

# Pharmacotherapy of Substance Use Disorders

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# Vt Opioid History

- 1840-Heavy reliance on alcohol as drug of choice. Homemade stills were commonly used as was cider making
- 1850 Vt enacted Prohibition against alcohol. Dram laws came about
- 1860's Post Civil War Morphine became available for soldiers with "military disease"
- 1870-1890 Widespread use of opium containing products-patent medicines from England, paregoric, tinctures of opium, heroin, morphine products. Taken with a dram of alcohol for ingestion.
- Led to widespread abuse, demise and death as doses were not regulated.
- Boston had regularly received shipments of opium from Turkey destined for VT

# Vt Opioid History

- 1890-1900 Abuse of opioids was so extensive that NH and Mass enacted laws to ban the export of opium containing products from VT into their states. Physicians, druggists and apothecaries and general stores dispensed opium products. 3 major manufacturers in the State
- 1900 Vt Medical Society speech by Dr. A.P. Grinnell indicated that based on an incomplete survey he performed of all of the above purveyors, 3,300,000 doses of opium were dispensed monthly-enough for 1 ½ doses for every man and woman above 21 a day for a year or ½ dose for every Vermonter and he estimated that this was underreported by a factor of 5.

# Vt Opioid History

- 1906 Pure Food and Drug Act required labeling of patent medicines with opium, coca, cannabis, alcohol, and other intoxicants
- As of 1911, an estimated one U.S. citizen in 400 (0.25%) was addicted to some form of opium and were mostly women who were prescribed and dispensed legal opiates by physicians and pharmacist for “female problems” (probably pain at menstruation) or white men and Chinese at the opium dens.
- 1914 Harrison Act was passed regulating the marketing of opiates.
- A clause applying to doctors allowed distribution "in the course of his professional practice only." This clause was interpreted after 1917 to mean that a doctor could not prescribe opiates to an addict, since addiction was not considered a disease. A number of doctors were arrested and some were imprisoned. The medical profession quickly learned not to supply opiates to addicts. In *United States v. Doremus*, 249 U.S. 86 (1919), the Supreme Court ruled that the Harrison Act was constitutional, and in [\*Webb v. United States\*](#), 249 U.S. 96, 99 (1919) that physicians could not prescribe narcotics solely for maintenance.<sup>[13]</sup>

# What drugs are likely to be abused?

- Cross the Blood Brain Barrier
- Cause euphoria
- Short onset of action
- Short half life
- Quick delivery mechanism
- Few side effects

# Physical Dependence vs. addiction

- Dependence-physiological state
  - Tolerance (need more for same effect)
  - Withdrawal (sick when no more drug)
  - Occurs with alcohol, cannabis, opioids, benzodiazepines, nicotine
  - Does NOT occur with cocaine, amphetamines
- Addiction-compulsive use despite consequences
  - Brain disorder due to mismatched reward mechanism

# Risk factors

- Biological predisposition toward SA (Family history)
- Genetics
- Psychological-depression and/or trauma/victimization
- Social-family, friends, peers

# Critical RISK Factors

- Onset of use before age 15
- Daily or weekly use of one drug
- Poly-drug use

“Youth who make it through the early teen years without substance use decrease the likelihood of developing the DISORDER by 4 times”  
McClellan, Lewis JAMA 2000 PLNDP



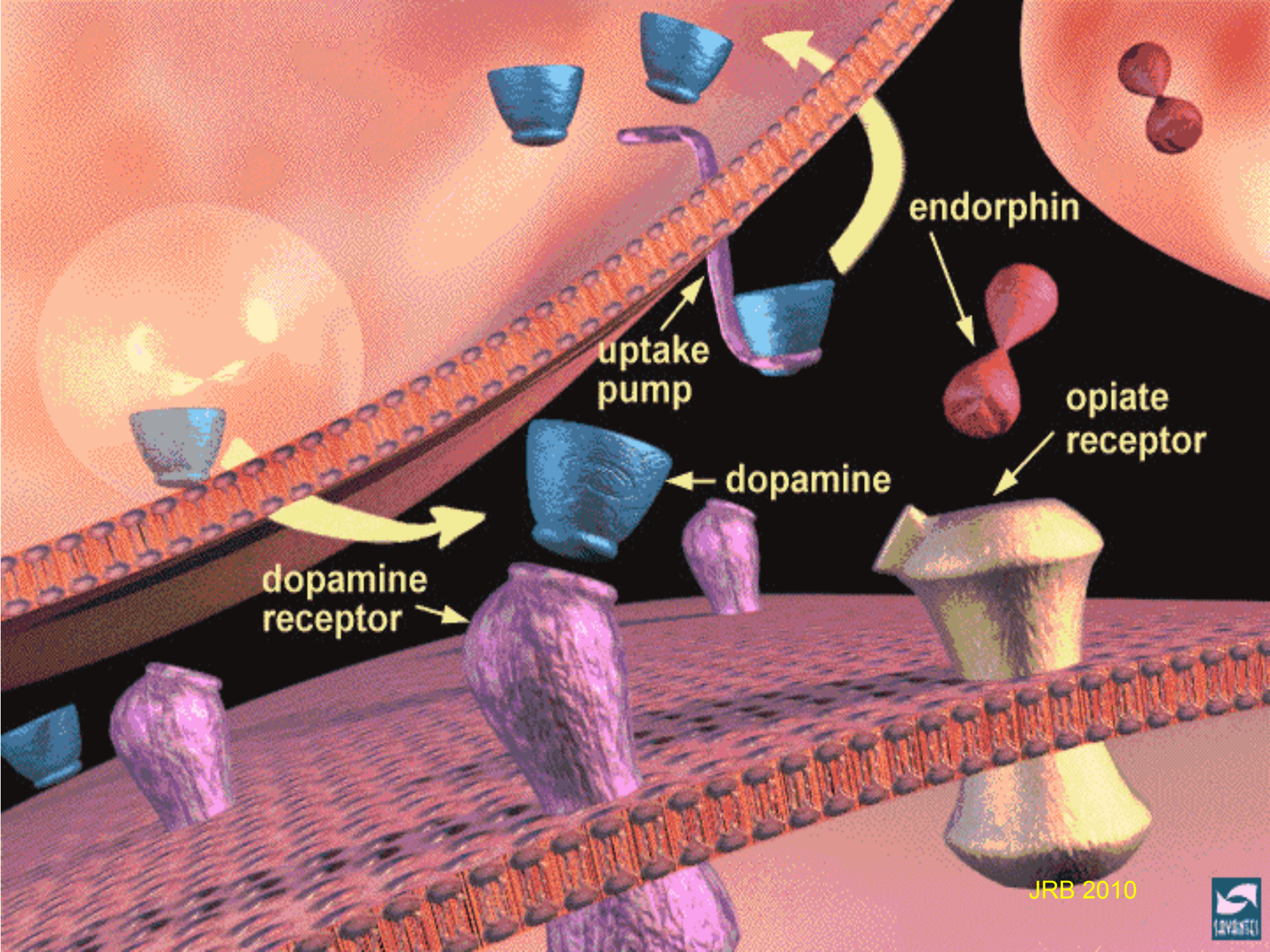


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- “Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium”

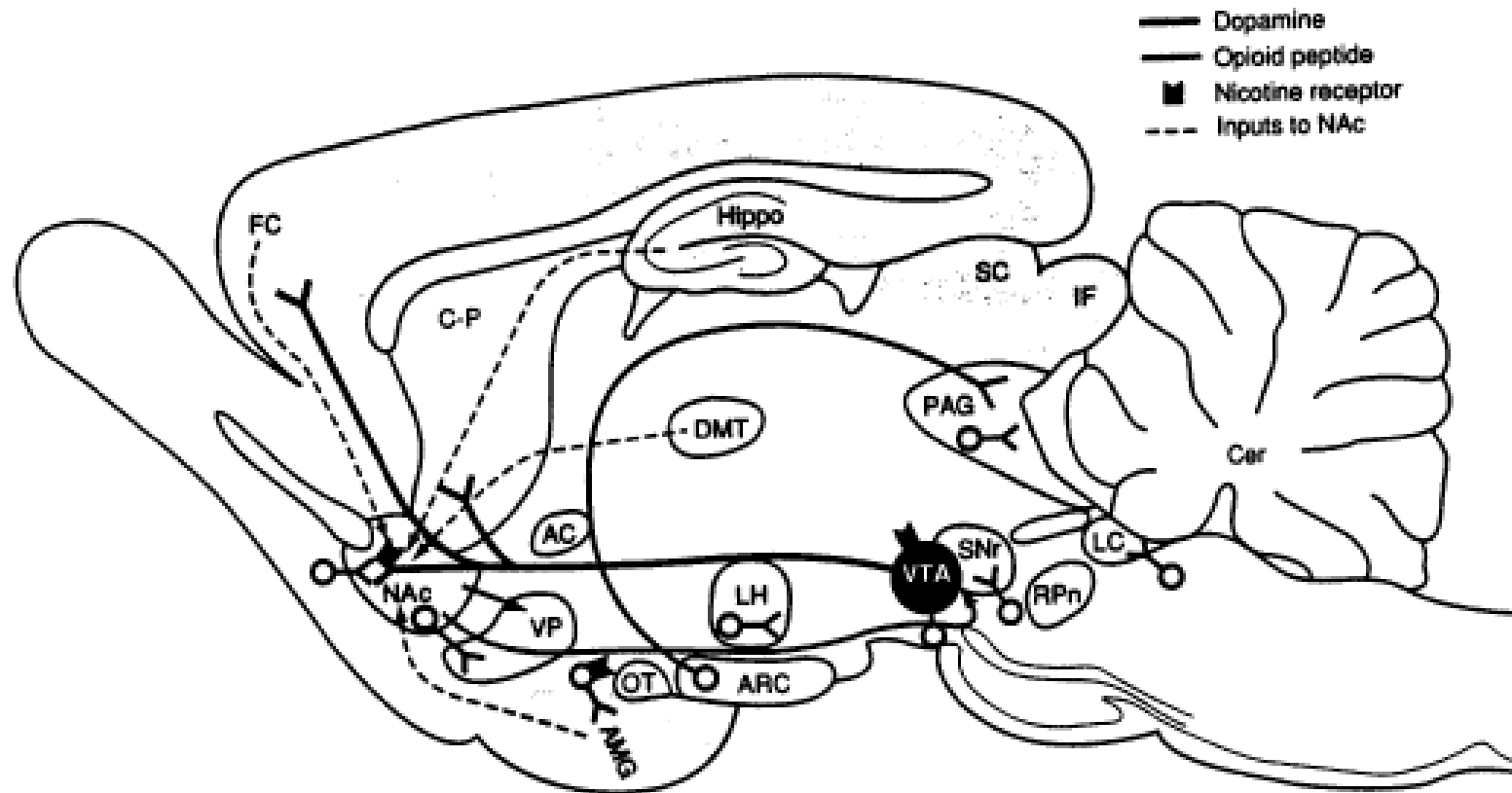
Sydenham, 1680





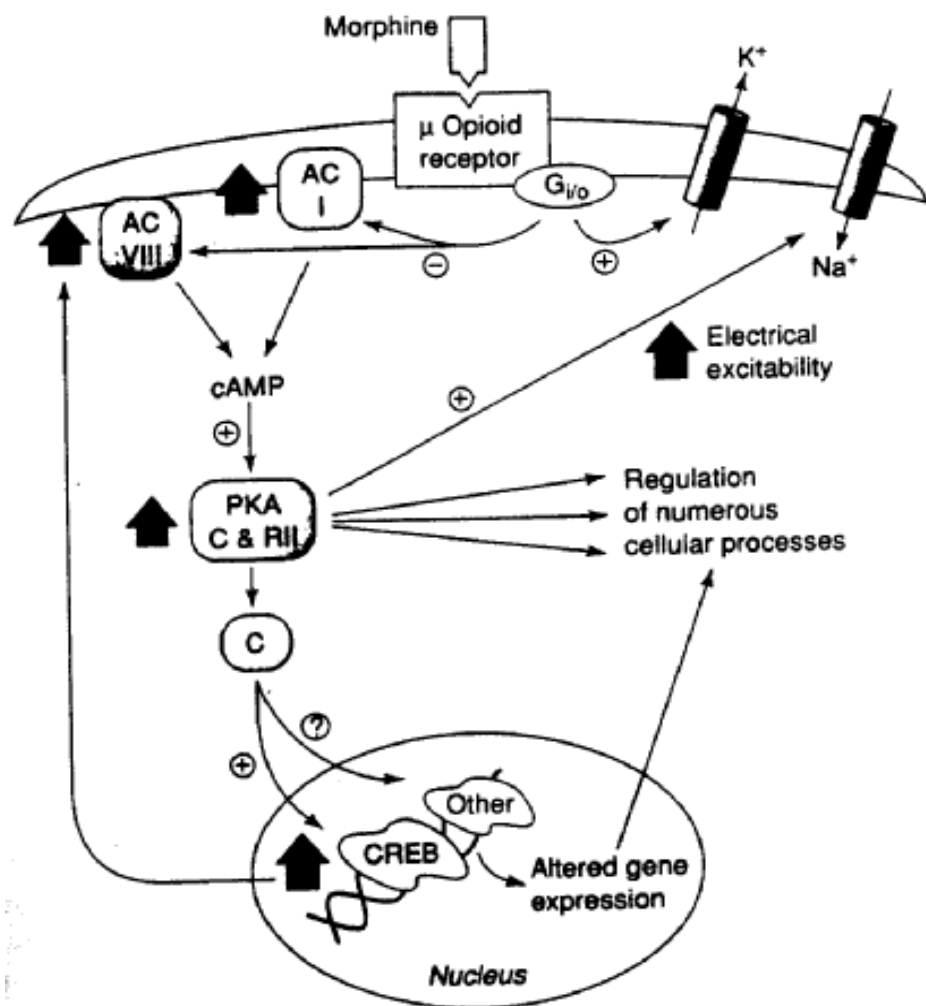
JRB 2010





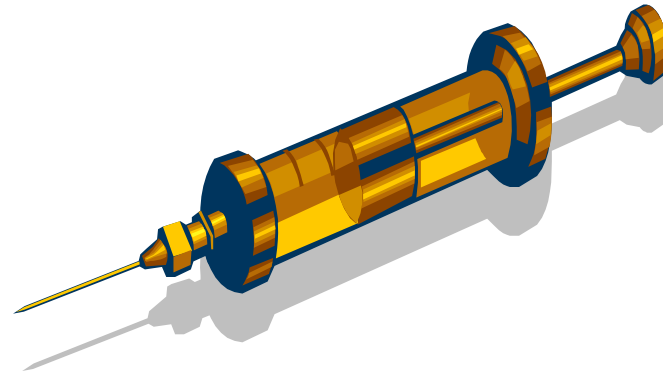
- Dopamine pathways in the Ventral Tegmentum(VT) to the Nucleus Accumbens(NA) and Medial Frontal Cortex(MFC) are activated during rewarding behaviors. Mu receptors in the VT,NA,MFC,and Locus Coeruleus(LC). Chronic opiates cause LC inhibition and stopping them causes excitation in the LC and withdrawal symptoms. Opiates also reduce glucose metabolism globally in the brain. GABA receptors are scattered throughout this area and are involved with reward for ethanol, BZD, and opiates.





**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.)

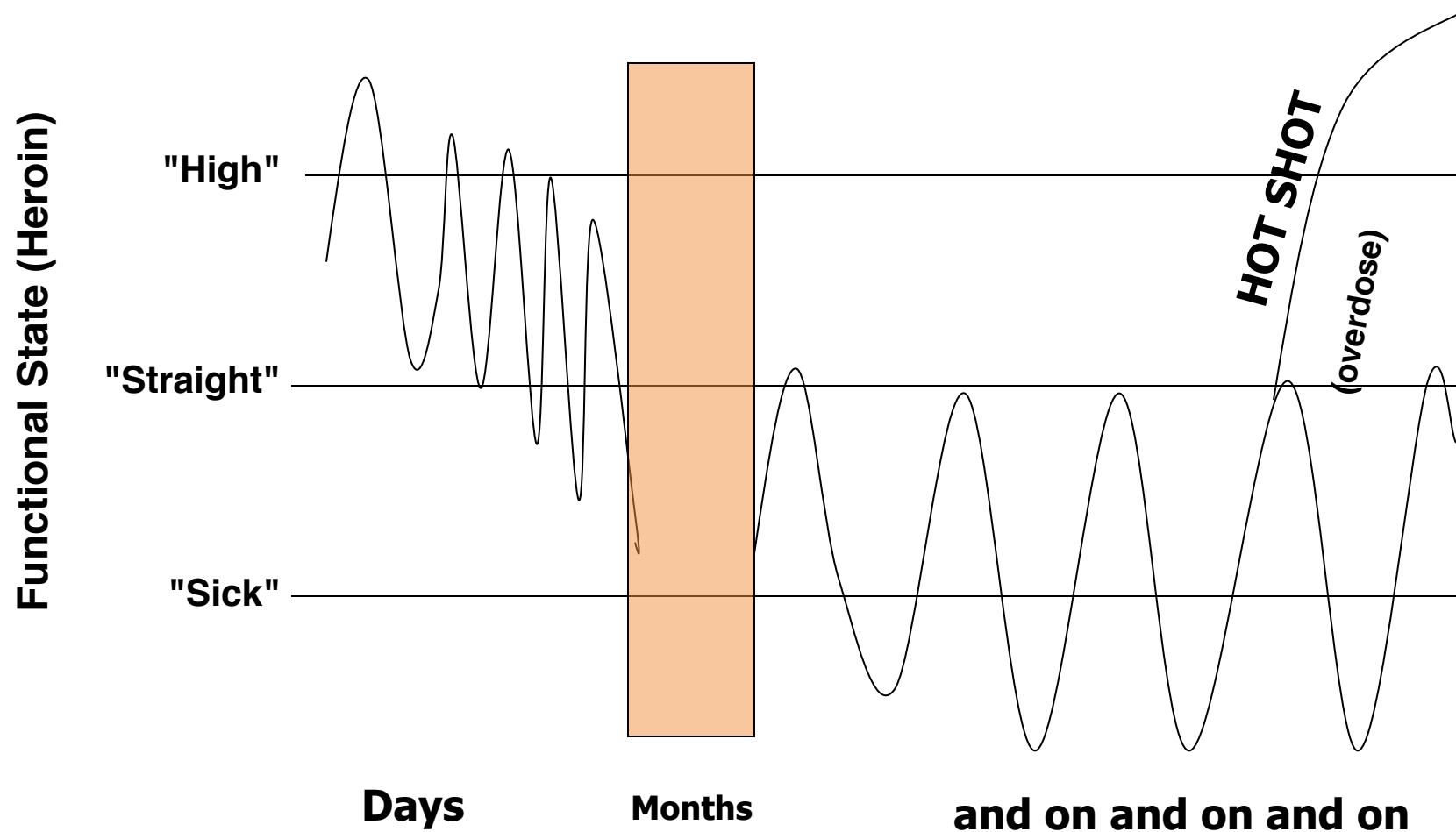
# Heroin



# Oxycodone



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





# Natural History

- Initial exposure often begins with random, recreational use of pills-oxycodone or hydrocodone combinations by mouth or by sniffing the crushed pills OR overprescribing by a medical professional
- May remain as a casual use
- Often progresses to need for increased amount for the same effect (tolerance) and this often leads to Oxycontin use (also crushed and snorted)
- Once dependence gets established then progresses to heroin and injection use.

# Natural history of heroin use

- Tolerance
- Injection
- Loss of everything- working to maintain habit, burglary, prostitution, school drop-out rate is much higher.
- This is often a planned economy of starting an unsuspecting teen on low cost pills, progressing to costly pharmaceuticals and then offering heroin. Users need to recruit new users.

# Opiate effects

- Pain relief as an analgesic
- Drowsiness
- Mood changes
- Mental clouding
- Constipating, nauseating
- Cough suppressant
- Smaller pupils
- Reduce respiration
- Itching

# Opiate withdrawal

- Pain/Dysphoria
- Diarrhea
- Vomiting
- Runny nose and eyes
- Dilated pupils
- Tremor
- Hot and cold feelings
- Anxious mood
- Aching
- Poor sleep

# Opioid Withdrawal

- Early: Anxiety, myalgias, mydriasis, rhinorrhea, lacrimation, yawning
- Mid: fever, chills, sweats, piloerection (cold turkey), leg muscle cramps (kicking), bone pain, abdominal cramps
- Late: vomiting, diarrhea, hyperventilation, insomnia
- Withdrawal is very unpleasant but not life threatening

# Opioid Misuse: Medical Complications

- Infections: HIV, Hepatitis B and C, Endocarditis, meningitis, septicemia, TB, Skin abscess, phlebitis
- Nephropathy, rhabdomyolysis, PE, lymphedema, menstrual irregularity
- Impaired immune function
- Hepatic and renal toxicity from acetaminophen and NSAID use

# Opioid Overdose

- Respiratory depression is the cause of death
- Coma, hypoventilation, cyanosis, pinpoint pupils. Pupils may dilate if cerebral hypoxia ensues.
- Non-cardiogenic pulmonary edema
- High dose meperidine may cause seizures.

# Treatment of Opioid Overdose

- Establish Airway
- Ventilate
- Inject Naloxone. Short  $\frac{1}{2}$  life
- Monitor and repeat as needed.
- Beware! You will precipitate withdrawal.
- Treatment for opioid dependence is often
- indicated.



# Pharmacological Treatment of Opioid Dependence

- Short term
  - Detoxification using non opioids
  - Detoxification using opioids
- Long term
  - Opioid agonist treatment
  - Opioid antagonist

# Opioid Detoxification Efficacy

- Extremely high relapse rates ~90%. Sometimes the same day after leaving facility
- High risk for HIV, Overdose upon relapse
- Must be followed up with structured treatment, 12 step, Recovery Centers
- Abstinence based approach is not the treatment for Opioid dependence

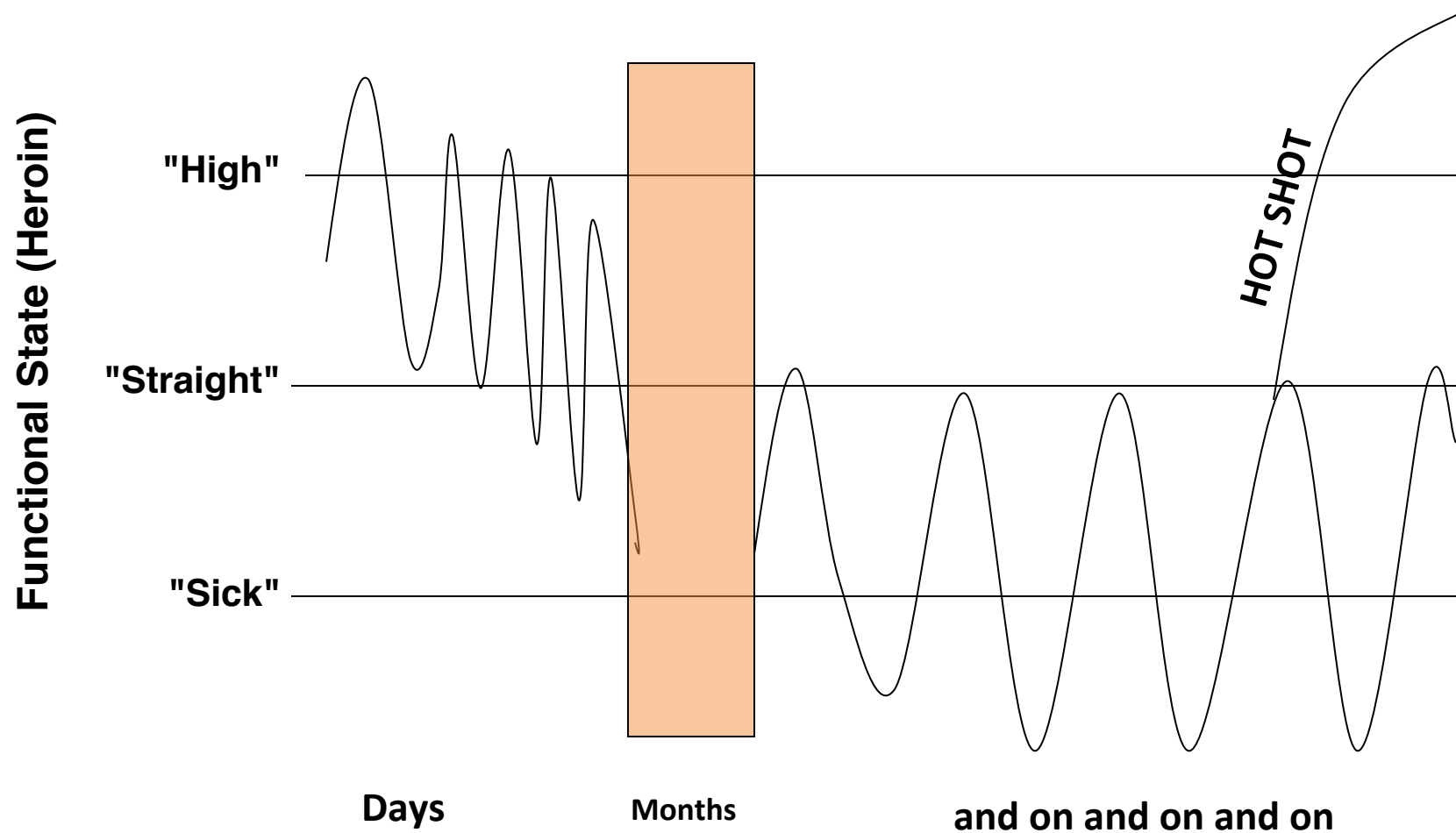
# Opioid Agonist Treatment

- The recommended treatment for Opioid dependence
- Best outcomes, treatment retention and lowest relapse rates.
- Methadone maintenance was the mainstay
- Buprenorphine for office based Rx.

# Opioid Agonist Treatment (OAT)

- Normalizes immune and endocrine systems, reduce death rates, OD
- Decreases criminal activities
- Decreases illicit opiate use, IVDU, HIV and Hepatitis C transmission
- Increases pro-social activities, employment
- Reduces ER visits and hospitalization

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



# Heroin

- Enters brain within 30 secs after injecting
- Lasts 30-60 minutes
- After time effects opiate receptor/ endorphin system in brain → stress, sleep, pain
- Stopping it causes physical symptoms within 12 hours and lasting up to 7 days
- Can permanently change the receptor in the brain causing chronic anxiety and a state of hyperexcitability

# Mortality

Death rate is 50-100 times greater than  
general population rate!

Cause of death

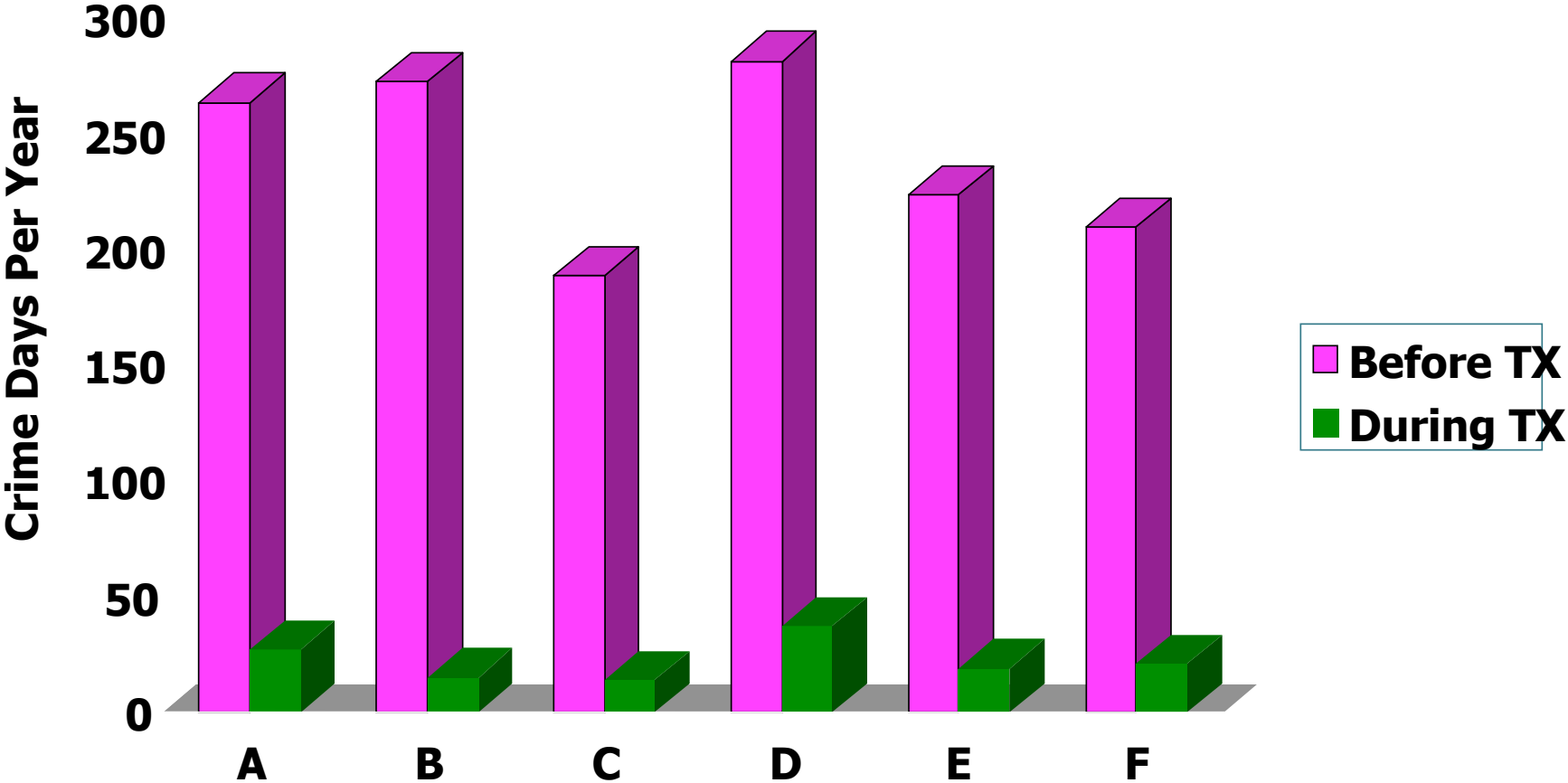
22% Accidental, OD

19% Homicide, Suicide, MVA

15% Liver disease

23% Cancer and cardiovascular

# Crime among 491 patients before and during MMT at 6 programs



Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991



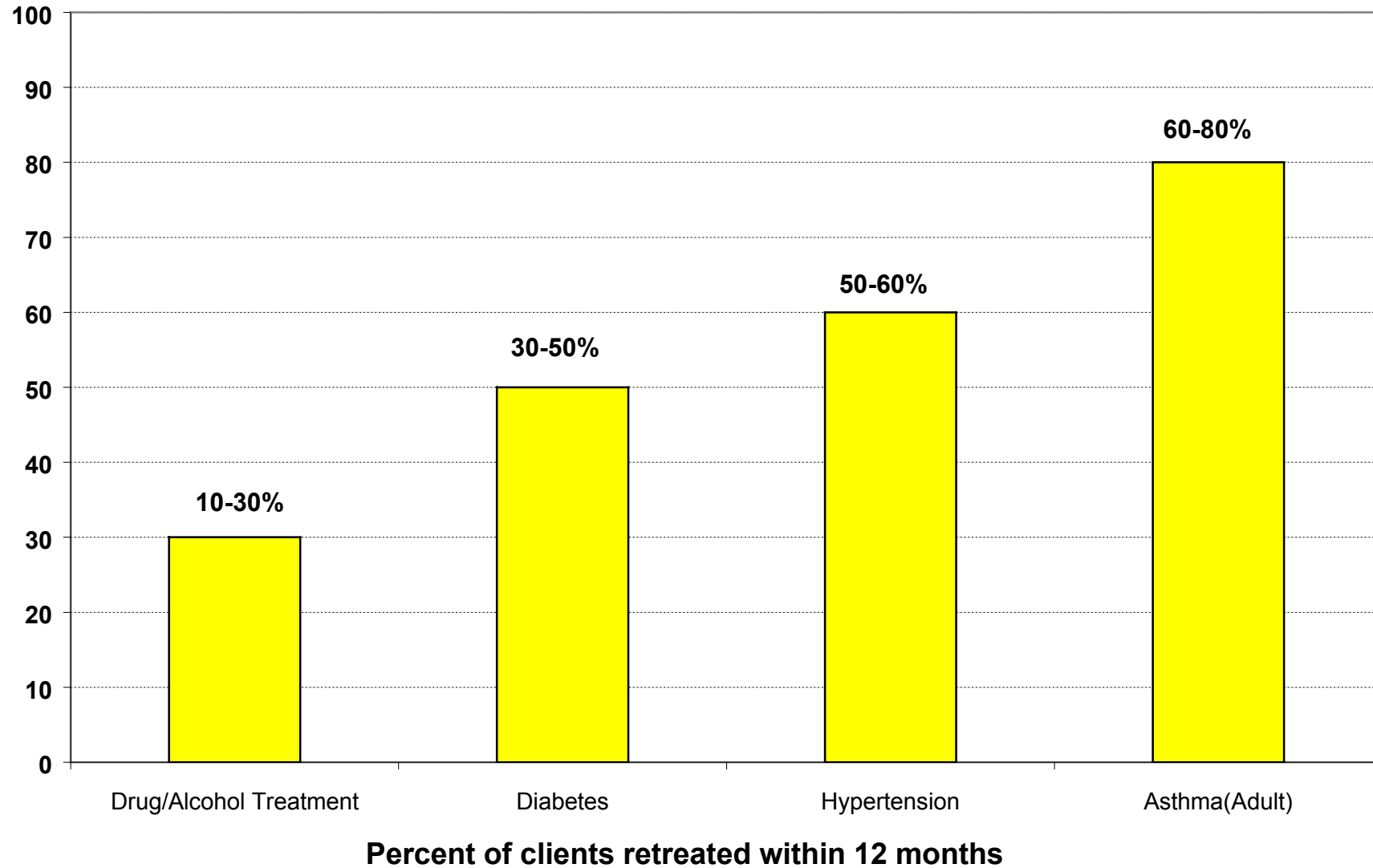
# Medication Assisted Treatment

- Both methadone and buprenorphine are “blockers”. They occupy the opioid receptors in the brain and don’t “allow” shorter acting opioids to activate the receptors and cause positive effects
- Once stable on a dose, it rarely has to be adjusted
- Allows behavioral changes to be made

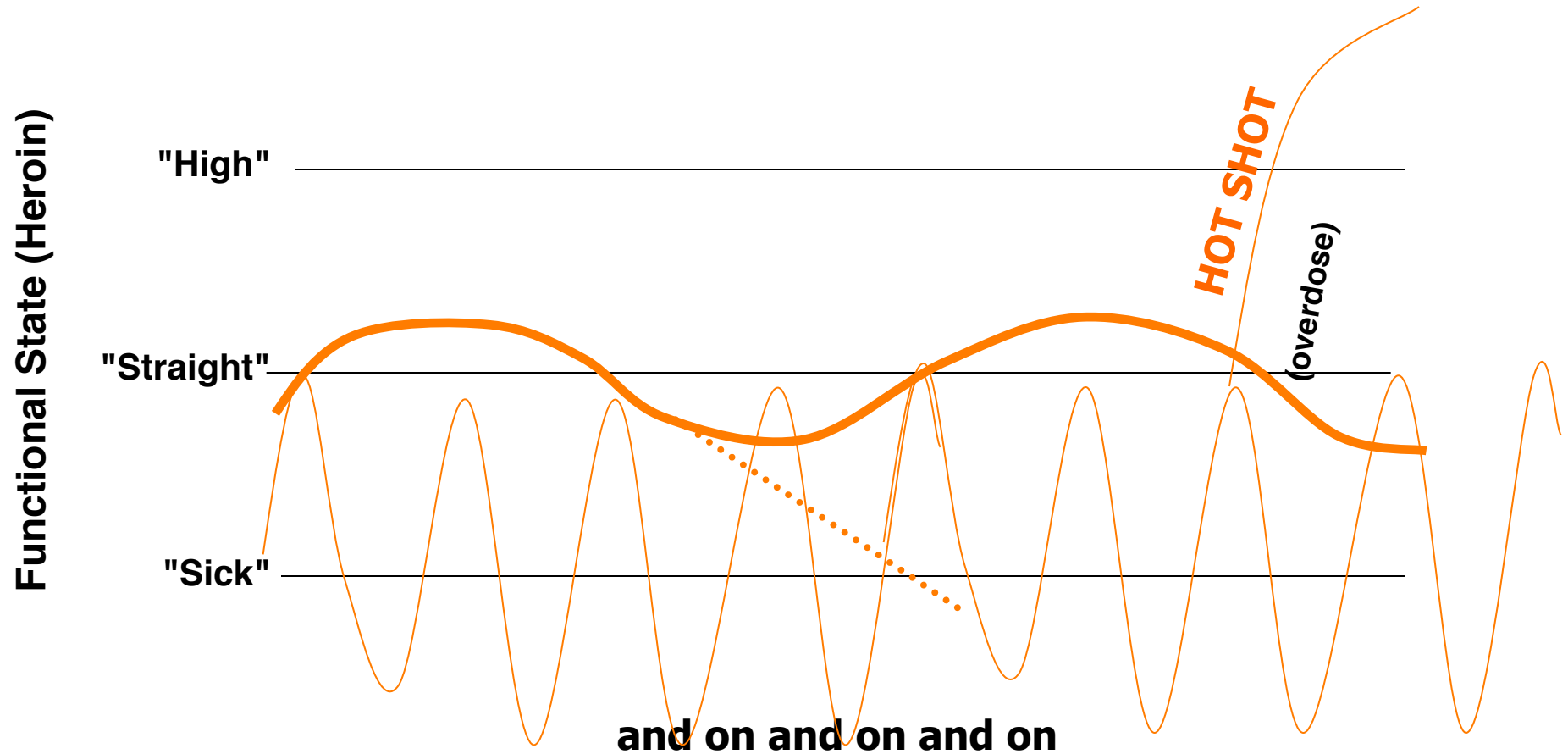
# MAT

- Methadone is only prescribed and dispensed in an OTP (Opiate Treatment Program)
- Buprenorphine is prescribed by doctors in an office based opioid treatment program (OBOT)
- However, in some OTPs buprenorphine is prescribed and dispensed instead of methadone

## Relapse Outcomes in Selected Medical Disorders



# NOW SIMPLY ADD METHADONE



JRB 2010

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

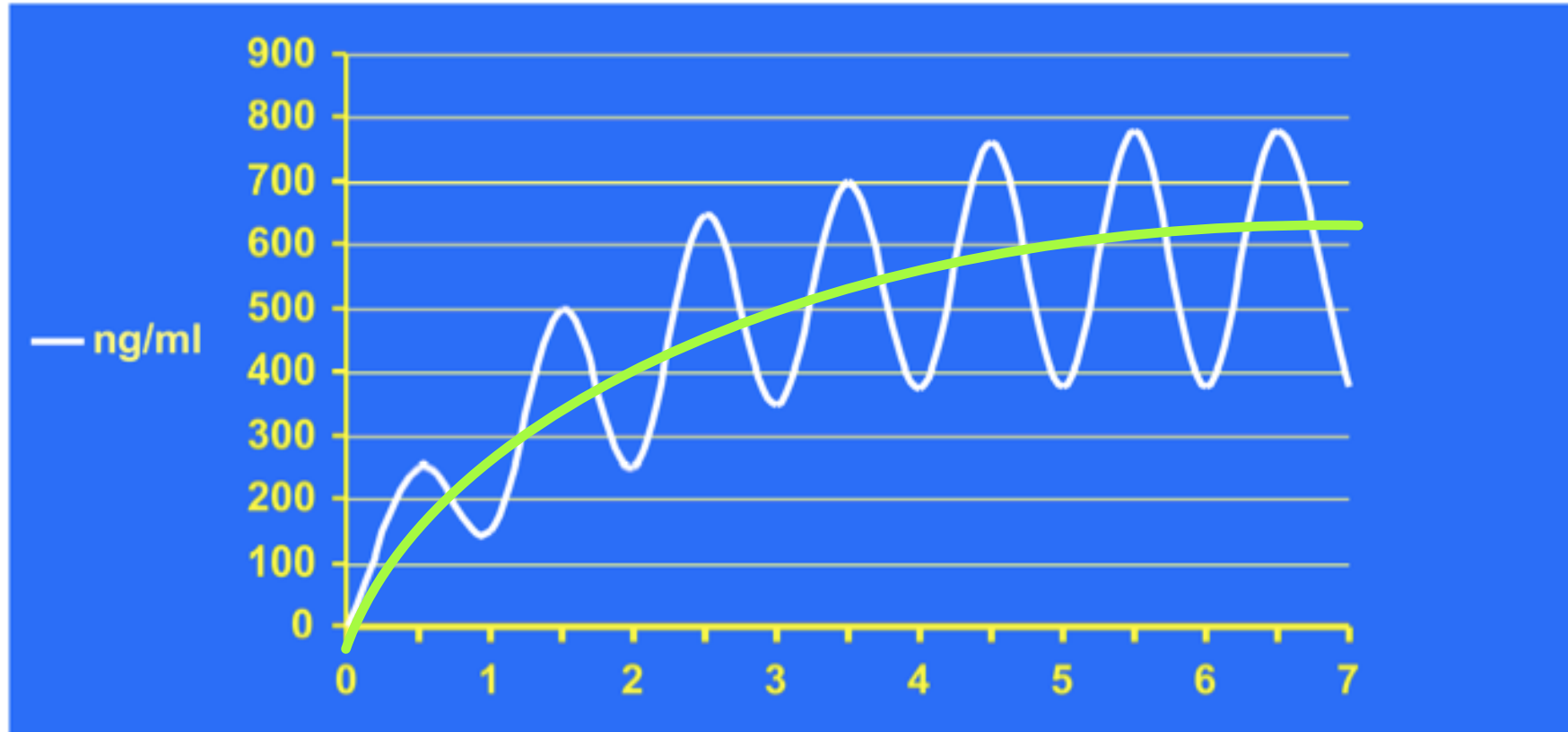
# Methadone

- Methadone, synthetic opioid, created in 1930s in Germany with the intent to develop an analgesic for wounded soldiers while allied forces controlled opium exports from the East.
- The drug was undergoing laboratory-based preclinical study. Soon after World War II, the U.S. military commission had identified this compound as being of possible therapeutic value and had officially brought it to the United States for study in the treatment of pain (at Lexington).

# Methadone

- Taken too frequently, or by opioid-naïve patients, methadone will accumulate and cause sedation or respiratory depression, but once-a-day dosing will generally achieve relatively stable blood levels.
- Methadone has high oral bioavailability, reaches peak blood concentration between 2 and 4 hours after and is relatively lipid-soluble. Less than 3% enters the CSF.

# Steady-State Simulation - Maintenance Pharmacotherapy Attained after 4-5 half-times, 1 dose / half-life



Adapted from  
Goodman &  
Gilman

Time (multiples of elimination half-lives)  
Daily dose remains constant to steady-state

# Methadone

- Steady state is not attained until methadone is fully distributed and bound in tissues, and so blood levels continue to rise slowly for 4 to 6 weeks.
- Although patients sometimes complain about drug formulation changes (tablets versus liquid; differing flavors), there are no correlated changes in pharmacokinetics or dynamics.
- It can take up to 6 months for most patients to become stabilized and for heroin use to be significantly reduced and stress hormone levels to normalize

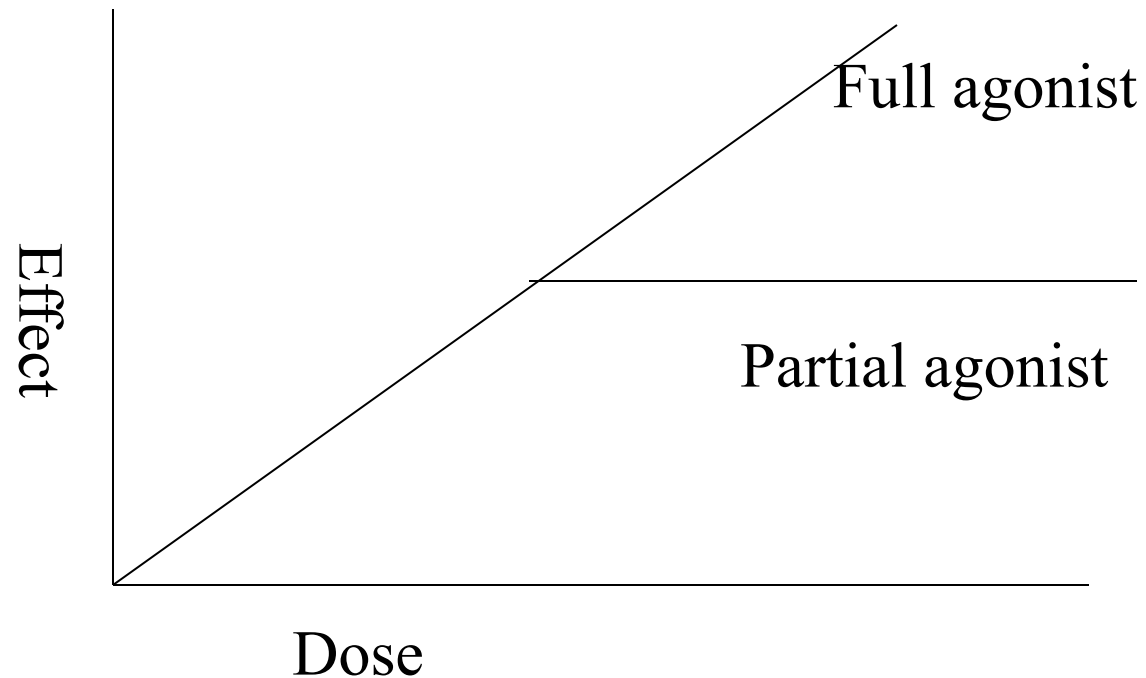


# Side effects

- Constipation
- Weight gain.
- Increased perspiration,
- Decreased libido and menstrual abnormalities are common during cycles of heroin use, secondary to disruption of the pulsatile secretion of luteinizing hormone (LH). Methadone maintenance allows normalization of LH levels.
- Female patients should be advised that they will regain their normal chance of becoming pregnant as secondary amenorrhea disappears and normal menstrual cycles with ovulation recommences within 1 year.

# Buprenorphine

Partial agonist used for the treatment of opiate dependence in a doctor's office



# Buprenorphine

- Subutex<sup>®</sup>-Buprenorphine only
- Suboxone<sup>®</sup>-Buprenorphine/Naloxone 4:1 ratio
  - Strips and tablets
- Zubsolv<sup>®</sup>-new formulation
- Both Subutex<sup>®</sup> and Suboxone<sup>®</sup> are now generic
- 9.3 million dollars in Medicaid dollars for fiscal year 2013

# Buprenorphine

- Was studied in the 1980's with promise as an alternative to MTD
- Ceiling effect on respiratory depression
- Long half life
- Less reinforcing to addict
- Could expand treatment to 50% of all heroin addicts
- Harrison Act of 1914 was reversed by DATA 2000
- Any waivered MD/DO was eligible to treat

# Buprenorphine

- Only MDs or DOs can prescribe
- Have to take an 8 hour training
- Allows one to get a waiver on the DEA license in order to prescribe for addicts
- Cap of 30 people the first year
- Can apply to lift the cap to 100 after 1 year
- Vt is #1 in the US in number of waived MDs/DOs and number of doses of buprenorphine prescribed per capita in the US

# Naltrexone

- Full opiate antagonist
- Given in select circumstances
- Doses range 50-100 mg/ day orally or
- Once a month injection (Vivitrol)
- Reducing craving for alcohol
- S/E's: depression, nausea, GI upset, HA, drowsiness, serious effects on liver

# Naltrexone IM (Vivitrol)

- Monthly injection
- About \$800 a shot
- Better compliance
- Concern about pain as it is a full opioid blocker

# Narcan

- Reverses opioid overdose with one dose
- Is added to Buprenorphine to make Suboxone
- If injected, kicks all opioids from the brain and precipitates withdrawal.
- Can be given as a shot or as a nasal spray
- Works within minutes
- Wide variation in availability around VT



# Hub and Spoke

- Idea was to have methadone clinics also prescribe buprenorphine and take more difficult patients and keep them from being discharged from OBOT (HUBS)
- Once stable, some on buprenorphine could go back to OBOT (SPOKES)
- OBOT could enroll new people knowing there was a back up if the patients relapsed
- 5 Hubs and >30 Spokes around the state
- 1 FTE nurse and case manager in the Spokes to provide services based on Blueprint for Health waiver in the State Chronic Care Initiative