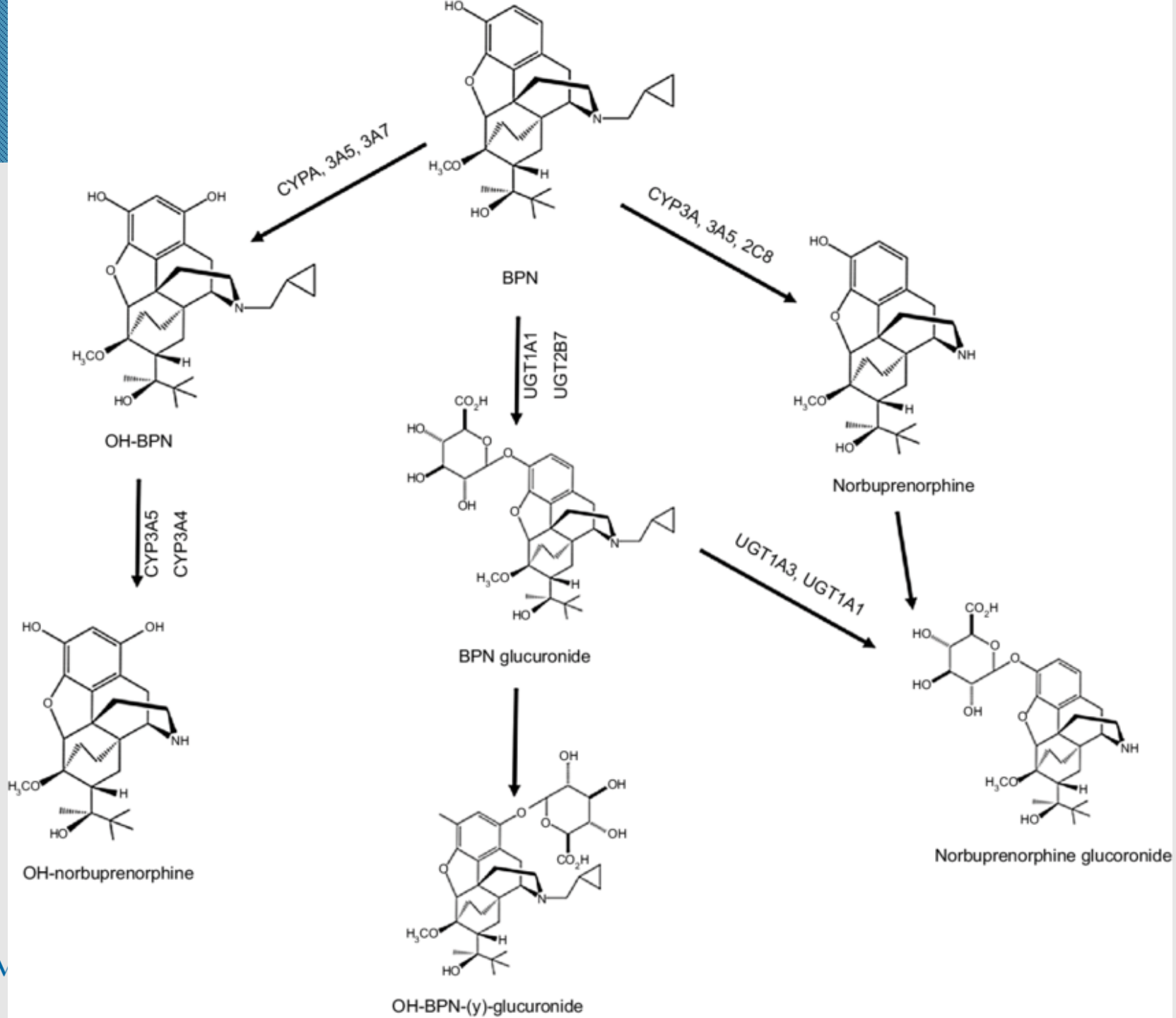

Hydrocodone
~5%
Hydromorphone
minor
Codeine
minor
10-20%
5-13%
32-46%
Norcodeine
~100%
Codeine glucuronide
Morphine
75%
Morphine 3-glucuronide
Heroin
100%
2-6 min
6-Monoacetylmorphine
100%
6-25 min
5%
Normorphine
~80%
Normorphine glucuronide

# POSSIBLE PRODUCTION OF SECONDARY HYDROMORPHONE

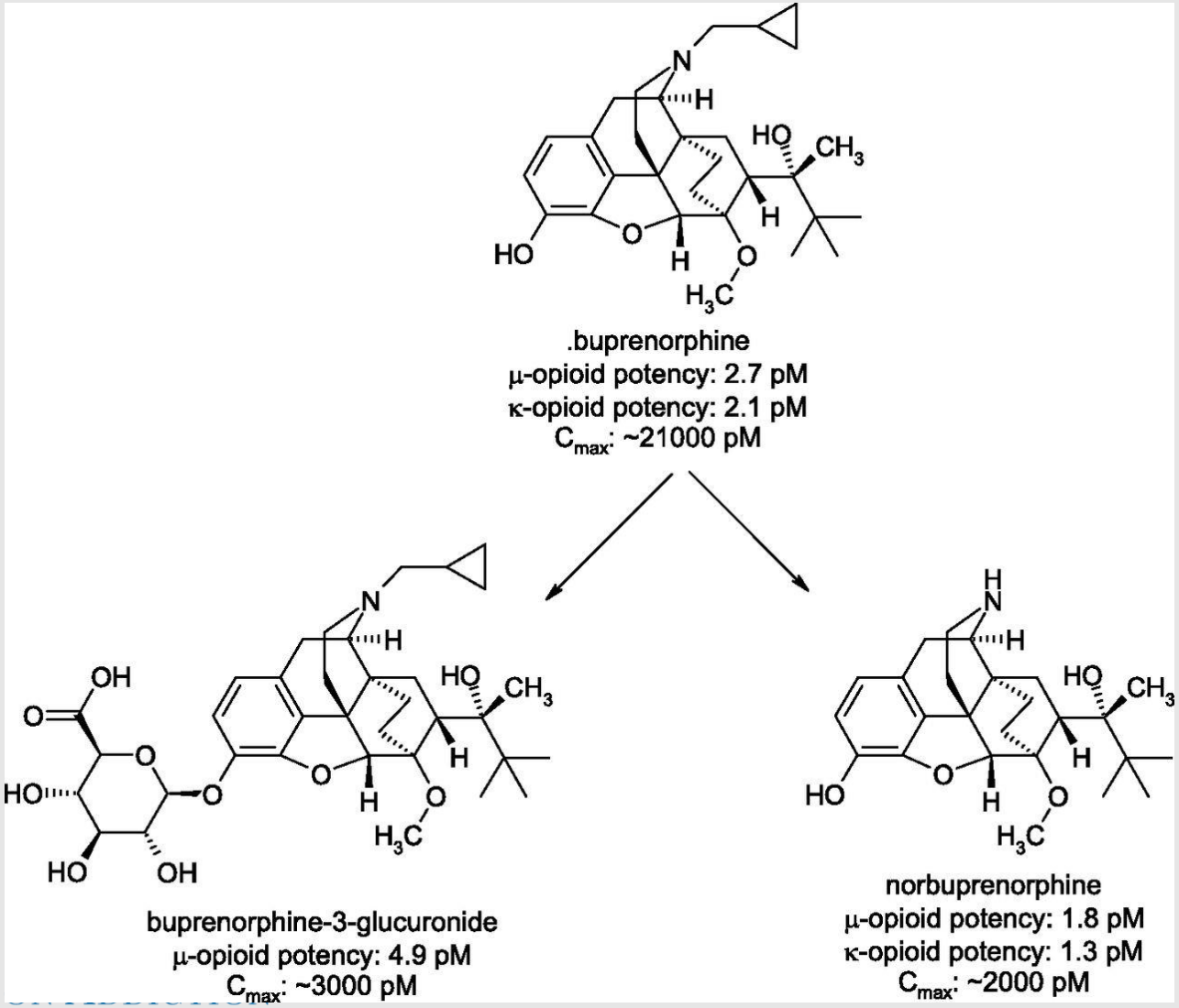


# TOXICOLOGY


N–CH3
OH
H3CO
O
O
Oxycodone
NH
OH
H3CO
O
O
Noroxycodone
N–CH3
OH
O
H
O
O
Oxymorphone
NH
OH
O
H
O
O
Noroxymorphone


CYPA, 3A5, 3A7
CYP3A, 3A5, 2C8
UGT1A1
UGT2B7
CYP3A5
CYP3A4
UGT1A3, UGT1A1
BPN
OH-BPN
Norbuprenorphine
BPN glucuronide
OH-norbuprenorphine
Norbuprenorphine glucoronide
OH-BPN-(y)-glucuronide

# BUPRENORPHINE ACTIVE METABOLITES



# GOALS OF TREATMENT?

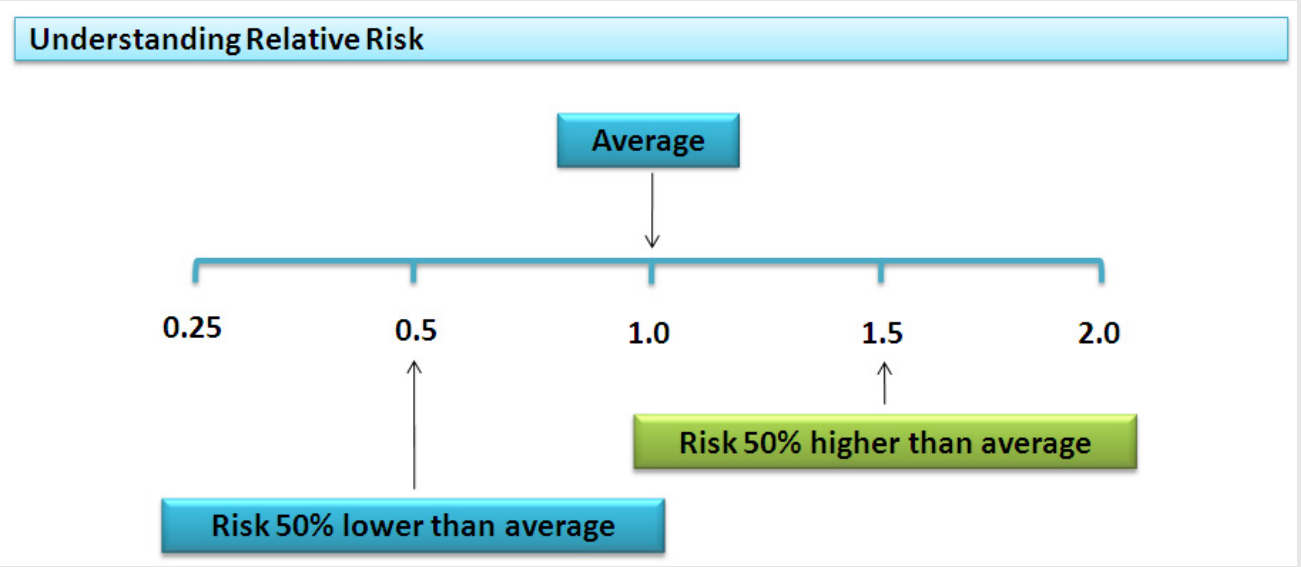
- Decreased illicit drug use
- Increased retention in treatment
- Decreased mortality

# QUICK STATS REVIEW

- Confidence Level
  - The true parameter in a proposed range
    - We are 95% confident that the true result is X (-EBM, +EBM)
    - EBM = error bound
- Confidence Interval
  - The proposed range of plausible values of X (standard deviation)
- We are 95% confident that if the entire population was evaluated that they answer would be 25 (CI 22.5-27.5)

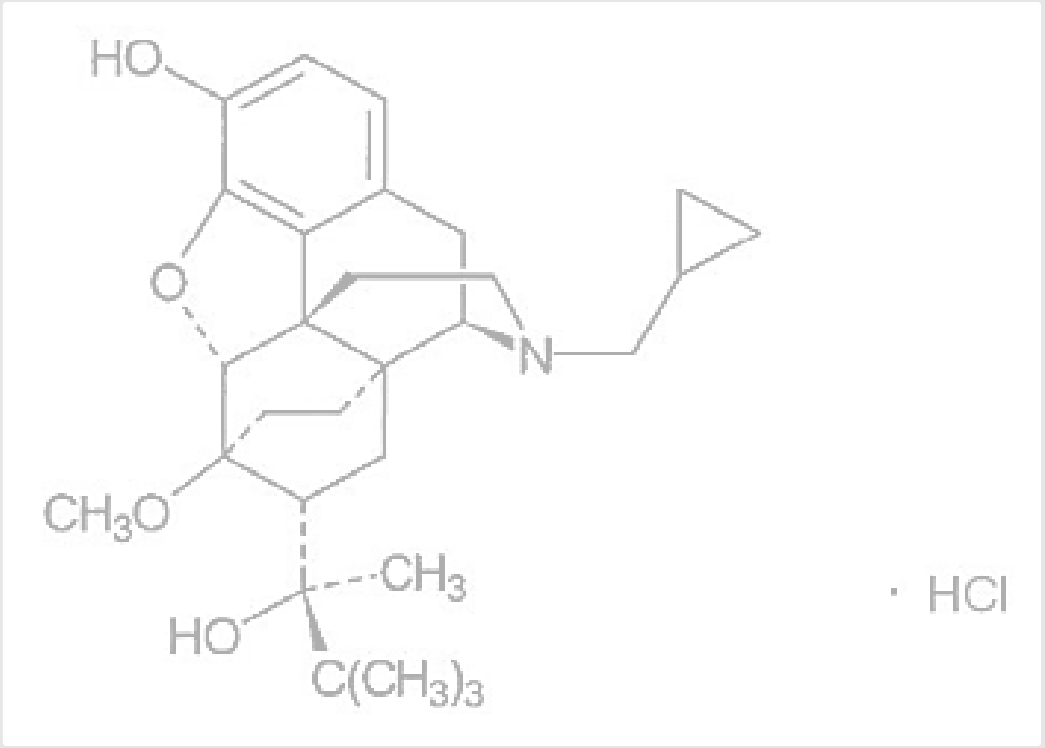
# QUICK STATS REVIEW

- Relative Risk (RR)
  - Relative Risk utilizes the probability of an event occurring in one group compared to the probability of an event occurring in the other group
  - Relative Risk values are greater than or equal to zero.  A value of 1 indicates a neutral result



# BUPRENORPHINE

- Semi-synthetic analogue of thebaine
- High receptor affinity
- Ceiling effect for respiratory depression
- Approved by the FDA in 2002 as Schedule III — up to 5 refills
- Slow dissociation
- Partial Mu-opioid agonist, k antagonist



# BUPRENORPHINE

| | | | |
|---|---|---|---|
| Metabolized in the liver, mainly by cytochrome P450 3A4 (CYP3A4), and has a less-active metabolite, **norbuprenorphine** | Most buprenorphine is ultimately excreted into the biliary tract, but small fractions enter the urine and are detectable in urine drug tests. | Because of extensive first-pass metabolism, buprenorphine has poor oral bioavailability when swallowed, and all therapeutic formulations use other routes. | Sublingual administration bypasses first-pass metabolism and allows bioavailability around 30%. |

# BUPRENORPHINE KAPPA-OPIOID RECEPTOR ANTAGONIST

- Stimulation of kappa-opioid receptor with dynorphin-like peptides
  - Inhibits dopamine release in the striatum (nucleus accumbens and caudate putamen), inducing negative mood state in humans and animals
- Buprenorphine is an antagonist at the kappa receptor
  - Antidepressant-like effects
  - Anxiolytic effects
  - Prevent stress-induced negative emotional states



Falcon, E., Browne, C., Leon, R. *et al.* Antidepressant-like Effects of Buprenorphine are Mediated by Kappa Opioid Receptors. *Neuropsychopharmacol* **41,** 2344–2351 (2016). https://doi.org/10.1038/npp.2016.38

# BUPRENORPHINE

- Daily doses below 8 mg are not sufficient to provide opioid receptor blockade in most patients
- The data are inconclusive with regards to the relative effectiveness of a daily 8 mg versus a 16 mg SL BUP tablet dose to provide μOR blockade



Optimal dose of buprenorphine in opioid use disorder treatment: a review of pharmacodynamic and efficacy data
Drug Dev Ind Pharm. 2020 Jan;46(1):1-7. doi: 10.1080/03639045.2019.1706552. Epub 2020 Jan 8.

# BUPRENORPHINE EFFICACY: SUMMARY

- Studies (RCT) show buprenorphine (16-24 mg) more effective than placebo and equally effective to moderate doses (80 mg) of methadone on primary outcomes of:
  - Retention in treatment
  - Abstinence from illicit opioid use
  - Decreased opioid craving
  - Decreased mortality
  - Improved occupational stability
  - Improved psychosocial outcomes



Johnson et al. NEJM 2000; Fudala PJ et al. NEJM 2003; Kakko J et al. Lancet 2003; Sordo L et al. BMJ 2017; Mattick RP et al. Conchrane Syst Rev 2014; Parran TV et al. Drug Alcohol Depend 2010

# SAFETY

- Tested High dose buprenorphine for craving abetment
  - 32mg, 64mg, 96mg
- Side effects
  - 2 with hypotension in the 96 mg group (treated with NS bolus)
  - 5 nausea and vomiting (> 64 mg group)
  - 2 with Nausea (32 mg group)
  - No respiratory, cardiovascular or GI side effects were noted
- Cravings were decreased with maximal effect at 64mg



Single high-dose buprenorphine for opioid craving during withdrawal Jamshid Ahmadi,corresponding author Mina Sefidfard Jahromi, Dara Ghahremani, and Edythe D. London Published online 2018 Dec 10. doi: 10.1186/s13063-018-3055-z

# SAFETY

- Used secondary outcomes (not powered or randomized to determine these outcomes)
- Low <6mg, Medium 8-24mg, High dose >24mg
- Findings
  - Dose related to outcomes (16 or greater had increased retention at 6 months)
  - Moderate dose had decreased illicit drug use
  - Minor outcomes differed little based on dose with exception of illicit drug use and retention. (Better in the 16mg or higher group)

Jacobs, P., Ang, A., Hillhouse, M. P., Saxon, A. J., Nielsen, S., Wakim, P. G., … & Blaine, J. D. (2015). Treatment outcomes in opioid dependent patients with different buprenorphine/naloxone induction dosing patterns and trajectories. *The American Journal on Addictions*, *24*(7), 667-675.

# SAFETY

- 31 Trials (5430 participants)
- Retention in treatment
- Specifically, buprenorphine retained participants better than placebo:
  - at low doses (2 - 6 mg), 5 studies, 1131 participants, risk ratio (RR) 1.50; 95% confidence interval (CI) 1.19 to 1.88;
  - at medium doses (7 - 15 mg), 4 studies, 887 participants, RR 1.74; 95% CI 1.06 to 2.87;
  - and at high doses (≥ 16 mg), 5 studies, 1001 participants, RR 1.82; 95% CI 1.15 to 2.9

Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD002207. DOI: 10.1002/14651858.CD002207.pub4.

# CONT. ILLICIT OPIOID USE

- There is moderate quality of evidence that only high-dose buprenorphine (≥ 16 mg) was more effective than placebo in suppressing illicit opioid use measured by urinalysis in the trials, 3 studies, 729 participants, standardized mean difference (SMD) -1.17; 95% CI -1.85 to -0.49,
- Notably, low-dose, (2 studies, 487 participants, SMD 0.10; 95% CI -0.80 to 1.01), and medium-dose, (2 studies, 463 participants, SMD -0.08; 95% CI -0.78 to 0.62) buprenorphine did not suppress illicit opioid use measured by urinalysis better than placebo.

# CONCLUSIONS

- Buprenorphine is an effective medication in the maintenance treatment of heroin dependence, retaining people in treatment at any dose above 2 mg, and suppressing illicit opioid use (at doses 16 mg or greater) based on placebo-controlled trials
- However, compared to methadone, buprenorphine retains fewer people when doses are flexibly delivered and at low fixed doses.
- If fixed medium or high doses are used, buprenorphine and methadone appear no different in effectiveness (retention in treatment and suppression of illicit opioid use

# CONCLUSIONS

- The review of trials found that buprenorphine at high doses (16 mg) can reduce illicit opioid use effectively compared with placebo, and buprenorphine at any dose studied retains people in treatment better than placebo.
- Buprenorphine appears to be less effective than methadone in retaining people in treatment, if prescribed in a flexible dose regimen or at a fixed and low dose (2 - 6 mg per day).
- Buprenorphine prescribed at fixed doses (above 7 mg per day) was not different from methadone prescribed at fixed doses (40 mg or more per day) in retaining people in treatment or in suppression of illicit opioid use.

# GOALS OF TREATMENT?

- Decreased illicit drug use (16mg or > only)
- Increased retention in treatment (begins at 4mg and levels after 16 mg)
- Decreased mortality (improves with retention in treatment)

- My recommendations
  - Initial dose 16 mg
  - Reduce as tolerated, but would worry about less than 8 mg

# CONCLUSIONS

- The opioid system is complex
- Opioids are not subtle
- Buprenorphine is safe
- Doses less than 16 mg show little effect on illicit drug use