Introduction to opioids and medication-assisted treatment

J. Randall Webber, MPH, CADC, QMHP
JRW Behavioral Health Services
www.randallwebber.com

Drug overdose deaths* more common than

- Drunk driving
- Homicide
- Homicide with a firearm
- Accidental death involving a firearm

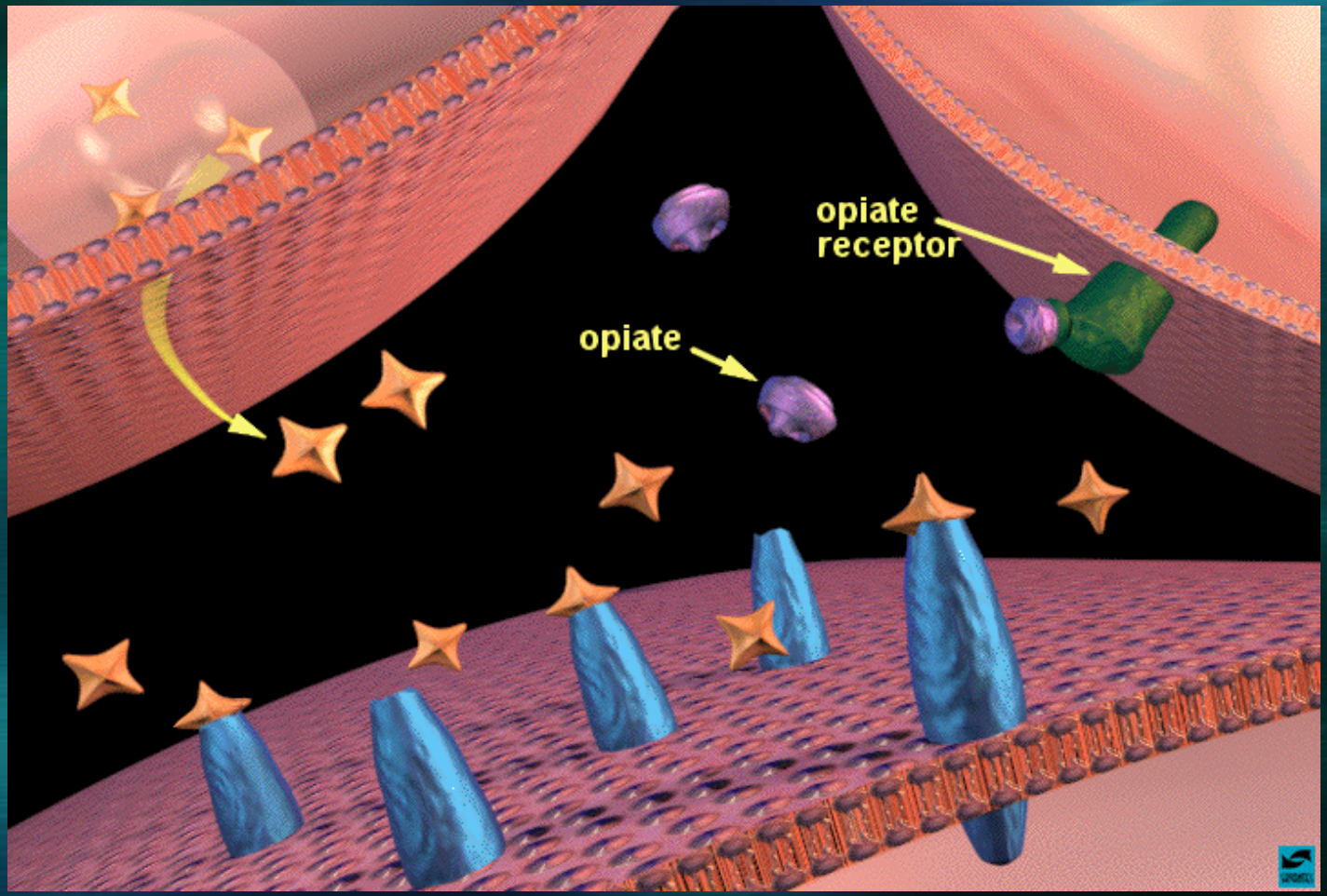
- * Over 50% involving heroin or an opioid

Opioids?
Opiates?
What's the difference?

Endogenous opioids

- Endorphins
- Endomorphins
- Enkephelins
- Dynorphins
- Nociceptin
- Specific brain receptor sites
  - **Mu**
  - Delta
  - Kappa
  - Nociceptin

Endogenous Opiate Receptors



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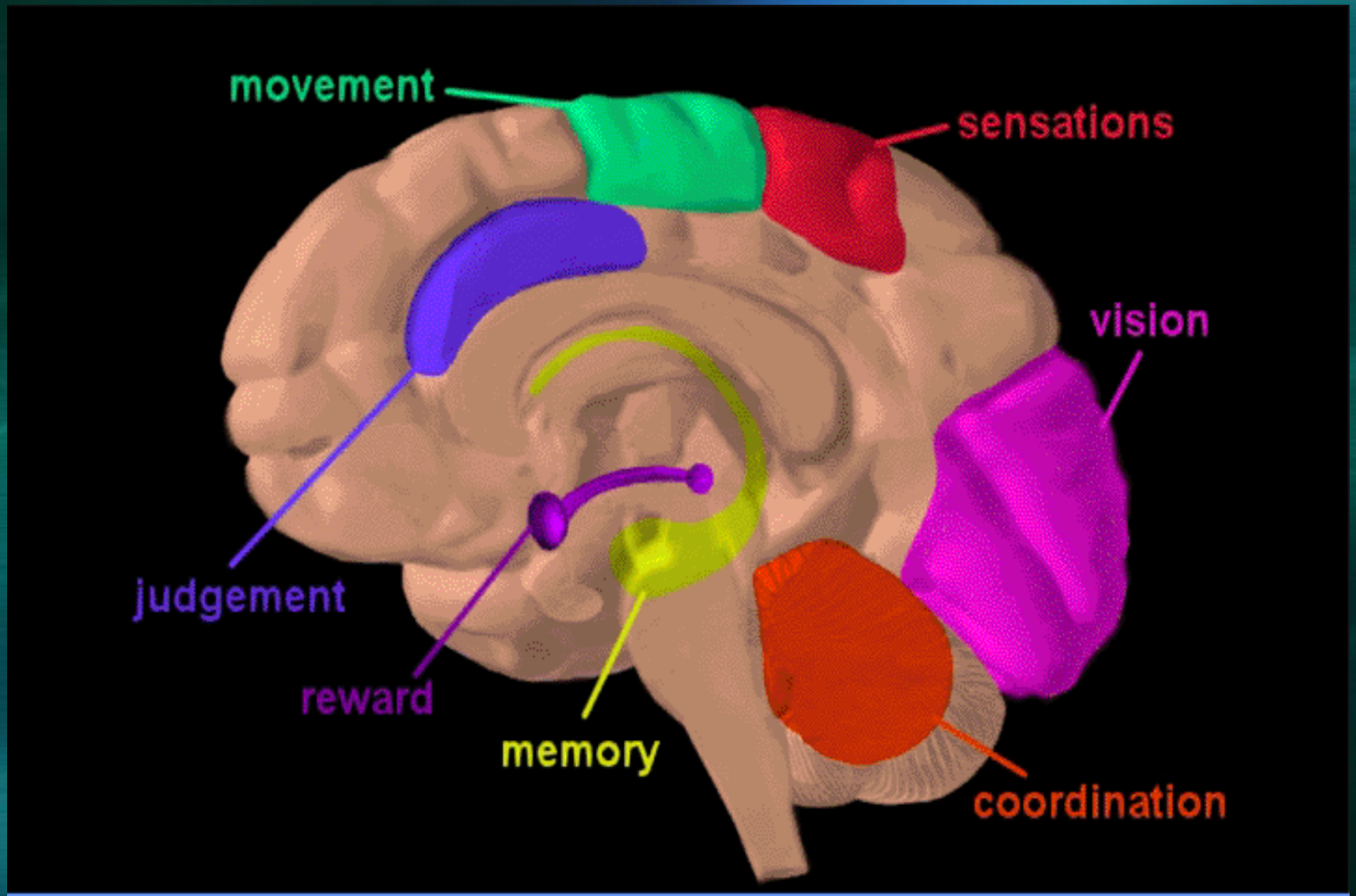
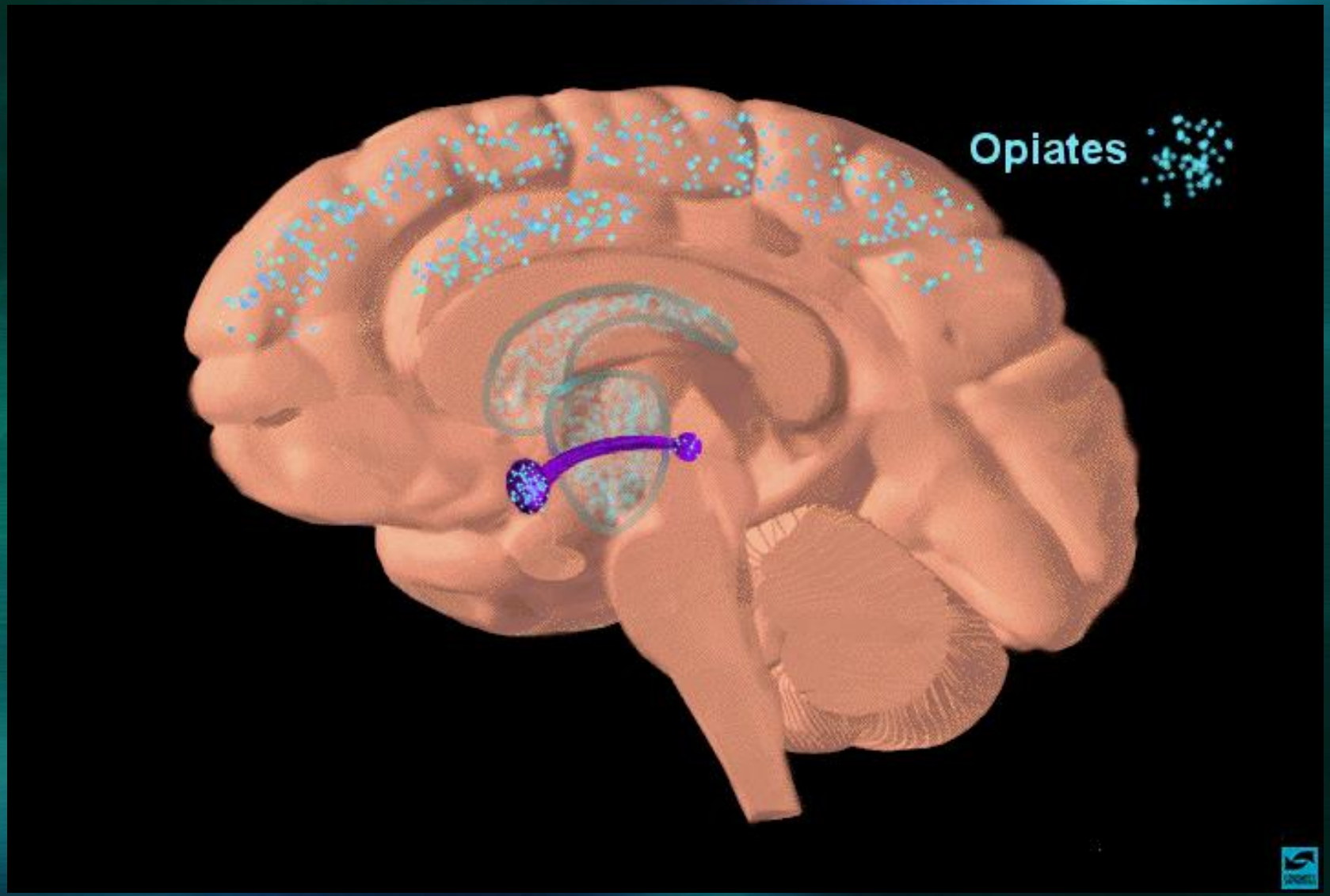

movement
sensations
vision
judgement
reward
memory
coordination

Portions of the Brain Affected by Opiates



Opioid agonists

- Attach to opioid receptor and activates cell
- Morphine, heroin, Vicodin, fentanyl

Opioid antagonists

- Attach to opioid receptor but do not activate cell
- Blocks effects of other opioids
- Blocks efficacy of acupuncture

- Naloxone, naltrexone

Partial opioid agonist/antagonists

- Attach to opioid receptor site
- Can act as agonist or antagonist depending on dose

- Buprenorphine, Talwin

3,500 B.C.: Sumarians wrote of opium’s medicinal and intoxifying effects

"Thou has the keys of Paradise, oh just, subtle and mighty opium"
Thomas de Quincy
Confessions of an English Opium-Eater

AFGHANI OPIUM WORKERS

Important dates in opiate history

- 1807: Morphine is isolated from opium
- 1832: Codeine is isolated from opium
- 1853: Hypodermic needle invented
- 1861: American Civil War
- 1866: Morphine addiction known as “soldier’s illness”
- 1898: Heroin is synthesized from morphine

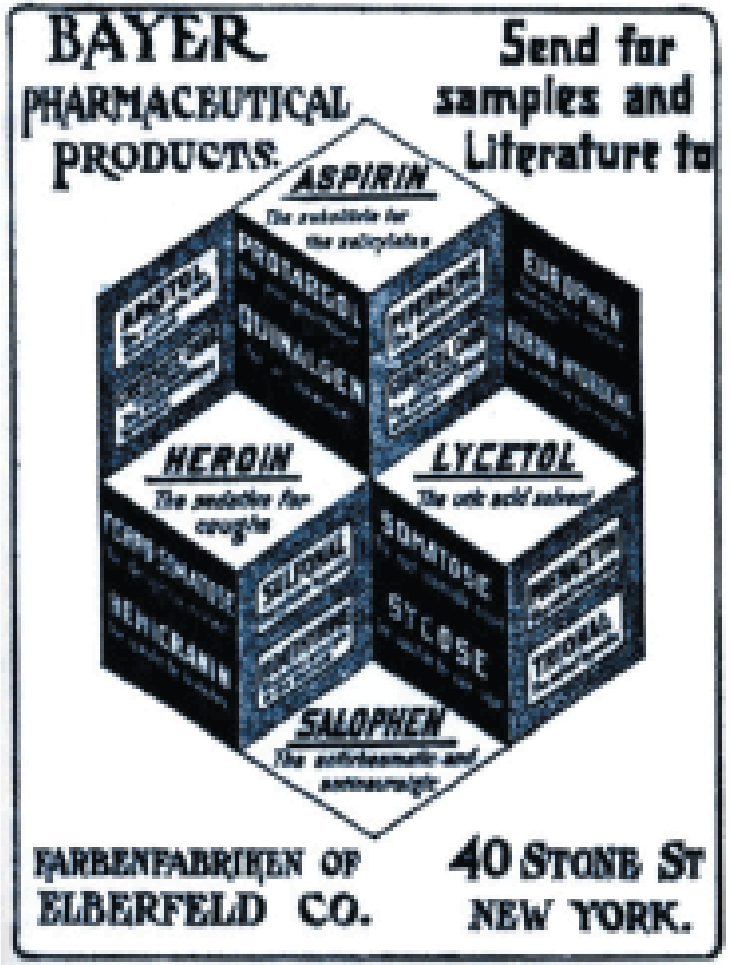


FIGURE 1. Source: National Library of Medicine

Opiates

Natural alkaloids

- morphine
- codeine
- thebaine

Semi-synthetics

- heroin
- Oxycodone (OxyContin/Percodan)
- Hydrocodone (Vicodin)
- buprenorphine
- naloxone

Types of Opiates

Synthetic opiates

- **Demerol (meperidine)**
- **Dilaudid (hydromorphone)**
- **Numorphan (oxymorphone)**
- **Sublimaze (fentanyl)**
- **Methadone (dolophine)**
- **diphenoxylate/atropine (Lomotil)**

Types of Opiates

Newly emerging synthetic opiates

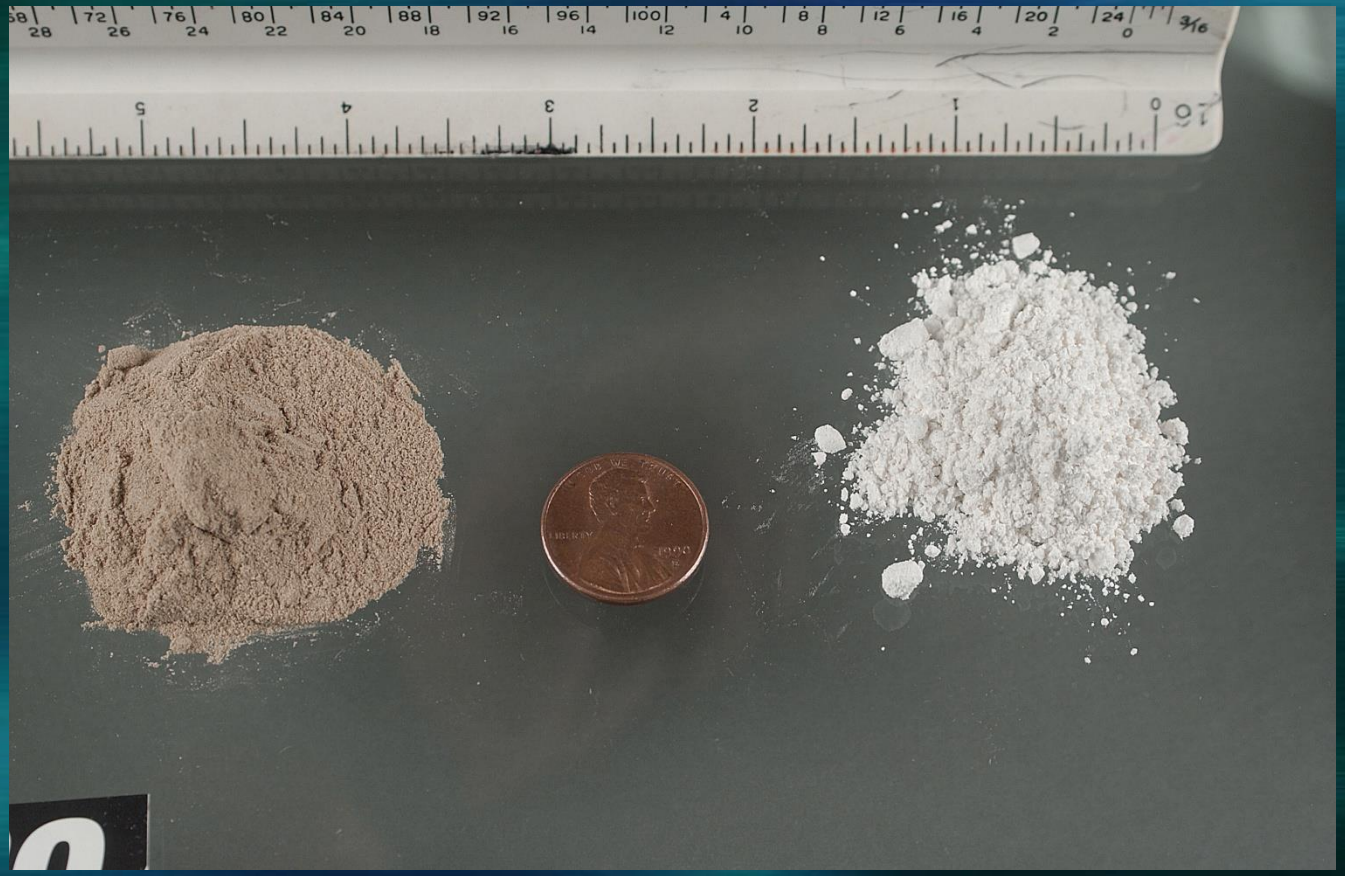
- Acetyl fentanyl
- Butyryl fentanyl
- Furanyl fentanyl
- Carfenanil
- U47700 (As of September in Schedule I)

Types of Opiates

Semi-Synthetic Opiates

Heroin

Brown and White Heroin

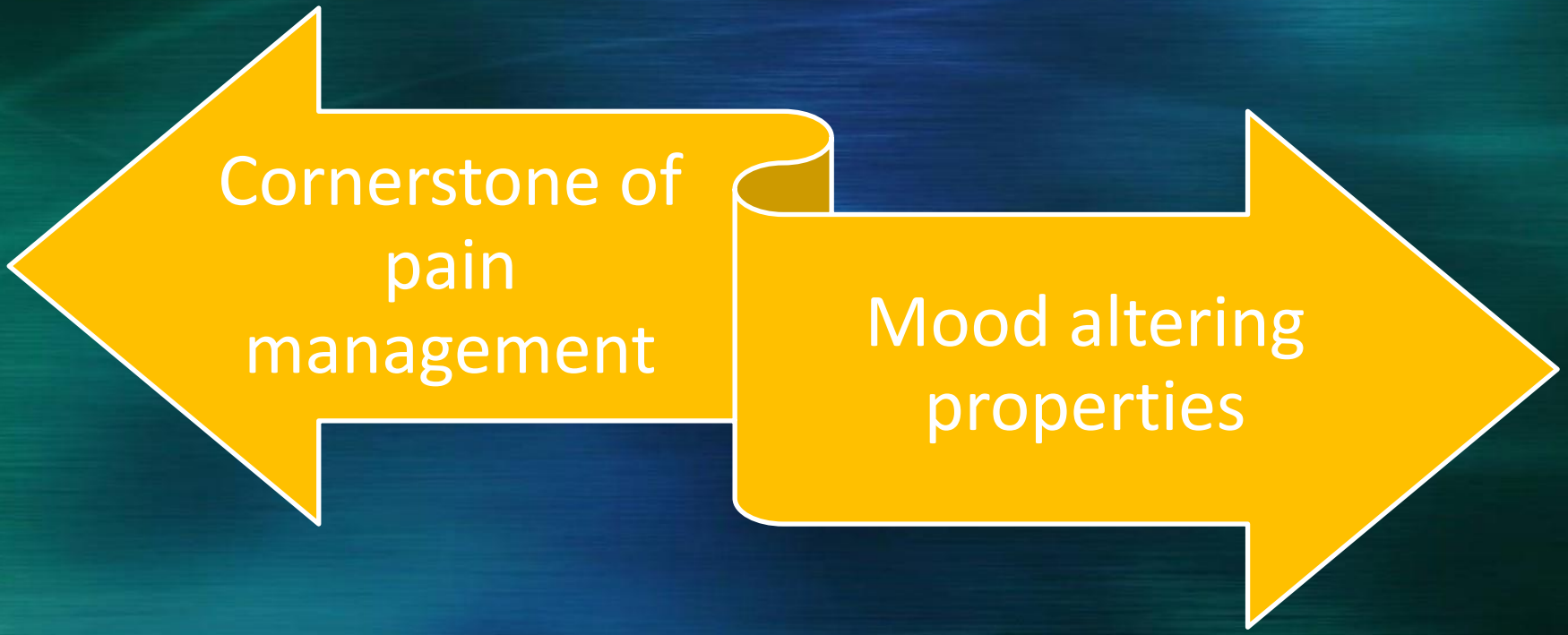


Black Tar Heroin ("El Chicle")

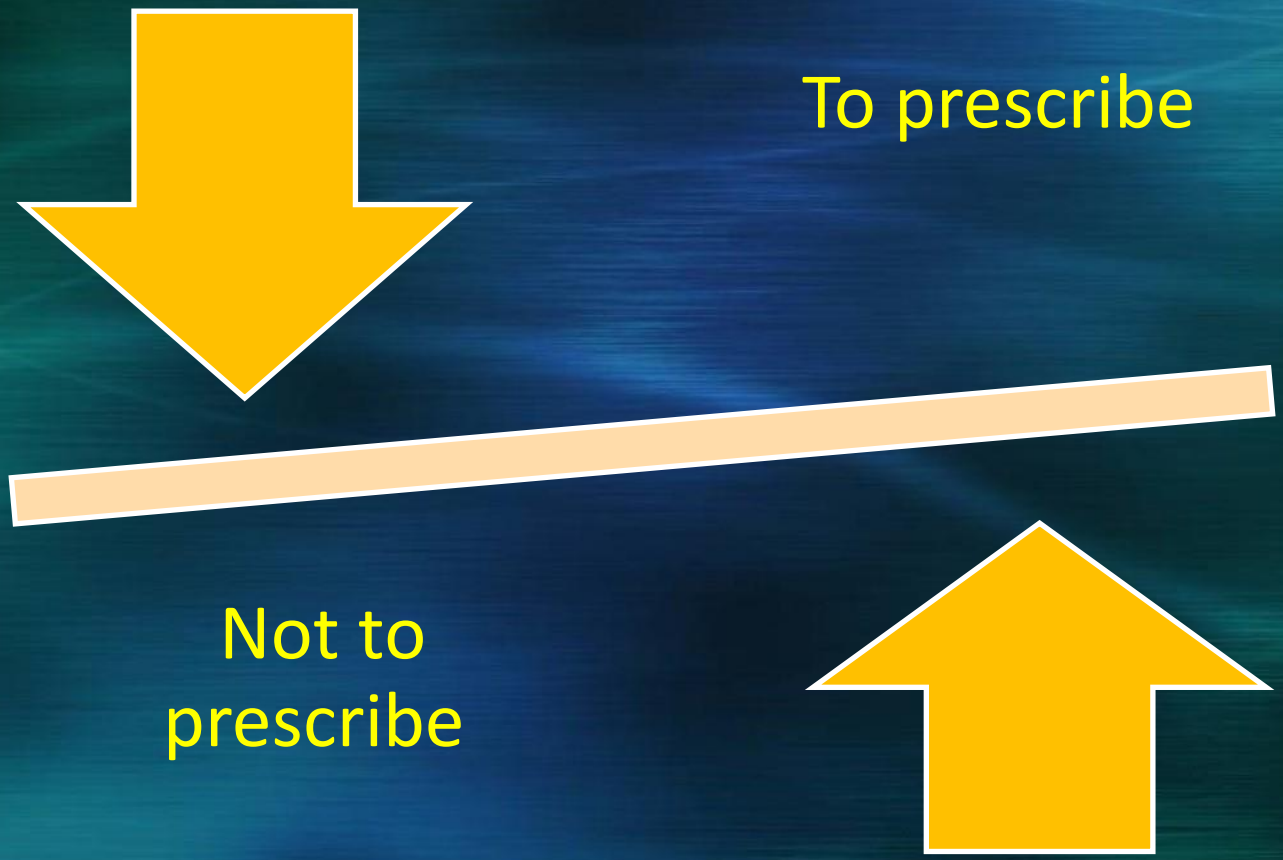
Opioids: Basic characteristics

- High addiction potential
- Tolerance develops
- Physical withdrawal symptoms moderate in intensity
- Moderate to high potential for immediate physical toxicity (overdose)
- Long-term physical toxicity unlikely
- Potential for acute and chronic psychiatric impairment low

Opioids: Double-edged sword



Physicians' Dilemma and Challenge



Narcotic (Opiate) Effects

- **Analgesia (pain relief)**
- **Cough suppression**
- **Sedation (drowziness)**
- **Euphoria (contentment, well-being, elimination of anxiety, depression, anger)**
- **Decrease in breathing, pulse and blood pressure)**
- **Constipation**
- **Constricted pupils**

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- Normal pupils

- Constricted pupils

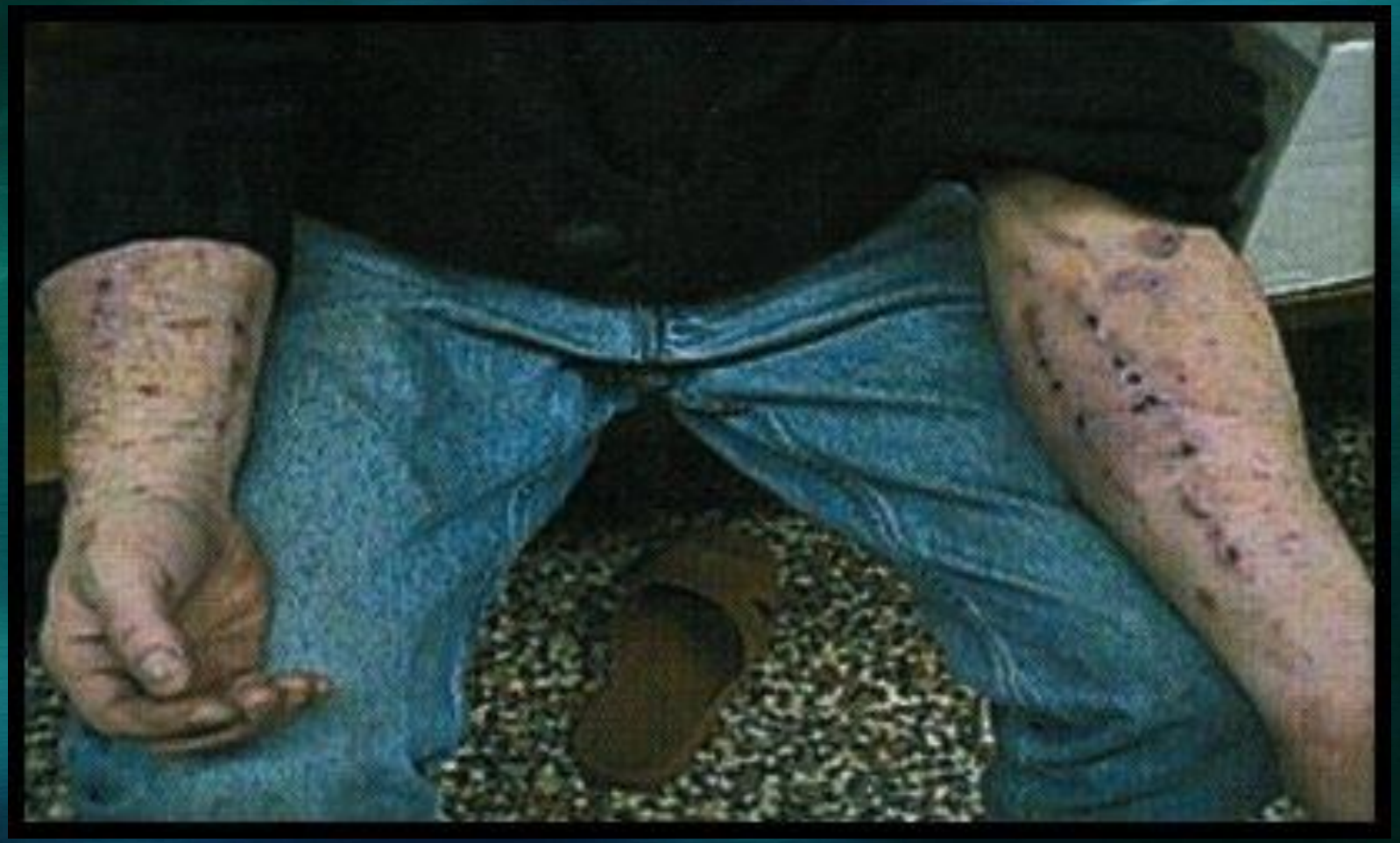
Medical complications of chronic heroin use

- Often related less to heroin itself and more to:
  - Method of administration
  - Lifestyle or health of the individual user
  - Contaminants and additives found in street heroin.

Medical complications of chronic heroin use

- **Track marks (injection marks/scars)**
- **Collapsed veins**
- **Abscesses (boils) and other soft-tissue infections**
- **Bacterial infections of the blood vessels and heart valves (e.g., bacterial endocarditis)**
- **Other blood-borne diseases (STDs, HIV, hepatitis B & C)**
- **Liver or kidney disease.**

Tracks and Abscesses



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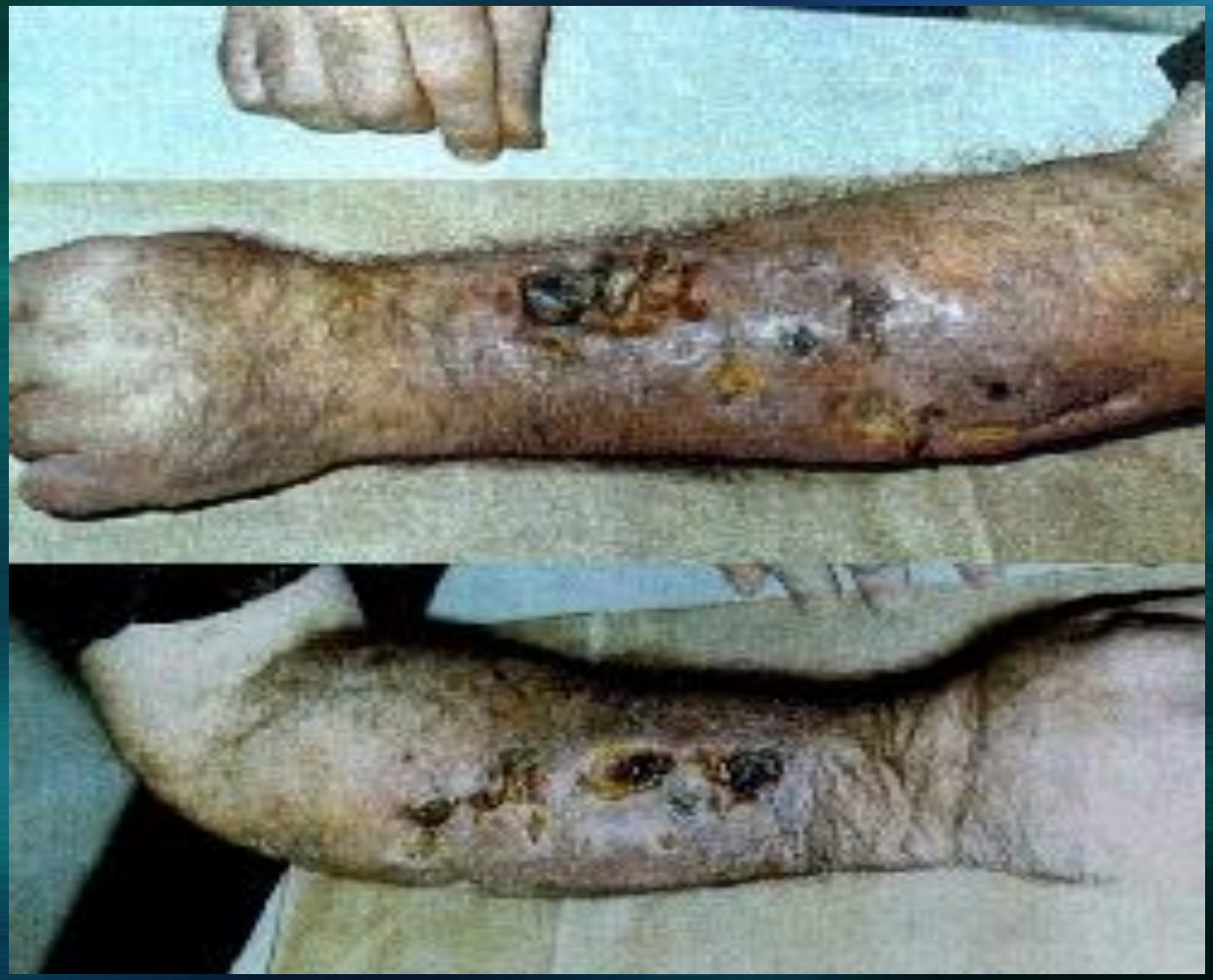

Medical complications of chronic heroin use

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Medical complications of chronic heroin use

- Lung complications (including various types of pneumonia and tuberculosis) may result from the poor health condition of the abuser as well as from heroin's depressing effects on respiration.
- Lung disease as the result of smoking heroin

Opiate Withdrawal

- Severity depends on:
  - Length of use
  - Level of use (dose)
  - Frequency
  - Type of opioid
- Onset after drug discontinuation depends on specific opioid
- Duration: 96-120 hours
- Post acute withdrawal syndrome (PAWS): 6-18 months
- Methadone usually eliminates PAWS

Opiate Withdrawal

- Signs of w/d:
  - **Drug hunger (craving)**
  - **Dilated pupils**
  - **Yawning**
  - **Lacrimation (eyes tear)**
  - **Rhinitis (runny nose)**
  - **Fever**
  - **Restlessness**
  - **Stomach, leg and back cramps**

Opiate Withdrawal

- Signs of w/d:
  - **Insomnia**
  - **Nausea**
  - **Diarrhea**
  - **Vomiting**
  - **Chills/cold flashes with goose bumps ("cold turkey“)**
  - **Sweating**
  - **Leg spasms (“kicking the habit”)**

Opiate Withdrawal

- Signs of w/d:
  - **Rapid pulse**
  - **Increased blood pressure**
  - **Anxiety**
  - **Depression**
  - **Muscle and bone pain**

Evidence-based strategies (Opioids)

- Contingency management/motivational incentives
- Community reinforcement approach plus vouchers
- 12-step facilitation

Contingency management/motivational incentives

- Contingency management (CM) principles involve giving patients tangible rewards to reinforce positive behaviors such as abstinence.
- Studies conducted in both methadone programs and psychosocial counseling treatment programs demonstrate that incentive-based interventions are highly effective in
  - increasing treatment retention
  - promoting abstinence from drugs

Motivational incentives: Voucher-based reinforcement

- Patient receives a voucher for every drug-free urine
- Voucher has monetary value that can be exchanged for food items, movie passes, or other goods or services consistent with a drug-free lifestyle
- Voucher values are low at first, increase as the number of consecutive drug-free urine samples increases; positive urine samples reset the value of the vouchers to the initial low value

Motivational incentives:
Prize Incentives

- Uses chances to win cash prizes instead of vouchers
- Clients supplying drug-negative urine or breath tests draw from a bowl for the chance to win a prize worth between $1 and $100
- Clients may also receive draws for attending counseling sessions and completing weekly goal-related activities.

Community reinforcement approach plus vouchers

- Uses a range of recreational, familial, social, and vocational reinforcers, along with material incentives, to make a non-drug-using lifestyle more rewarding than substance use.
- Focus on
  - improving family relations
  - Learning a variety of skills to minimize drug use
  - Receiving vocational counseling
  - Developing new recreational activities and social networks
- Clients submit urine samples 2-3 times/week and receive vouchers for drug-negative samples

12-step facilitation

- An active engagement strategy designed to increase the likelihood of a substance abuser becoming affiliated with and actively involved in 12-step self-help groups
- Three key ideas
  - Acceptance
  - Surrender
  - Active involvement in 12-step meetings and related activities.

Other evidence-based strategies

- Cognitive behavioral therapy
- Motivational enhancement therapy
- Matrix model
- Family behavior therapy

Medication-Assisted Treatment

MAT Misconception 1

- Methadone/buprenorphine is treatment

- Truth: These medications are adjuncts to treatment ("**Medication-assisted** treatment").

Medication-Assisted Treatment

Providing opioid agonist or partial agonist medication as an adjunct to psychosocial treatment in order to improve engagement, retention and outcomes.

Treating Opiate Dependency: A Dilemma

- Physical dependence and craving are major barriers to abstaining from opiate use
- Detoxifying addicts with increasingly smaller doses of heroin or morphine is not an effective approach
- “Cold turkey” withdrawal is painful and unpleasant and often results in relapse

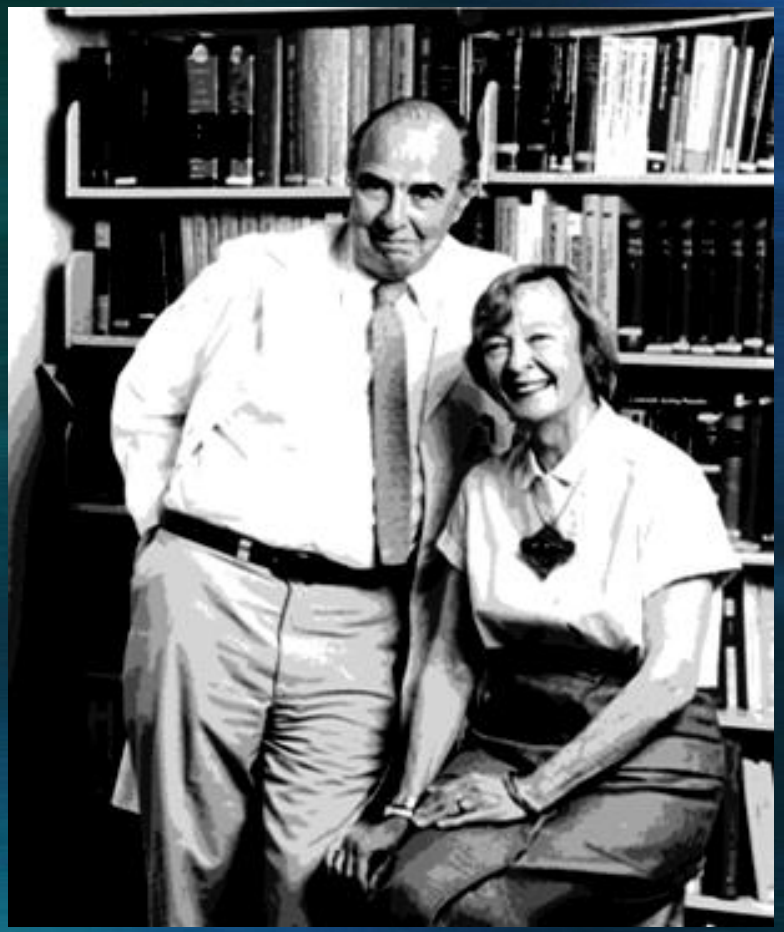
Using Medication to suppport opiate dependence treatment

PROFILE FOR POTENTIAL PSYCHOTHERAPEUTIC AGENT

- Effective after oral administration
- Long biological half-life (>24 hours)
- Minimal side effects during chronic administration
- Safe, no true toxic or serious adverse effects
- Efficacious for a substantial % of persons with the disorder

Medications used to treat opiate dependency

- Methadone
- Clonidine
- Buprenorphine
- Naltrexone



Methadone Pioneers
Drs. Vincent Dole and Marie Nyswander

A brief history of methadone

- 1939: Dolophine is first synthesized in Germany
- 1947: The effects of dolophine (Methadone) are discovered by Dr. Vincent Dole and Dr. Marie Nyswander.
- 1961: Methadone is first used experimentally to treat heroin dependency

A brief history of methadone

- 1960s and 70s: The Illinois Drug Abuse Program (IDAP) becomes the nation's leading provider of methadone

Advantages of methadone treatment

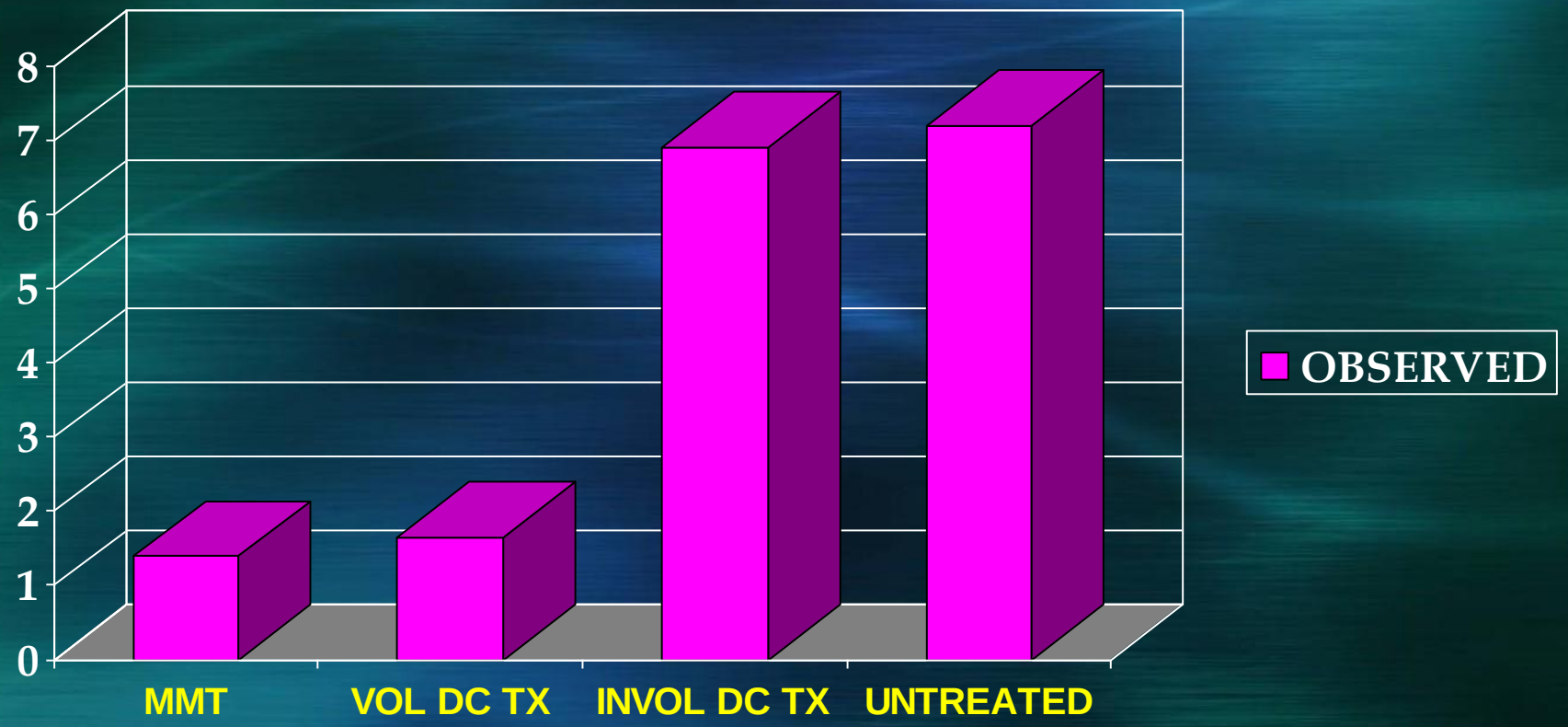
- Individual
- Community/society

Advantages of methadone treatment

- 8-10 fold reduction in death rate
- Reduction of drug use
- Reduction of criminal activity
- Engagement in socially productive roles; improved family and social function
- Increased employment
- Improved physical and mental health
- Reduced spread of HIV
- Excellent retention

Reduction in death rate

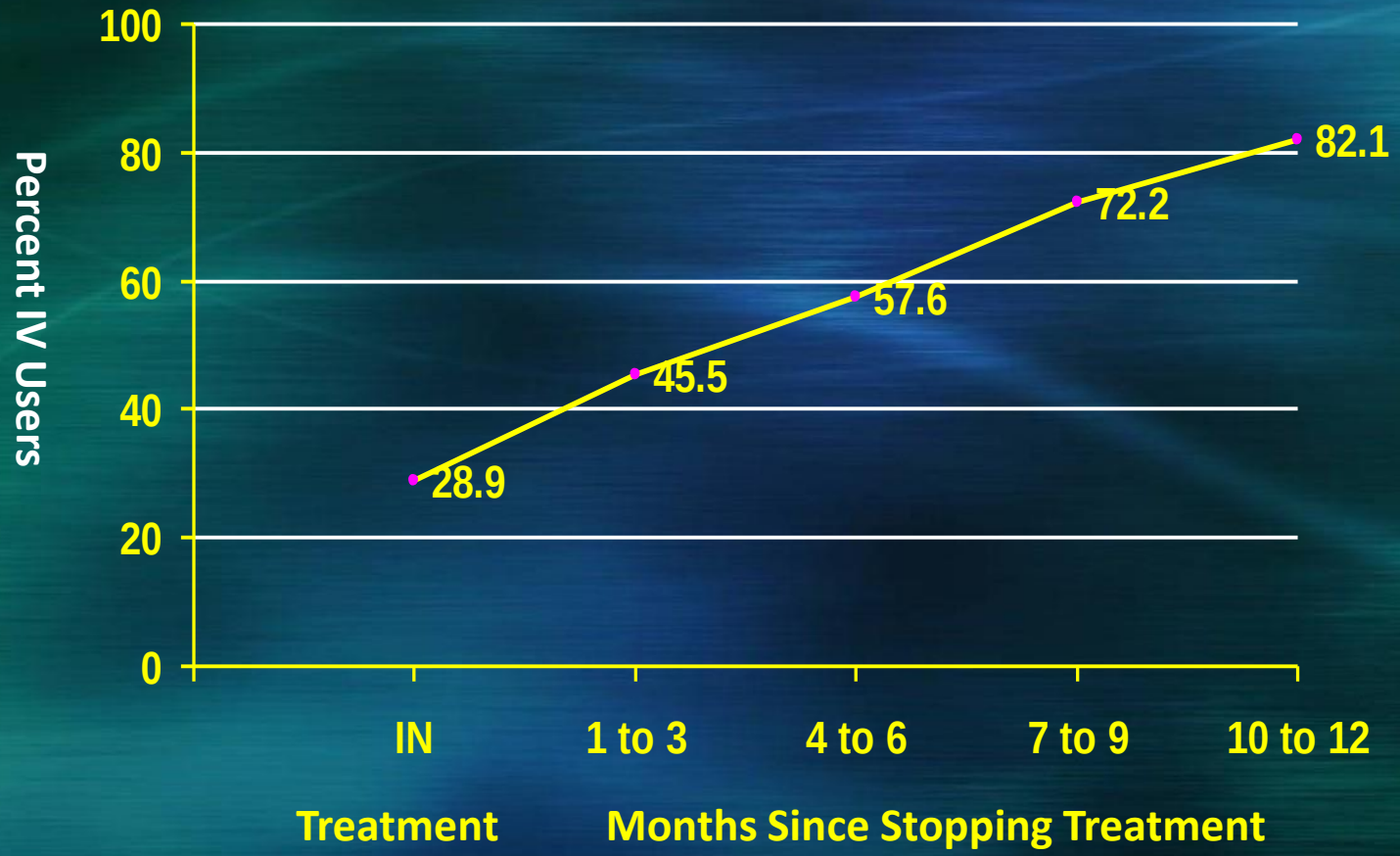
DEATH RATES IN TREATED AND UNTREATED HEROIN ADDICTS



Slide data courtesy of Frank Vocci, MD, National Institute on Drug Abuse

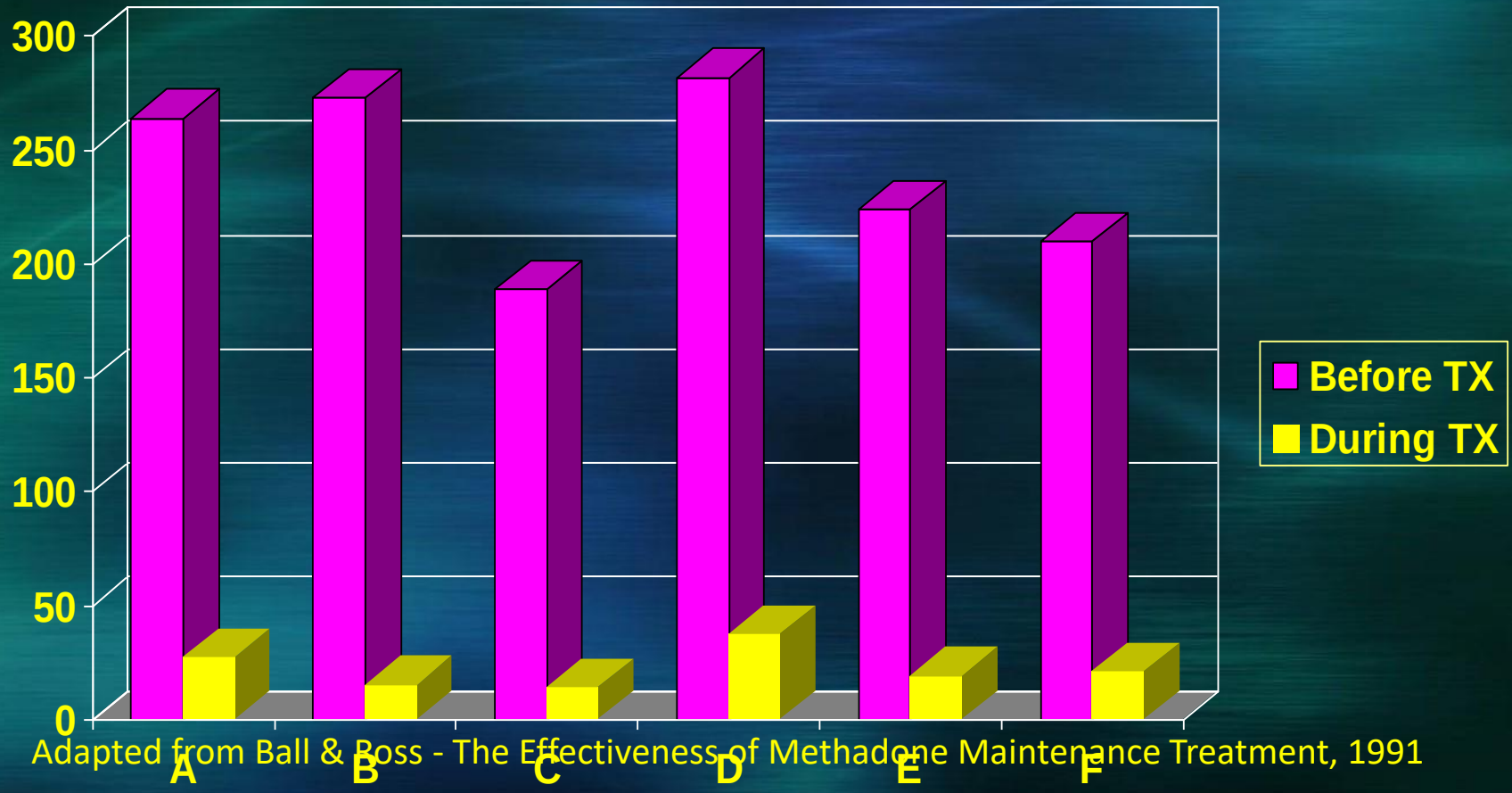
Reduction of drug use

Relapse to IV drug use after MMT
105 male clients who left treatment



Reduction of criminal activity

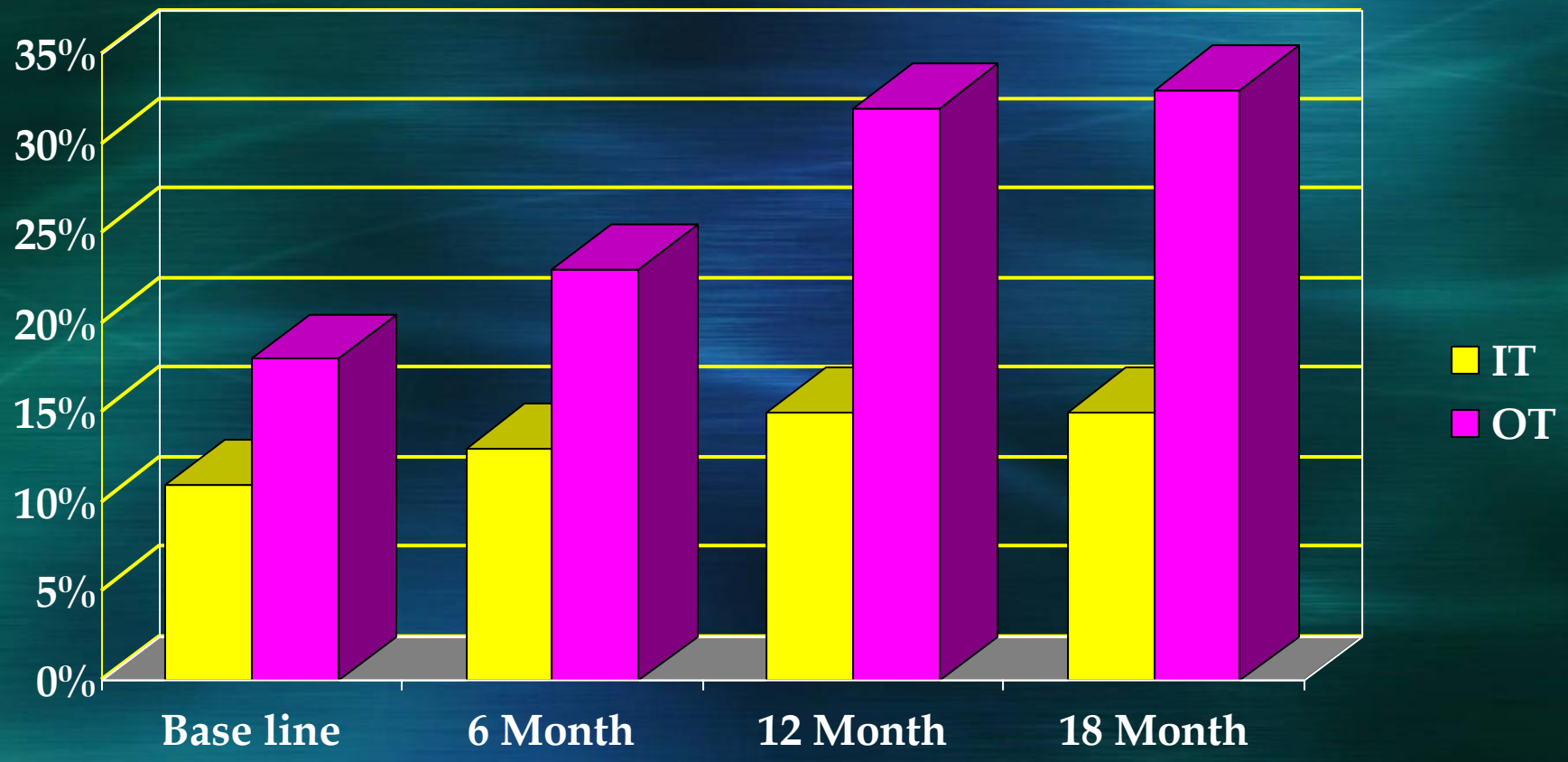
Crime among 491 clients before and during MMT at 6 programs



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

Reduced spread of HIV

HIV CONVERSION IN TREATMENT



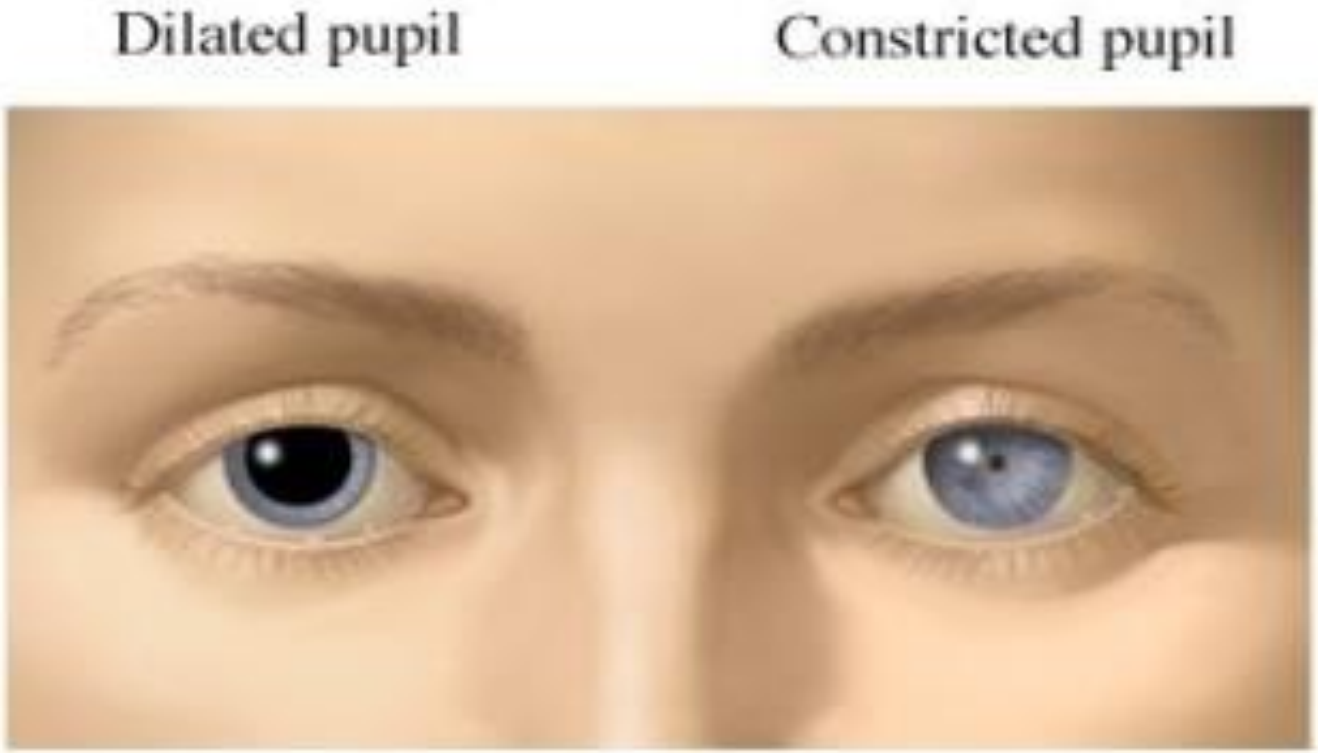
HIV infection rates by baseline treatment status:
In treatment (IT) n=138 not in treatment (OT) n=88

Source: Metzger, D. et. al. J of AIDS 6:1993. p.1052

The methadone maintenance process

- Client is accessed for physical dependency (a requirement for methadone treatment)
- A starting dose is administered
- Client is observed for effects of starting dose

Pupillary constriction/dilation



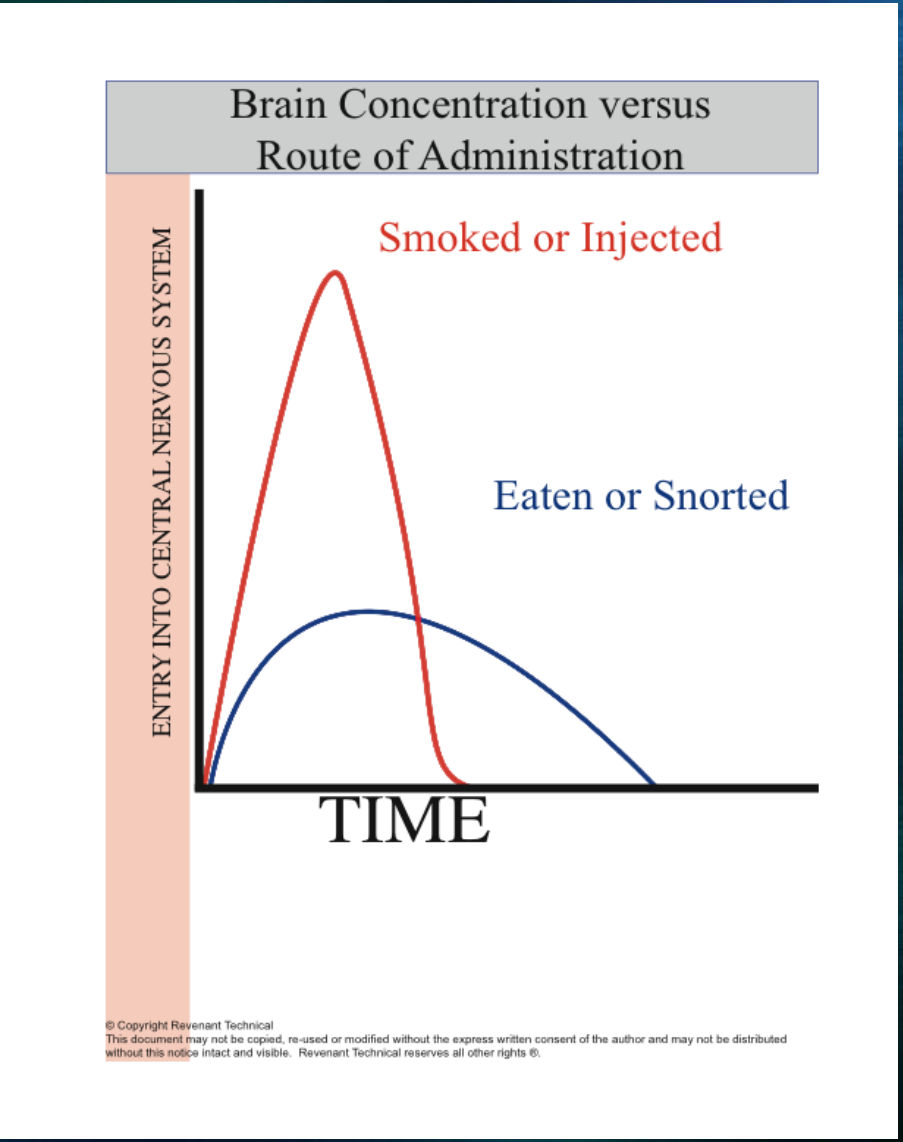
The methadone maintenance process

- Client is accessed for physical dependency (a requirement for methadone treatment)
- A starting dose is administered
- Client is observed for effects of starting dose
- Dose is increased if necessary
- Client participation in program is ruled out if low dose of methadone causes sedation

Methadone vs Heroin

Heroin	Methadone
Usually administered by injection or smoking	Administered by mouth
Rapid onset of action	Slow onset of action
Tolerance continuously increases	No continuing increase in tolerance levels after optimal dose is reached; relatively constant dose over time
Use is specifically for the sedating & euphoric effect	Client on stable dose rarely experiences euphoric or sedating effects

Rapid onset=More pleasurable reaction



Methadone vs Heroin

Heroin

- Client
  - feels less physical pain
  - Has blunted emotions
  - Can not drive or perform daily tasks normally and safely

Methadone

- Client able to
  - Perceive pain
  - Experience have emotional reactions
  - Perform daily tasks normally and safely

Methadone vs Heroin

Heroin

- Short-acting: effect lasts 4-6 hours
- May produce medical consequences based on adulteration and method of administration

Methadone

- Long acting: prevents withdrawal for 24 hours, permitting once-a day-dosing
- At sufficient dosage, blocks euphoric effect of normal street doses of heroin
- Medically safe when used on long-term basis (10 years or more)

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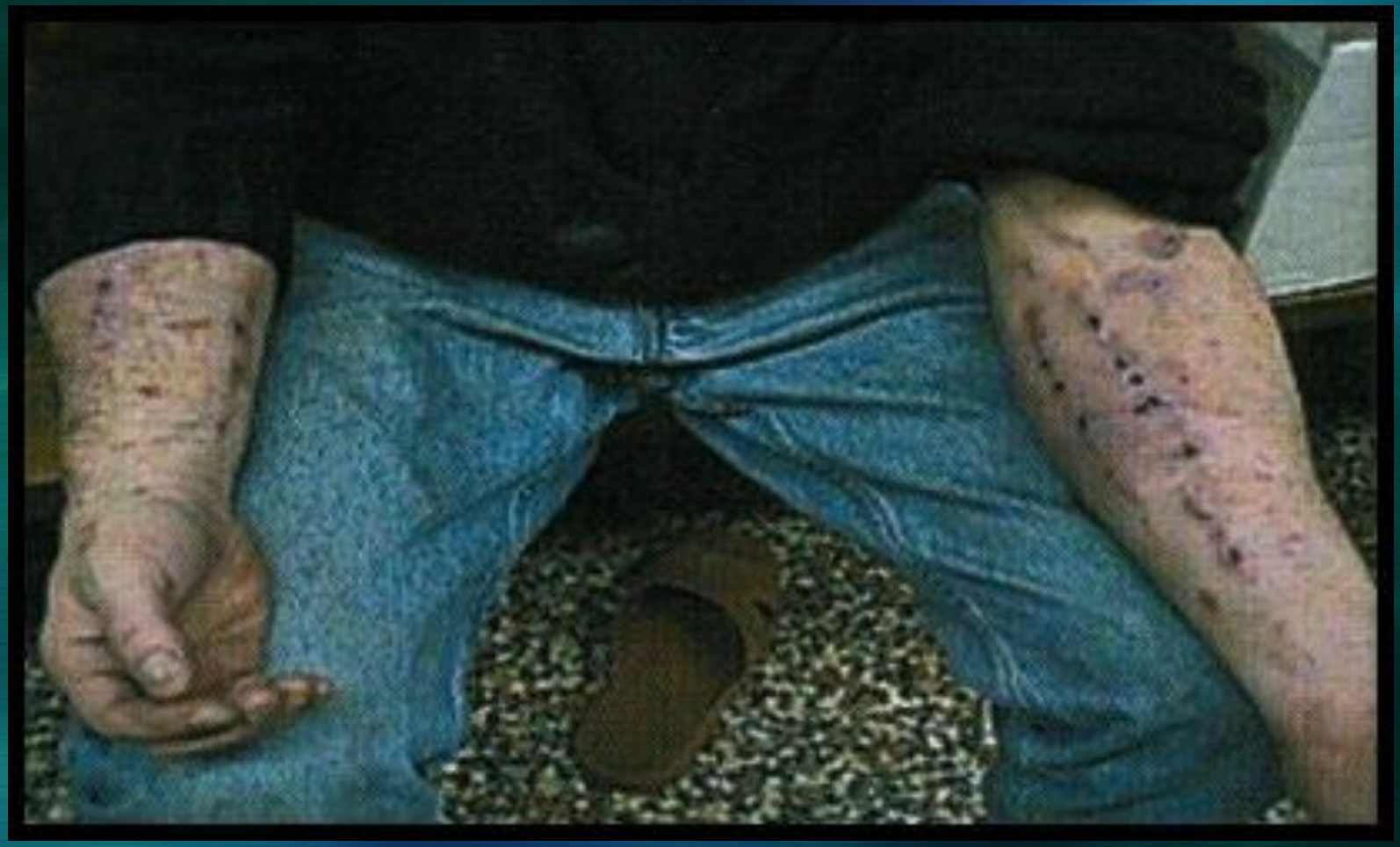
Tracks and abscesses from i.v drug use



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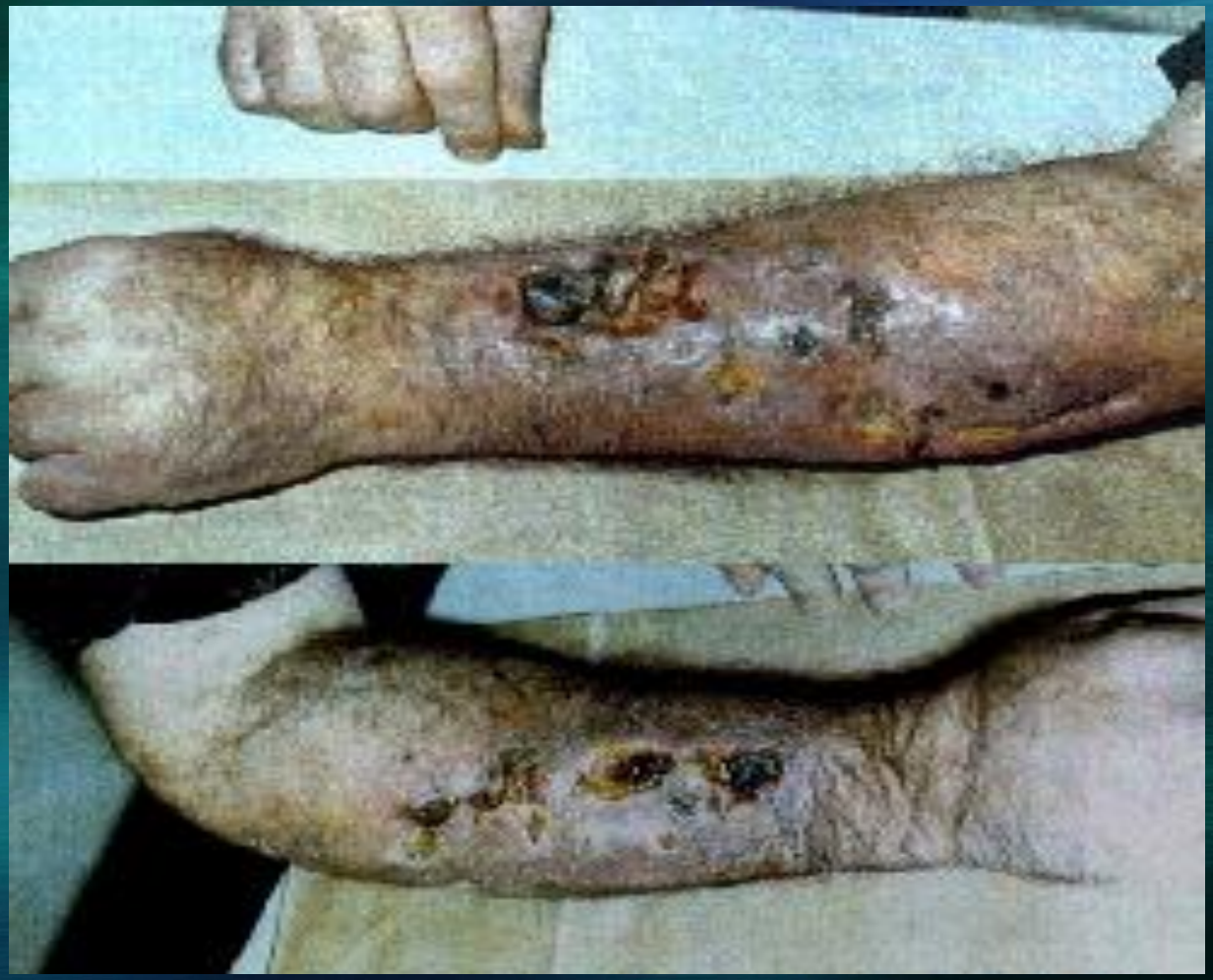
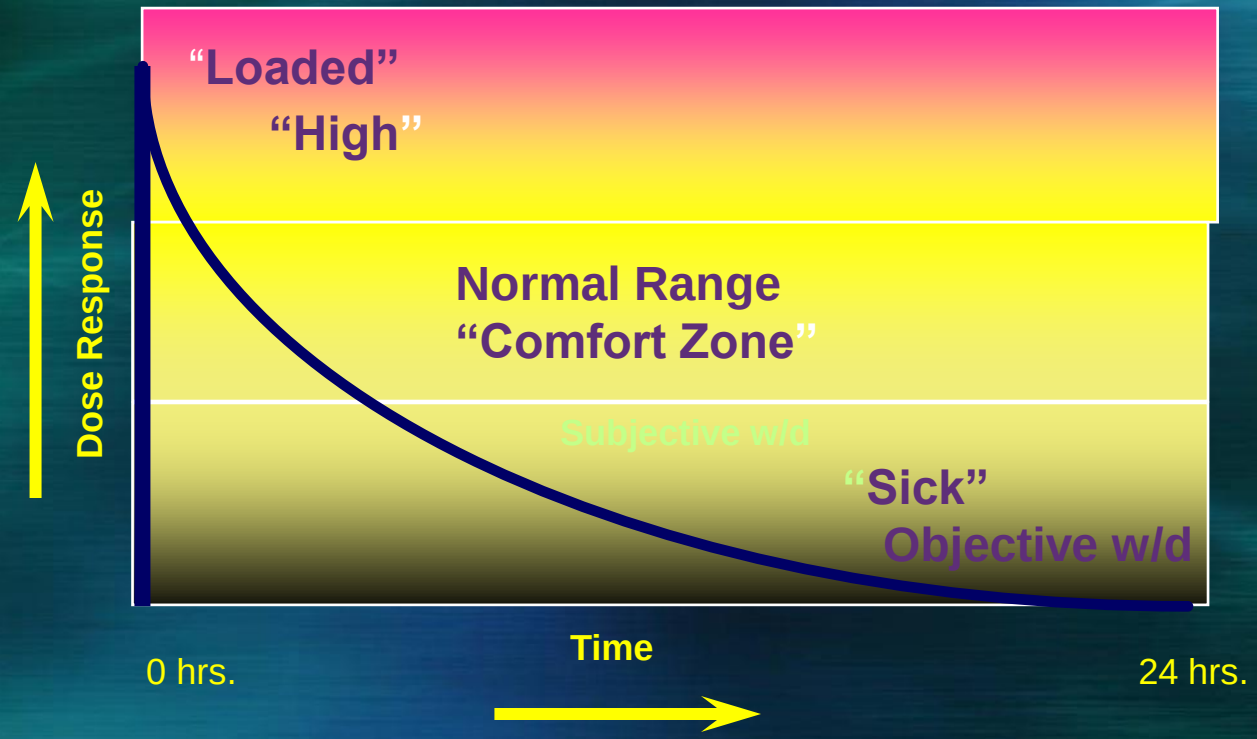


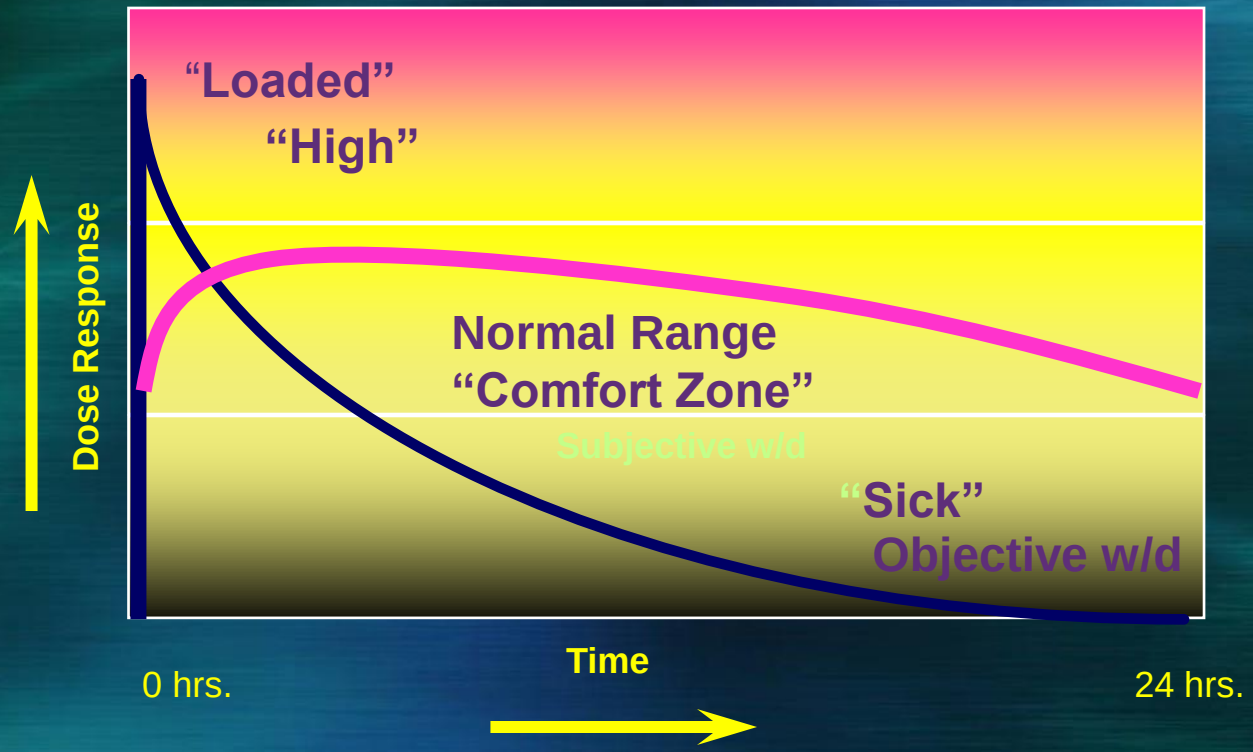
Heroin Simulated 24 Hr. Dose/Response

With established heroin tolerance/dependence



opiate Agonist Treatment of Addiction - Payte - 1998

Methadone Simulated 24 Hr. Dose/Response
At steady-state in tolerant patient



opiate Agonist Treatment of Addiction - Payte - 1998

How is methadone better than heroin?

- Legal
- Avoids needles
- Known amount ingested
- Slow onset: no “rush”
- Long acting: can maintain “comfort” or normal brain function
- Stabilized physiology, hormones, tolerance

MAT Misconception 2

- MAT clients are still addicted

- Truth: MAT clients will experience withdrawal symptoms if they stop taking their medication. However, withdrawal is not a diagnostic criteriuum when the client is taking opioids solely under medical supervision
- DSM-V requires at least 2 criteria out of a possible 11

DSM-V Criteria: Opiate Use Disorder

- Mild: 2-3 symptoms
- Moderate: 4-5 symptoms
- Severe: 6 or more symptoms

- Substance taken in larger amount and for longer period than intended
- Persistent desire or unsuccessful efforts to cut down or control use
- Great deal of time spent in activities to obtain, use, recover from effects
- Craving or a strong desire to use

DSM-V Criteria: Opiate Use Disorder

- Recurrent use resulting in failure to fulfill major role obligation at work, school or home
- Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by effects of the substance
- Important social, occupational, or recreational activities given up or reduced
- Recurrent use in physically hazardous situations
- Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by use

DSM-V Criteria: Opiate Use Disorder

- Use continues despite knowledge of adverse consequences (e.g., failure to fulfill role obligation, use when physically hazardous)
- Tolerance
- Withdrawal

Summary

- Methadone:
  - is a safe medication when used properly
  - Does not cause intoxication if used appropriately
  - Is an adjunct to treatment
  - Blocks withdrawal symptoms/effects of other opiates
  - Reduces crime, death, HIV conversion & costs to society
  - Benefits the client, the community and the human services, child welfare and criminal justice system

Medication-assisted treatment: Buprenorphine

- Buprenorphine (Buprenex)
- Subutex® (buprenorphine sublingual tablets).
- Suboxone® (buprenorphine and naloxone sublingual tablets).
- Naloxone is not effective as an agonist unless it is injected
  - Guards against cooking and injecting Suboxone

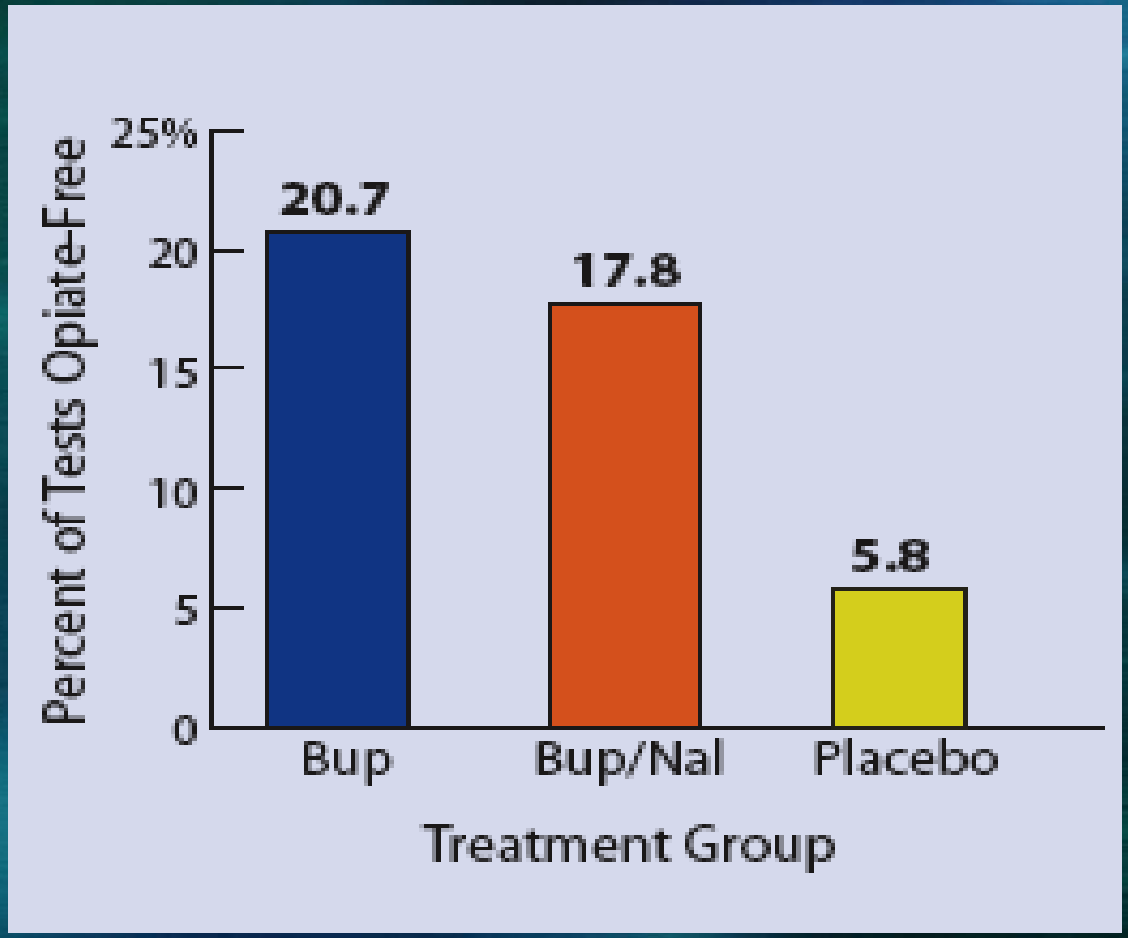
Buprenorphine

- Buprenorphine has duration of 24 hours.
- Buprenorphine produces less euphoria than morphine and heroin.
- Has an “agonist activity ceiling” with no increased benefits on increasing the dose.
- Compared with other opiates, causes a significantly lower degree of sedation and respiratory depression

Buprenorphine

- High doses of buprenorphine (≥100 times the analgesia dose) do not produce dangerous respiratory effects.
- Withdrawal syndrome less rapid and less intense than with a pure agonist such as heroin or methadone.
- Buprenorphine can be given to clients every other day rather daily like methadone

Buprenorphine and Buprenorphine/Naloxone Help Clients Stay Opiate-free



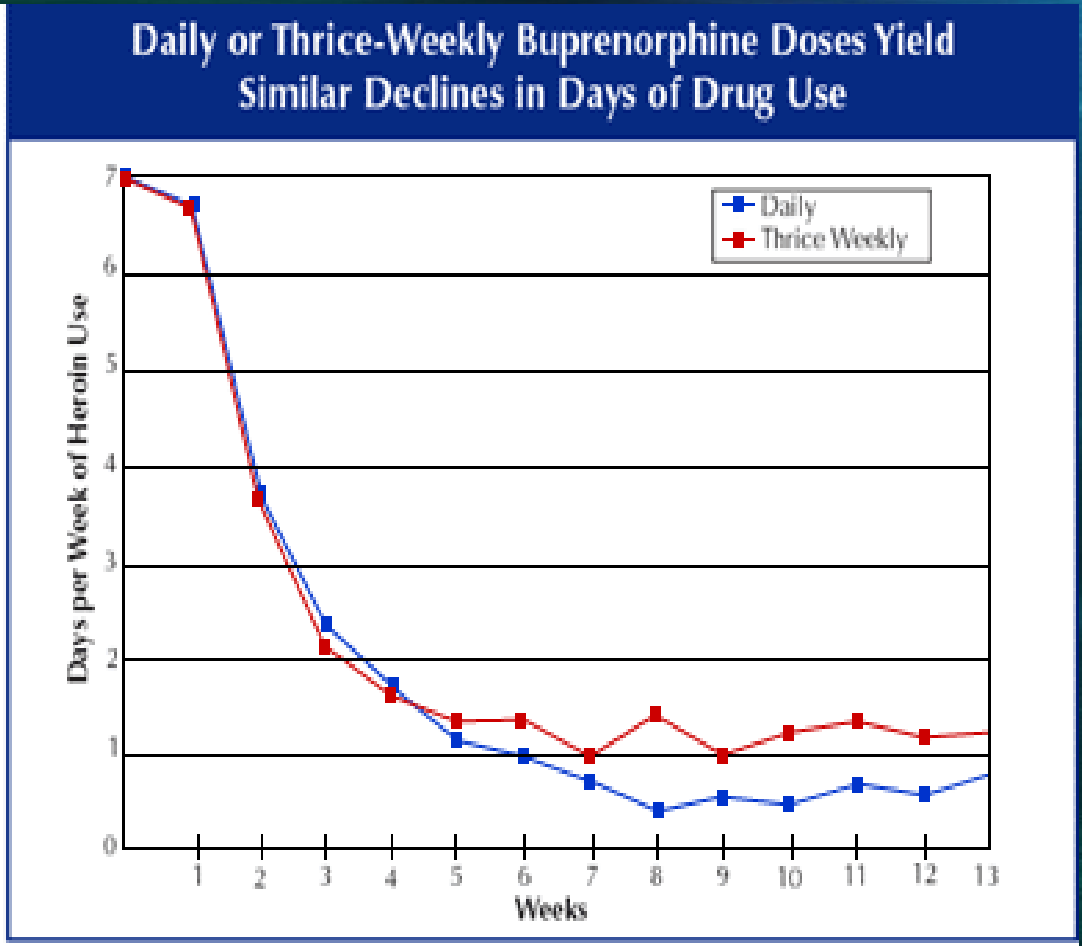
Buprenorphine 3x/week as Effective as Daily Doses

- 92 participants (73 percent white, 75 percent male)
- 45 received **daily** buprenorphine (average 16 mg)
- 47 received average doses of 34 mg on **Fridays** and **Sundays**, 44 mg **Tuesdays**, and a placebo on other days.
- Urine samples on Mondays, Wednesdays, and Fridays analyzed for opioids and cocaine metabolites
- One sample per week tested for benzodiazepines.

Buprenorphine 3x/week as Effective as Daily Doses

- No significant differences between groups in:
  - Reduction of opioid use
  - Retention in the treatment program
  - Use of cocaine
- Clients couldn't reliably tell whether they were receiving the medication daily or three times each week.

Buprenorphine 3x/week as Effective as Daily Doses

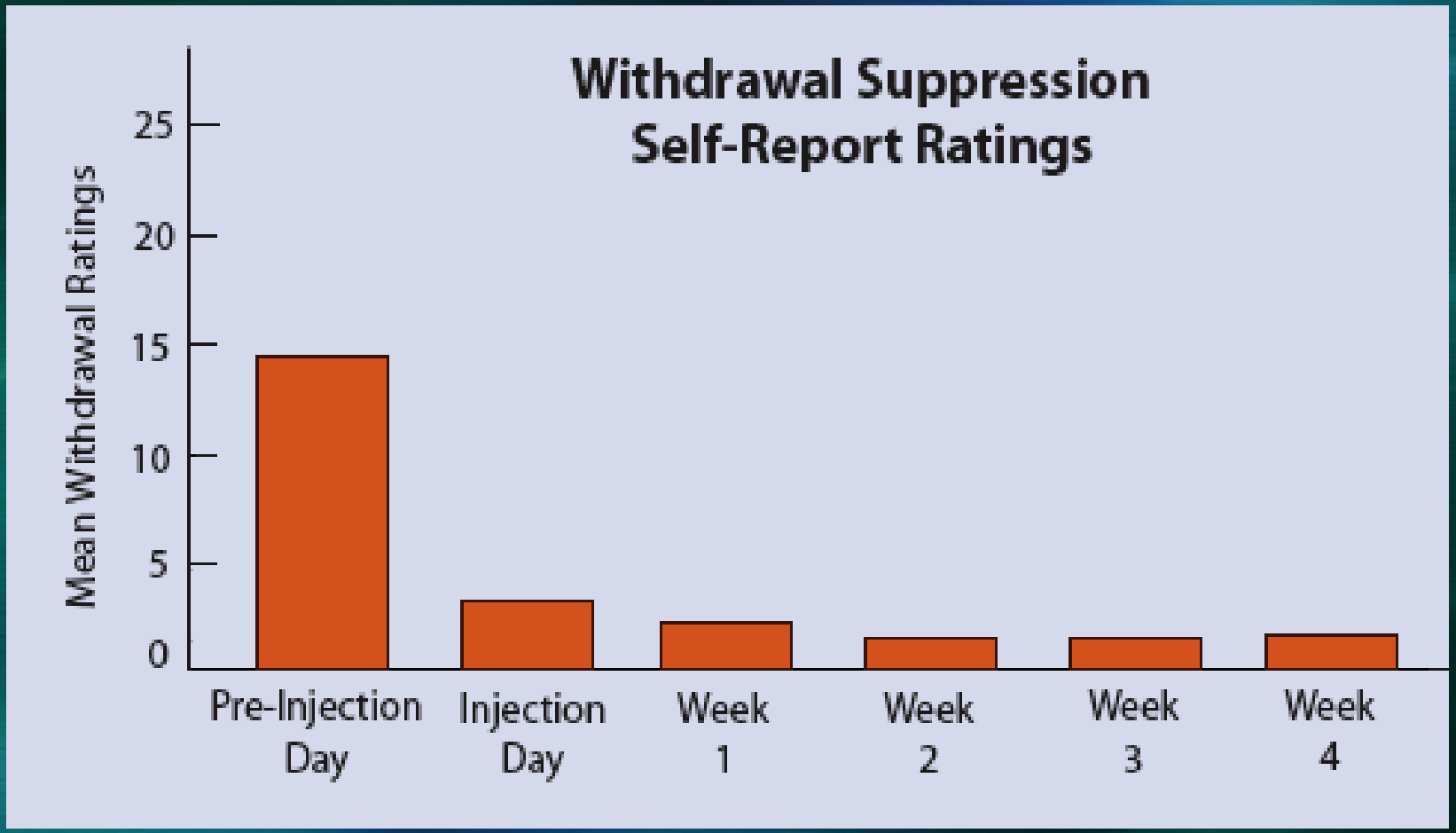


Patients in treatment for opioid addiction received either daily or thrice-weekly doses of buprenorphine. Both groups showed reductions in reported days of heroin use during a 13-week treatment program.

Sustained Release Buprenorphine

- One injection lasts for six weeks
- Treatment consists of a single injection of biodegradable polymer microcapsules containing 58 mg of “bup”
- For 6 weeks clients assessed for signs of heroin withdrawal and clients rated their withdrawal symptoms using a standard questionnaire.
- No client needed additional medication for withdrawal relief.

Long-Lasting Buprenorphine Reduces Withdrawal Symptoms in Heroin-Dependent clients



However:
Buprenorphine is not always the best choice

- Individuals with more severe heroin habits (need methadone ≥ 100 mg)

Medications used to treat opiate dependency

- Methadone
- **Clonidine**
- Buprenorphine
- Naltrexone

Medication-assisted treatment: Naltrexone

- Naltrexone is a long-acting opioid antagonist
- Clients must be withdrawn from opioids first
- Naltrexone block opioid effects
- Available in a depot formulation that can last 30 days

Medications used to treat opiate dependency

- Methadone
- **Clonidine**
- Buprenorphine
- Naltrexone

Clonidine Detoxification

- Clonidine = Catapres
- Used primarily as a treatment for high blood pressure
- (Reduces activity in locus coeruleus)
- Capable of suppressing most of the opiate withdrawal syndrome
- Will not suppress insomnia, bone ache or craving.
- Contraindicated in clients with low blood pressure
- May be tapered over a 6-7 day period.