Acentra HEALTH

Opioid Addiction and Medication Assisted Therapy

Part 2

J. Mitchell Simson MD, MPH, FASAM

January 22, 2025

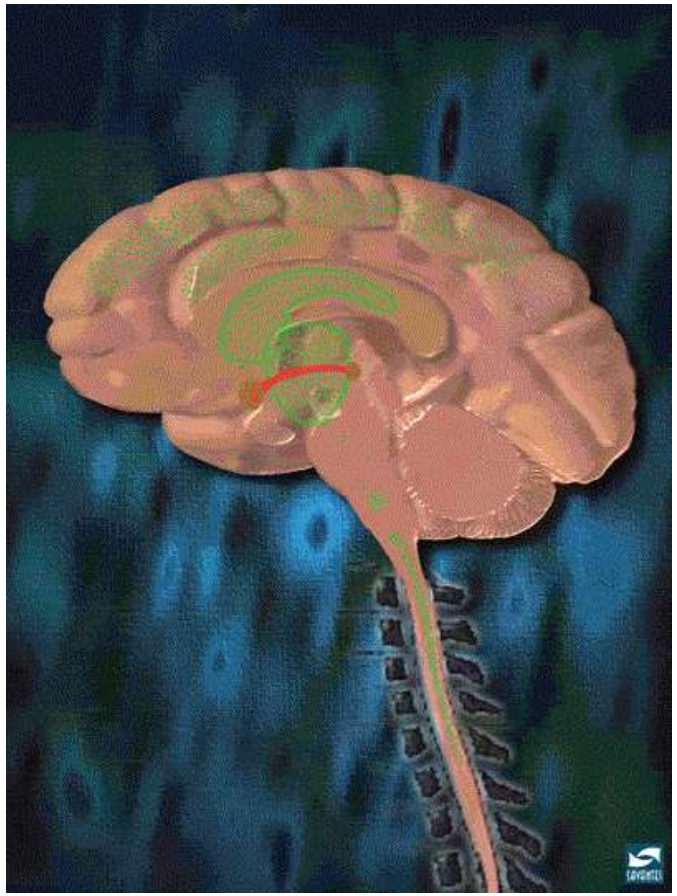
This is the 2nd session on opioids:

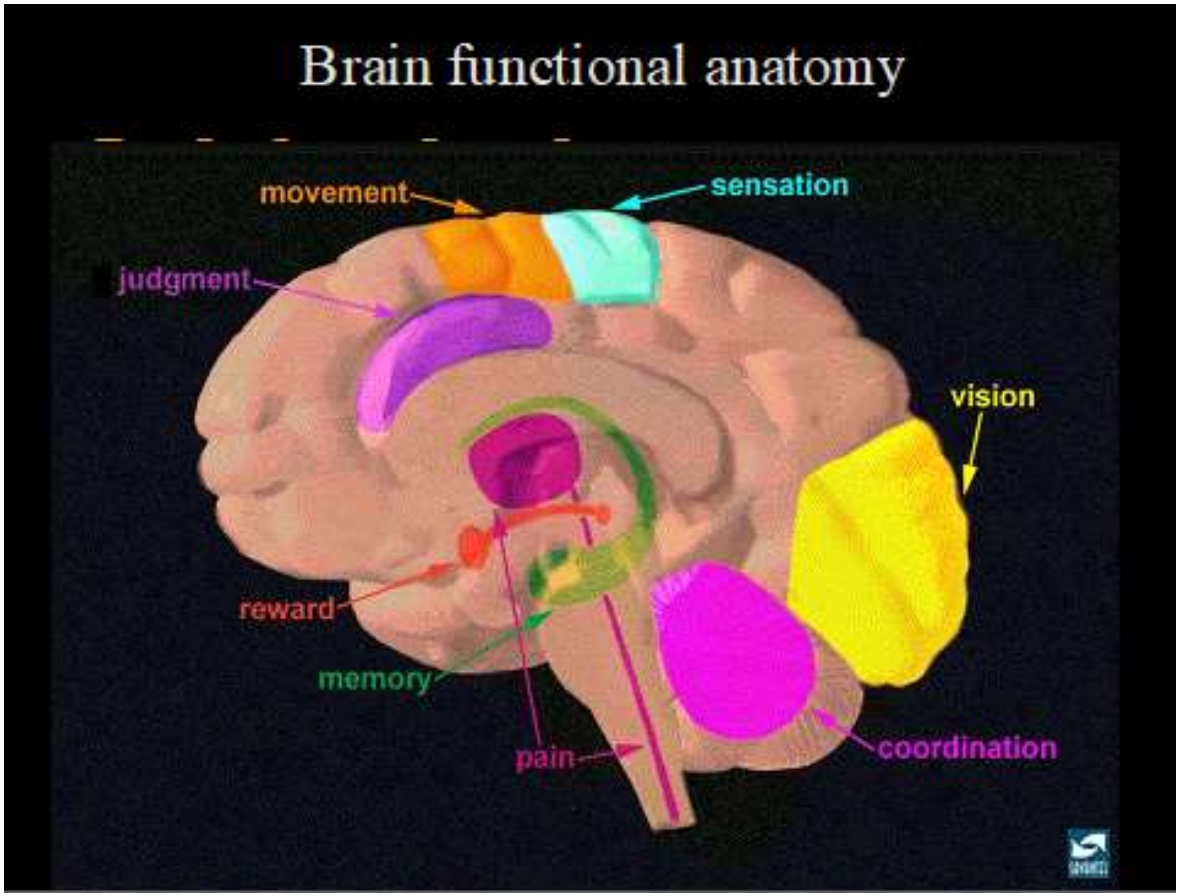
- Definition of Addiction
- History and Epidemiology
- Opiate use in USA
- Pharmacology

- Review of Opioid Neurochemistry
- Newer semi-synthetic opiates
- Medication Assisted Therapy

A Major Reason People Take a Drug is they Like What It Does to Their *Brains*

Opiate Binding Sites – Medial Brain



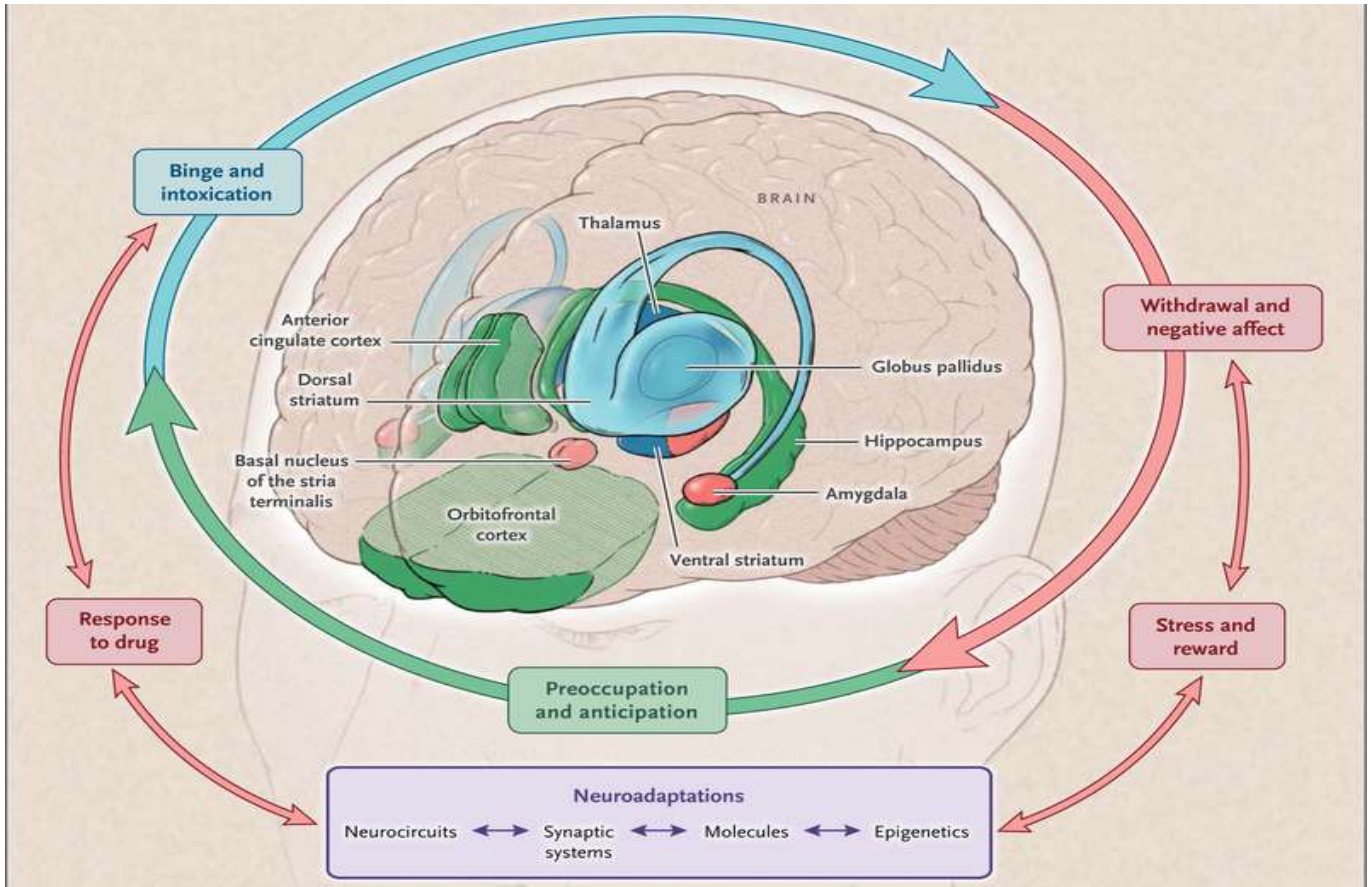


Review Article

Neurobiologic Advances from the Brain Disease Model of Addiction

Nora D. Volkow, M.D., George F. Koob, Ph.D., and A. Thomas McLellan, Ph.D.

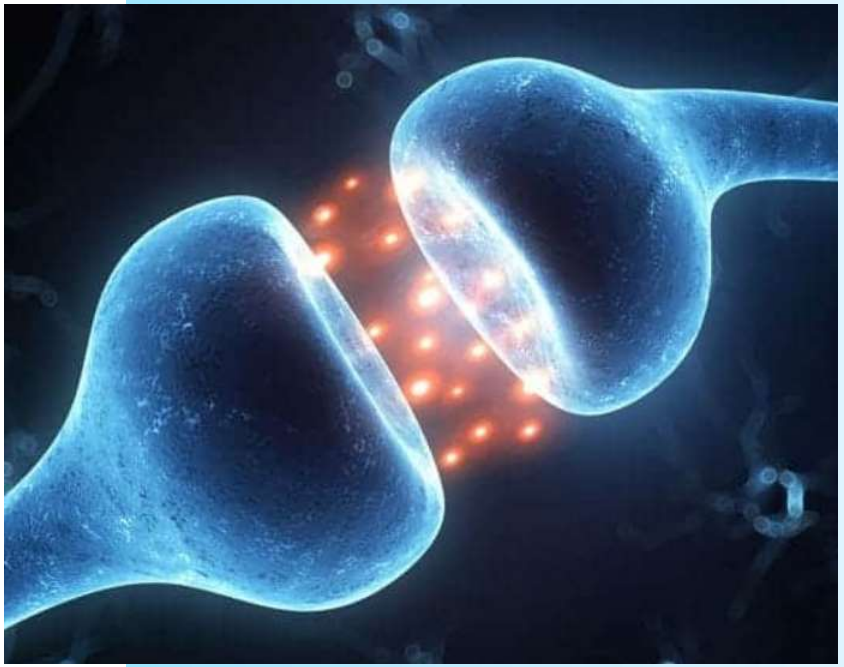
N Engl J Med
Volume 374(4):363-371
January 28, 2016



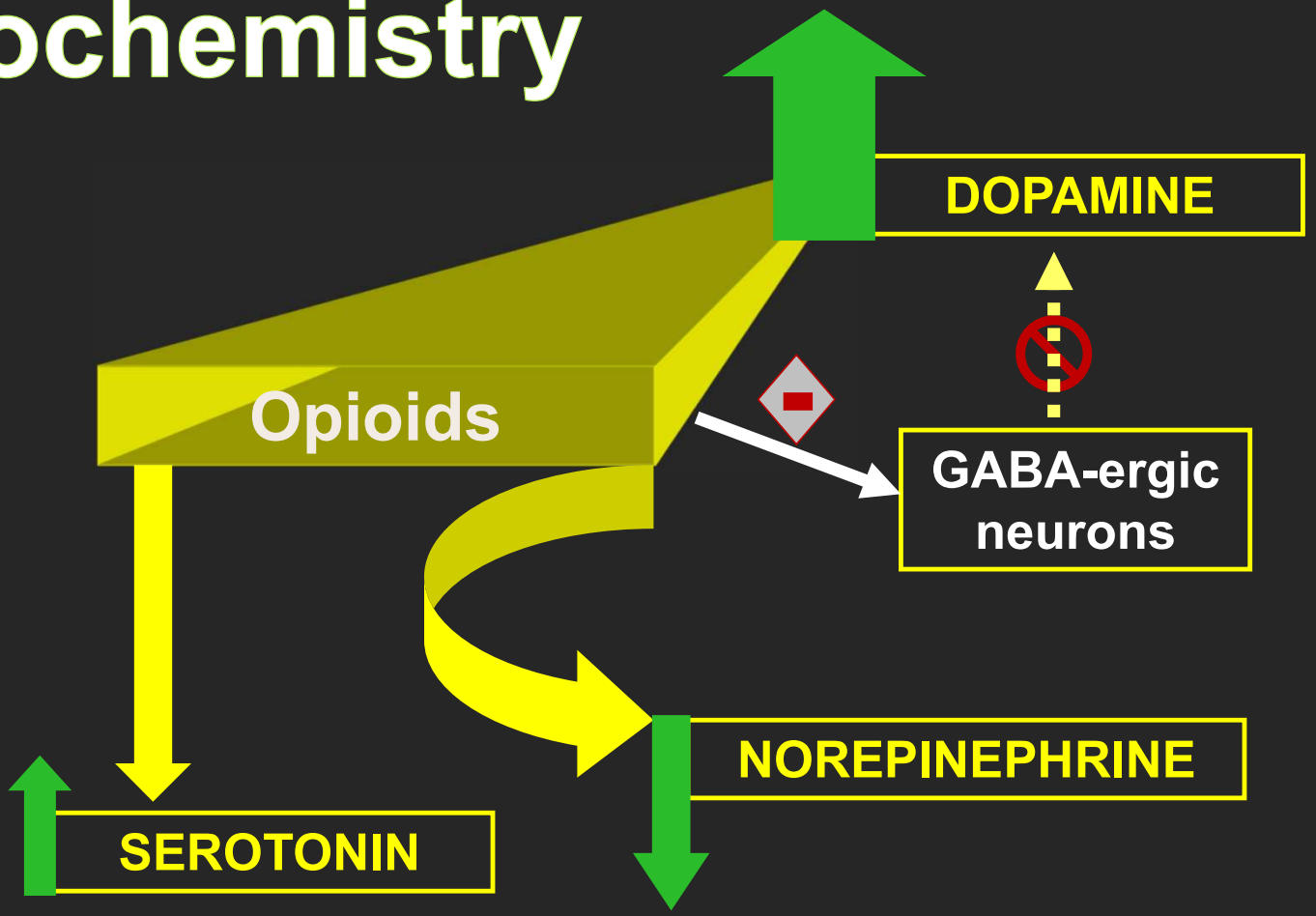
Stage of Addiction	Shifting Drivers Resulting from Neuroadaptations		
Binge and intoxication	Feeling euphoric	Feeling good	Escaping dysphoria
Withdrawal and negative affect	Feeling reduced energy	Feeling reduced excitement	Feeling depressed, anxious, restless
Preoccupation and anticipation	Looking forward	Desiring drug	Obsessing and planning to get drug

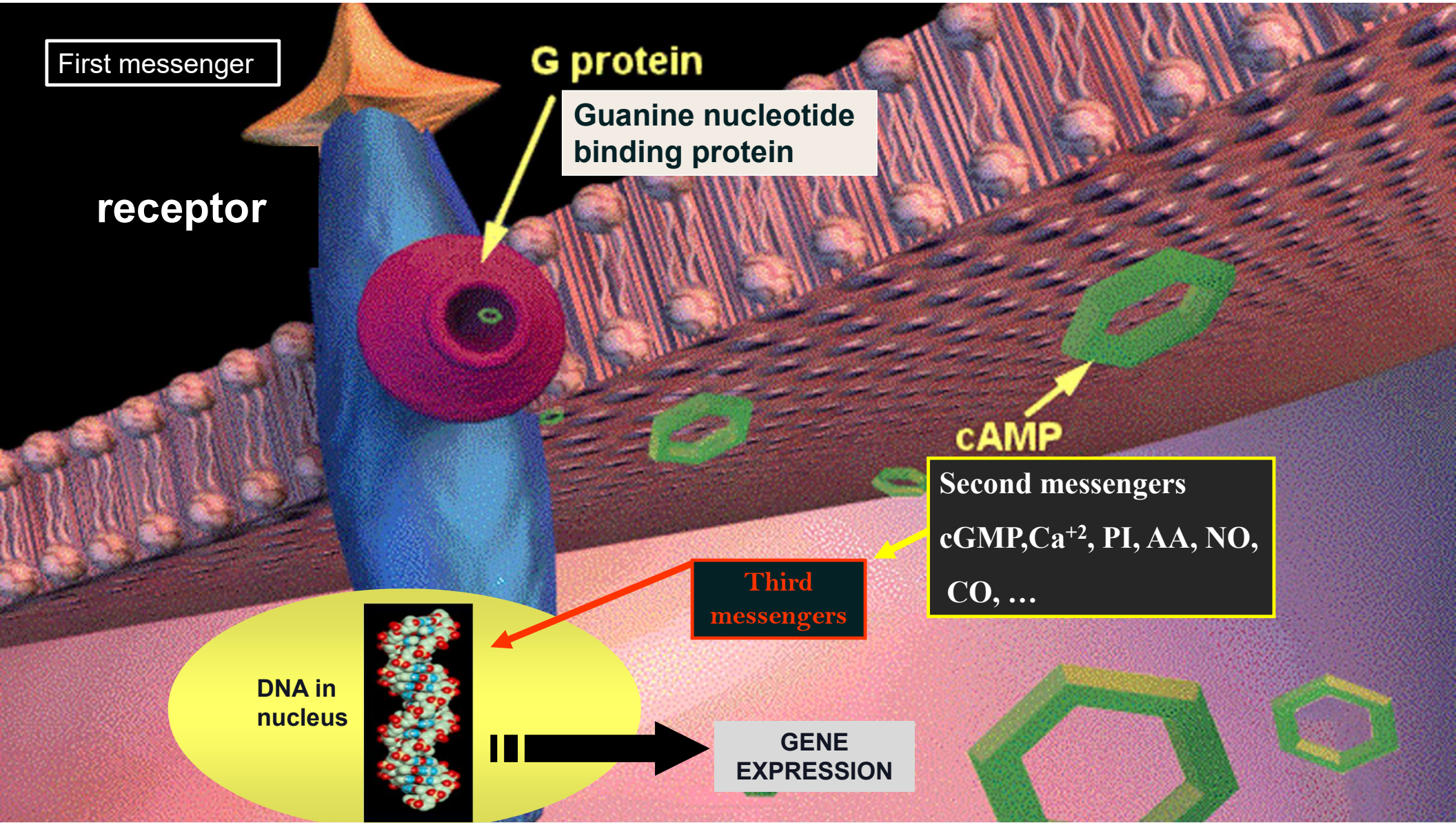
Behavioral Changes		
Voluntary action Abstinence Constrained drug taking	Sometimes taking when not intending Sometimes having trouble stopping Sometimes taking more than intended	**Impulsive action** Relapse Compulsive consumption

It is the amount and speed of the release of Dopamine in the nucleus accumbens that is most likely related to the addiction potential of a behavior, substance or drug.



Neurochemistry




First messenger
G protein
Guanine nucleotide binding protein
receptor
cAMP
Second messengers
cGMP,Ca+2, PI, AA, NO, CO, …
Third messengers
DNA in nucleus
GENE EXPRESSION

Neuroadaptation Model

Upregulation of cAMP pathway

- in locus ceruleus leads to typical constellation opiate withdrawal symptoms

- in nucleus accumbens may contribute to reinforcing behavior of most drugs of abuse

Repeated Administration and Withdrawal

Repeated administration of opioids that activate the *mu* receptor results in:

dose-dependent physical dependence and tolerance

Physical dependence and tolerance manifest as:

characteristic withdrawal signs and symptoms upon reduction or cessation of opioid use or administration

(the opioid withdrawal syndrome)

$2.1 Million

A single male heroin addict costs the taxpayer $2.1 million over 11 years in:

Court Costs | Jail Time | ER Visits | Hospital Care | Ambulances | Etc.

-SAMHSA

Addiction to Heroin

Chronic, relapsing disease

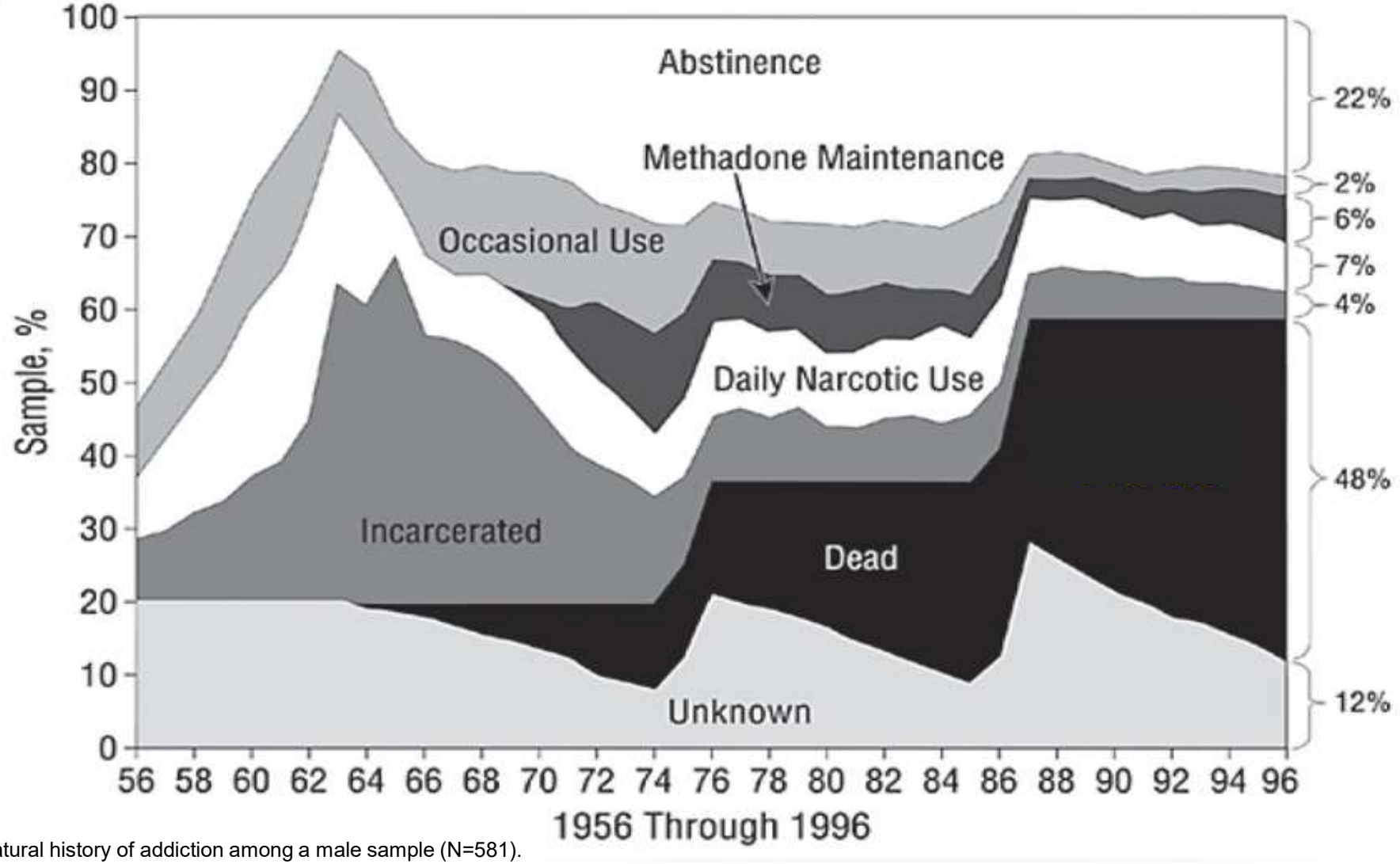
High Morbidity

High Mortality

- 33 year follow up of 581 male heroin addicts in Los Angeles found:
  - Nearly half had died
  - 20.7% of those living tested positive for heroin
  - 40% reported using heroin in past year
  - High rates of disability, hepatitis, mental health disorders, and criminal activity
  - Fewer than 10% were in methadone maintenance Rx.

"Methadone Maintenance and Other Pharmacotherapeutic Interventions in the Treatment of Opioid Addiction." April 2002, Vol.III, No. 1

581 Male Heroin Addicts Followed for 33 Years



The natural history of addiction among a male sample (N=581).
From: Yih-Ing, et. Al., 2001. A 33-Year Follow-up of Narcotics Addicts. Archives of General Psychiatry, 58:503-508

Opiate Replacement Therapy

Goal of Opiate Replacement Therapy

Reduce illegal heroin

Reduce other opioid use

Reduce crime, disease and deaths associated with opioid addiction

Why ORT/MAT in jails and prisons?

IDU are over-represented in incarcerated populations (18-24%)
Should have access to treatment for opioid dependence.

IDU not treated will most likely relapse, re-offend and return to incarceration. Treatment reduces recidivism.

IDU are reservoir for HIV, Hepatitis B & C.
Treatment reduces high risk behaviors.

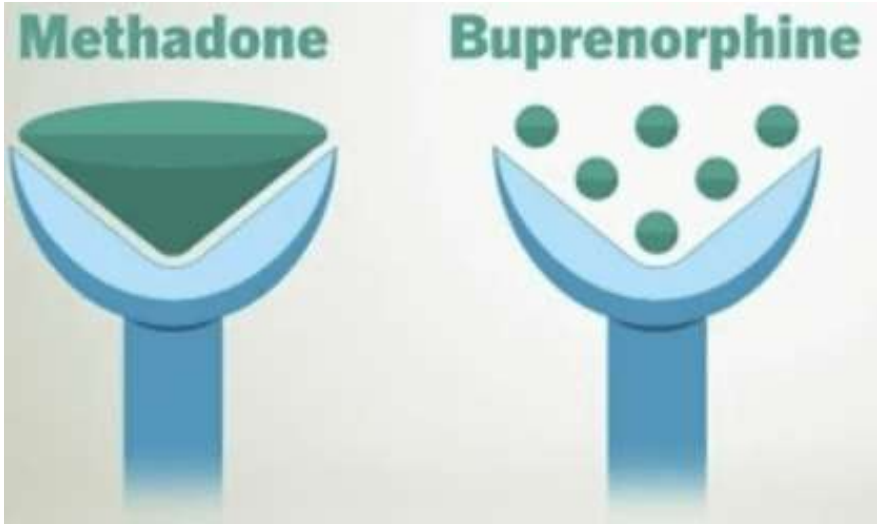
NIH Consensus Statement 1997

"All opiate-dependent persons under legal supervision should have access to methadone maintenance therapy…"

Effective Medical Treatment of Opiate Addiction.
NIH Consensus Statement 1997 Nov. 17-19;15(6):2

Opiate Replacement Therapy

- Only two approved drugs
  - Methadone
  - Buprenorphine
- Removed from market
  - LAAM (levo-alpha-acetylmethadol)
  - due to reports of prolonged QT interval and deaths from *torsades*, a form of ventricular fibrillation



Models for Opiate Replacement Therapy

Why Methadone?

It works and it’s cheap!

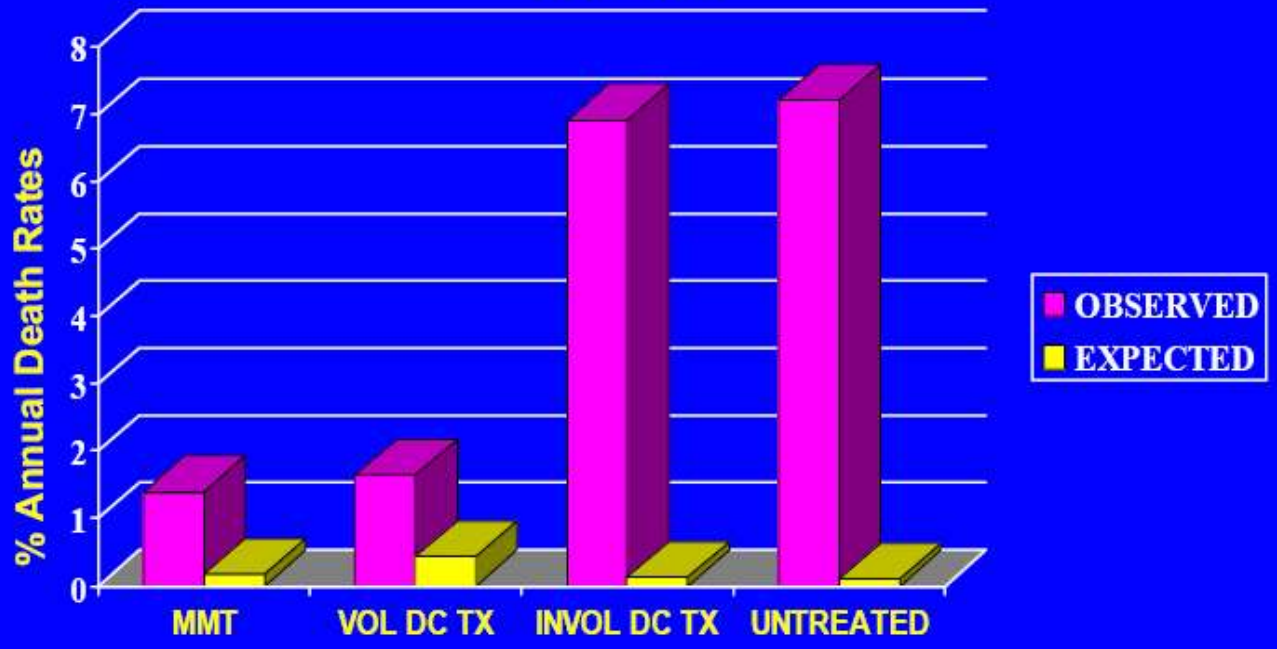
Methadone maintenance -- MMT

DATOS (Drug Abuse Treatment Outcome Studies) followed ~3000 heroin addicts for 1 year in MMT:

- Most effective treatment for heroin addiction
- Most retention of patients in treatment
- Reduced criminal behavior by 50%
- Reduced heroin use from 90% to 30%; about 17% continued daily use
- Reduced use of cocaine from 42% to 22%; reduced sedative use
- Alcohol use +/- change
- Lowers risk of HIV/AIDS, Hepatitis B and C
- Cost effective
- Reduced homeless and jobless rates

- Lowers injection risk behavior in prison
- Effective outside of traditional MMT clinic settings

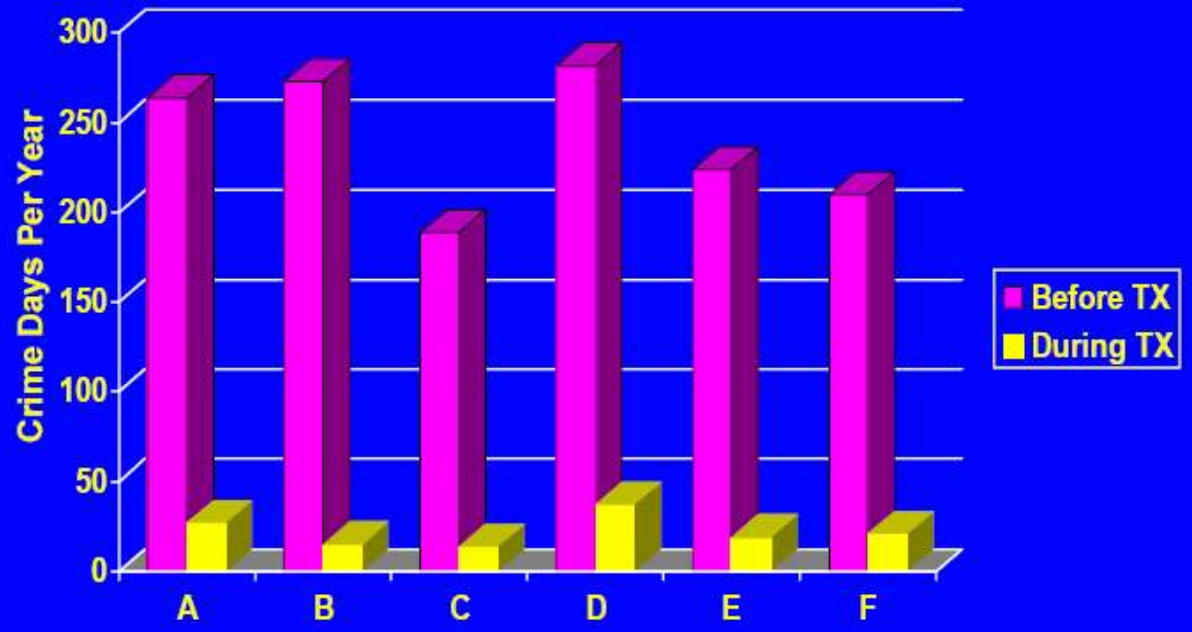
DEATH RATES IN TREATED AND UNTREATED HEROIN ADDICTS



Slide data courtesy of Frank Vocci, MD, NIDA - Reference: Grondblah, L. et al. ACTA PSCHIATR SCAND, P. 223-227, 1990

Opioid Agonist Treatment of Addiction - Payte - 1998

Crime among 491 patients before and during MMT at 6 programs

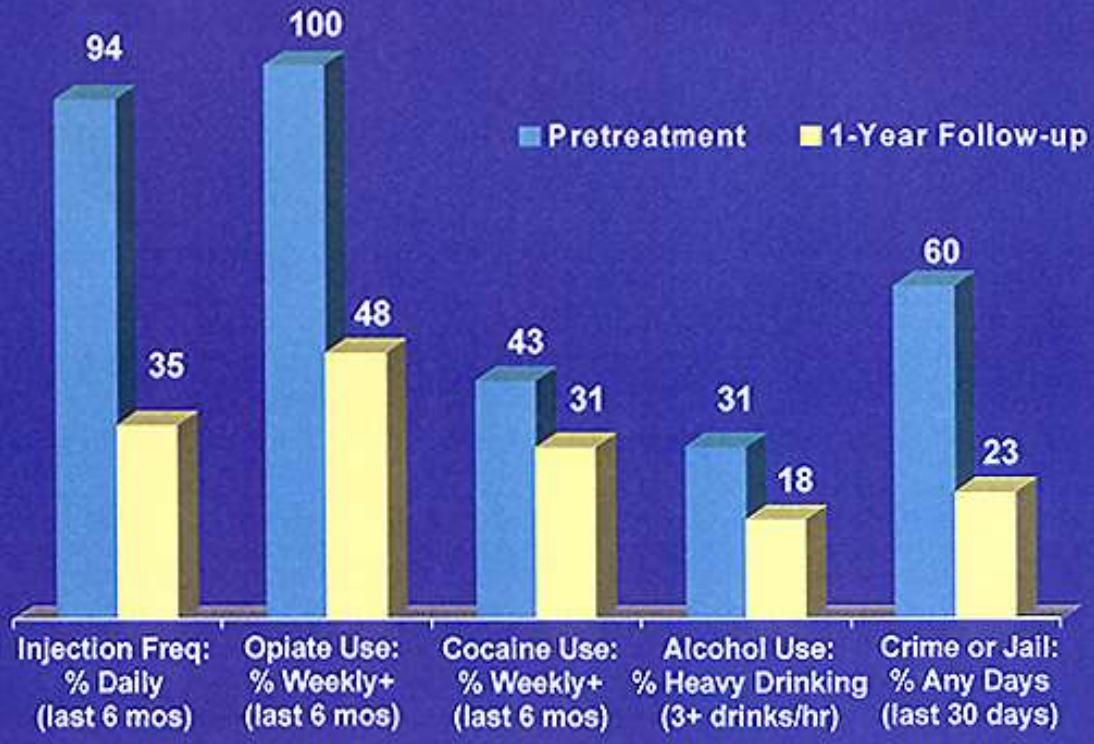


Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991

Opioid Agonist Treatment of Addiction - Payte - 1998

Strategies for Improving Methadone Treatment Process and Outcome

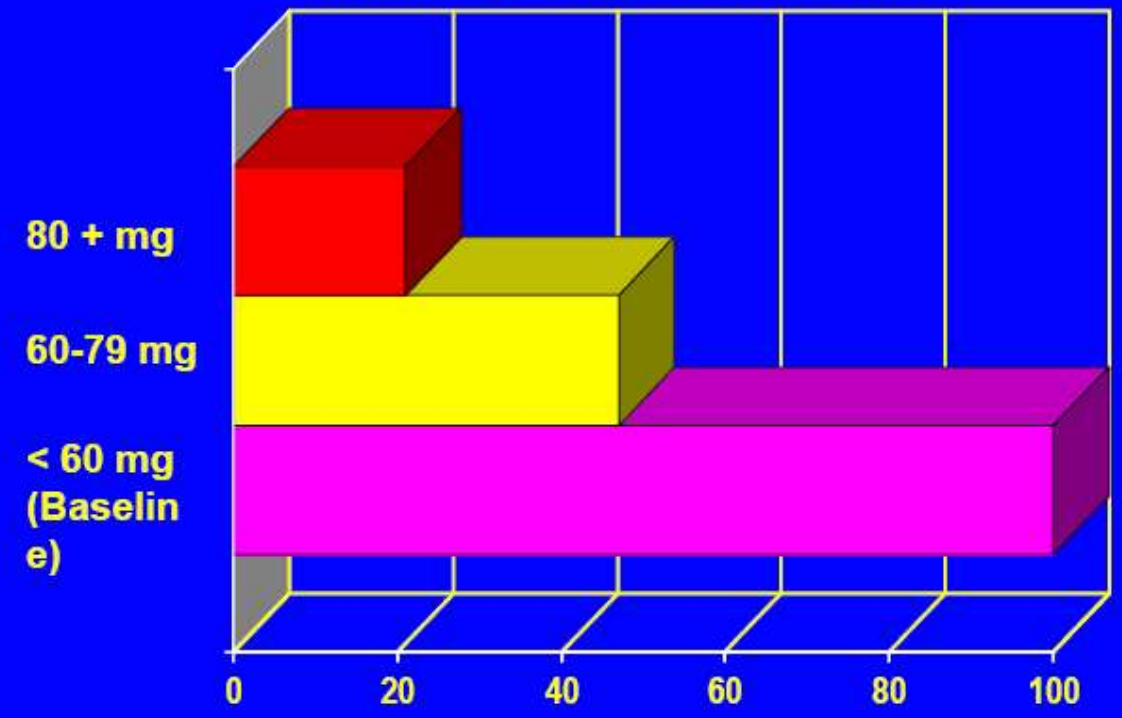
Changes from Before to After Methadone Treatment (N=435)



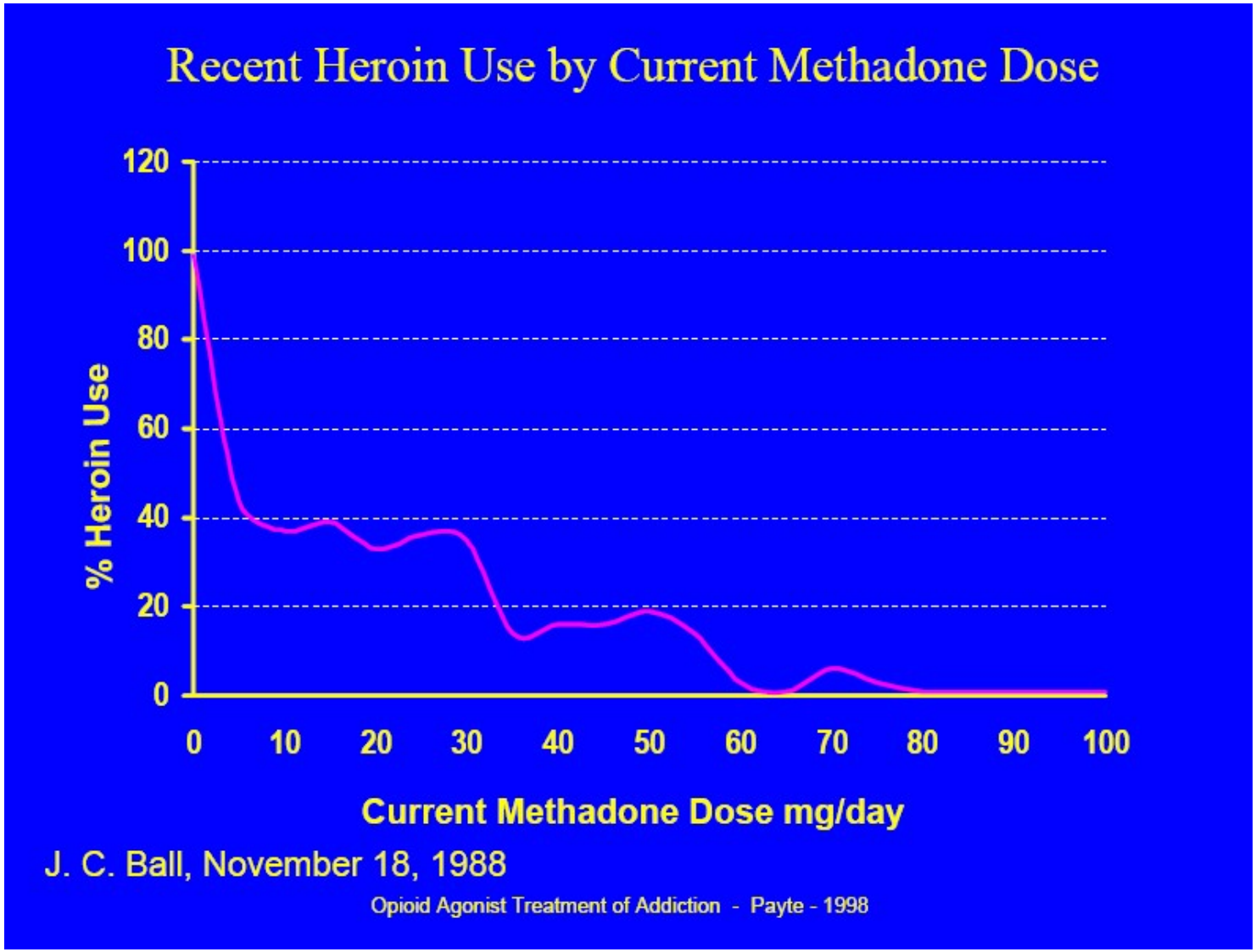
Journal of Drug Issues 1997 - Simpson, Joe, Dansereau, Chatham

Retention in Treatment Relative to Dose

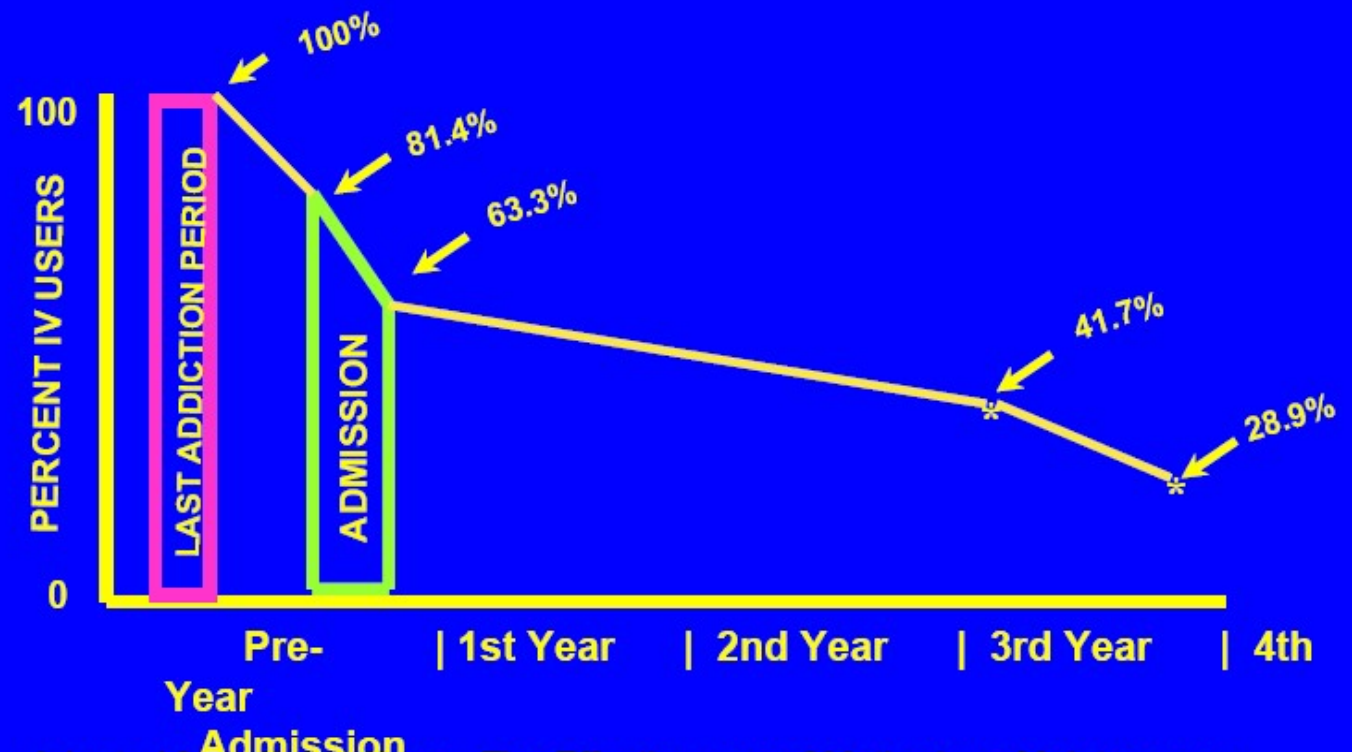
Relative Risk of Leaving Treatment



Adapted from Caplehorn & Bell - The Medical Journal of Australia


Recent Heroin Use by Current Methadone Dose
% Heroin Use
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
100
Current Methadone Dose mg/day
J. C. Ball, November 18, 1988
Opioid Agonist Treatment of Addiction - Payte - 1998

Recovery is a *process*, not an event!

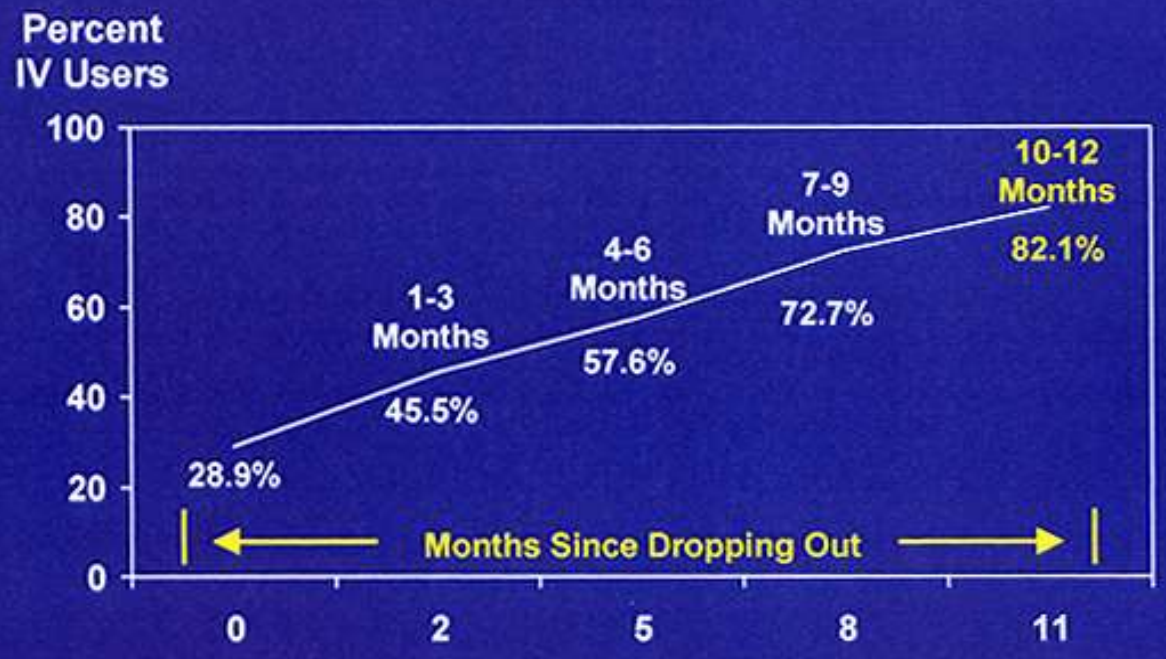


Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991

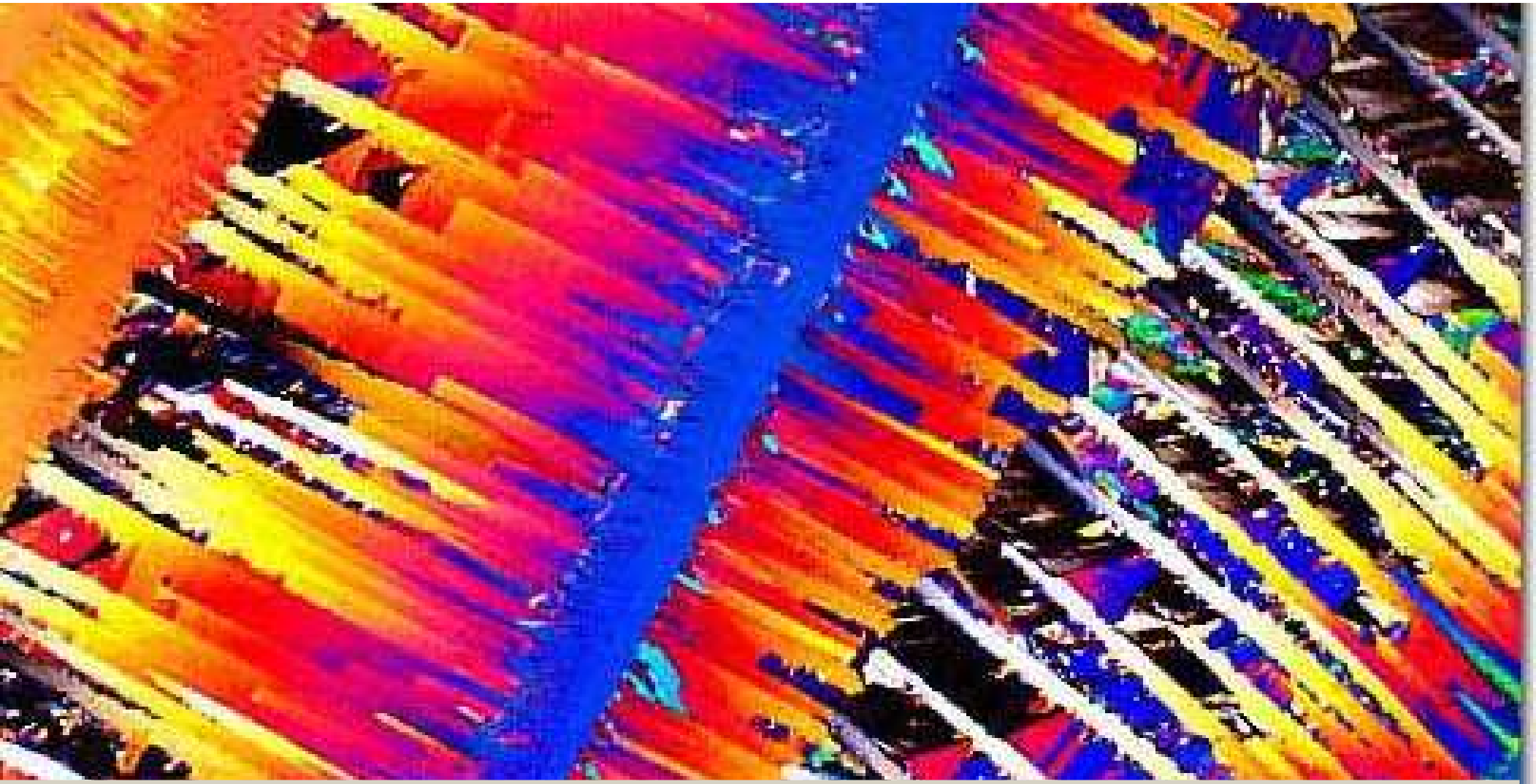
Opioid Agonist Treatment of Addiction - Payte - 1998

Relapse to IV Use After Methadone Maintenance Treatment

105 Male Addicts Who Dropped Out of Treatment



Reference: Ball & Ross: *The Effectiveness of Methadone Maintenance Treatment*



Heroin Phase Microcrystallography

Opiate Addiction Treatment Outcome*

Methadone Maintenance	50 - 80%
Naltrexone Maintenance	10 - 20%
“Drug Free” (non-pharmacotherapeutic)	5 - 30%
LAAM Maintenance	50 - 80%**
Buprenorphine-Naloxone Maintenance	40 - 50%
Short-term Detoxification (any mode)	5 – 20%

**One year retention in treatment and/or follow-up with significant reduction or elimination of illicit use of opiates*

***Maximum effective dose (24 mgsl) equal to 60 to 70 mg/d methadone. Data base on 6 month follow-up only.*

MEDICATION ASSISTED ADDICTION TREATMENT

"All treatments work for some people/patients."

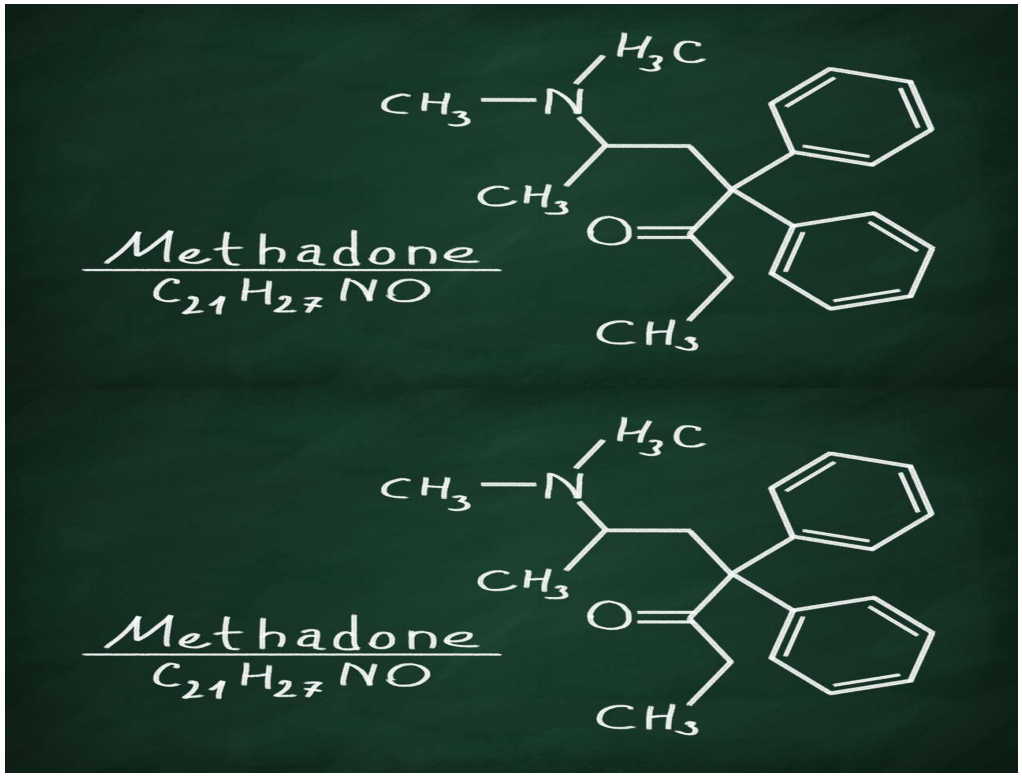
"No ONE treatment works for all people/patients."

Alan I. Lesner, Ph.D
Former Director NIDA

Treatment of opioid dependency with Methadone

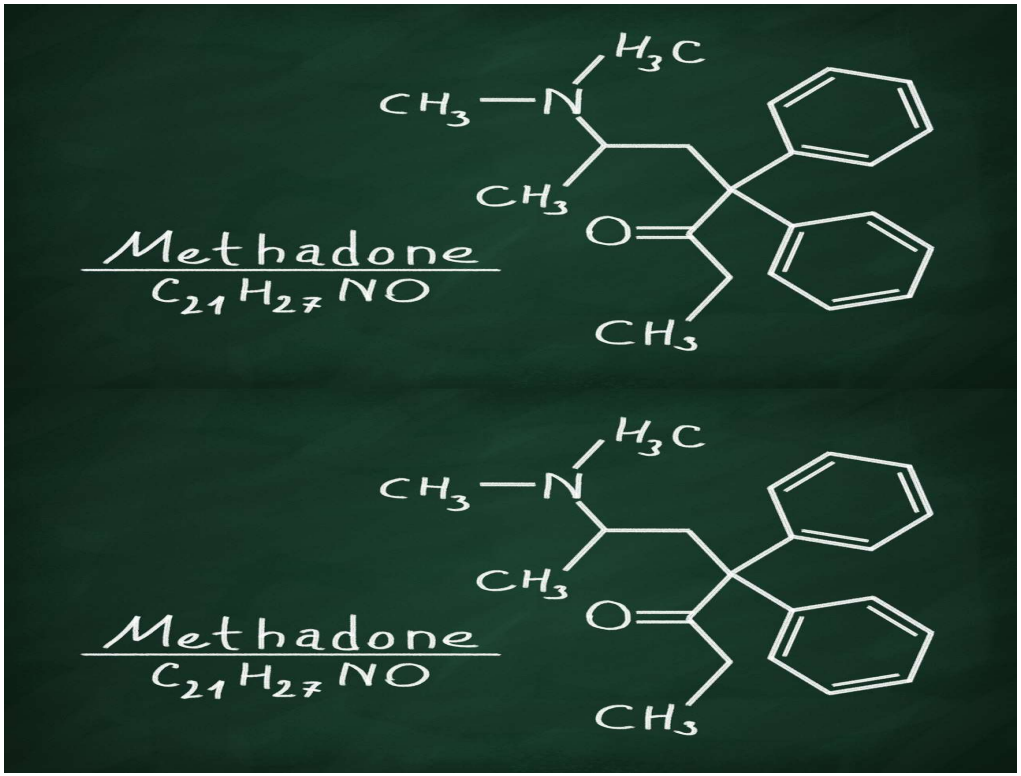
Methadone - History

- Discovered in Germany during WWII but not used as analgesic until after the war
- Initial human studies reported in the USA in 1947 involved injected doses in the range of 200-800 mg daily over 4 months
- Established as treatment for opioid withdrawal syndrome in US Public Health Service hospitals by 1950

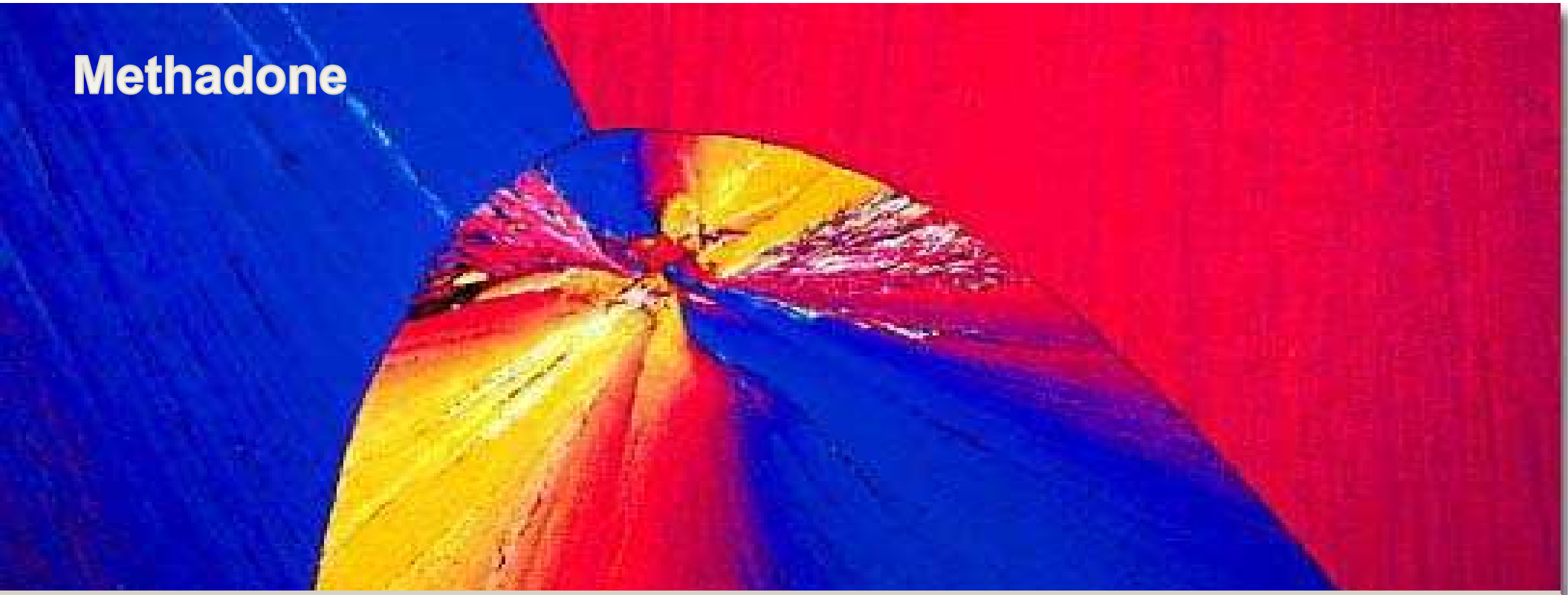


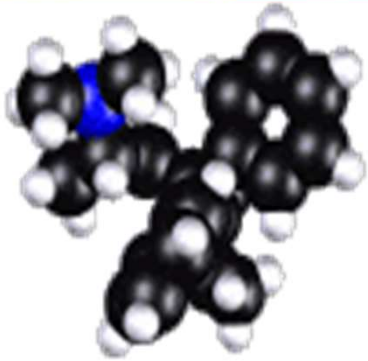
Methadone - History

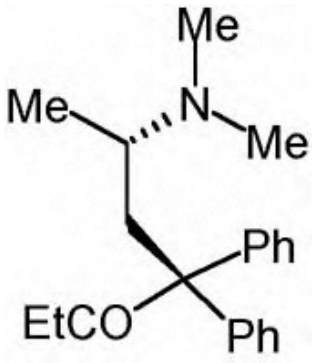
Research by Drs. Vincent Dole and Marie Nyswander in 1963 led to the discovery of the unique pharmacokinetics of methadone and eventually to Methadone Maintenance Therapy (MMT).



Methadone

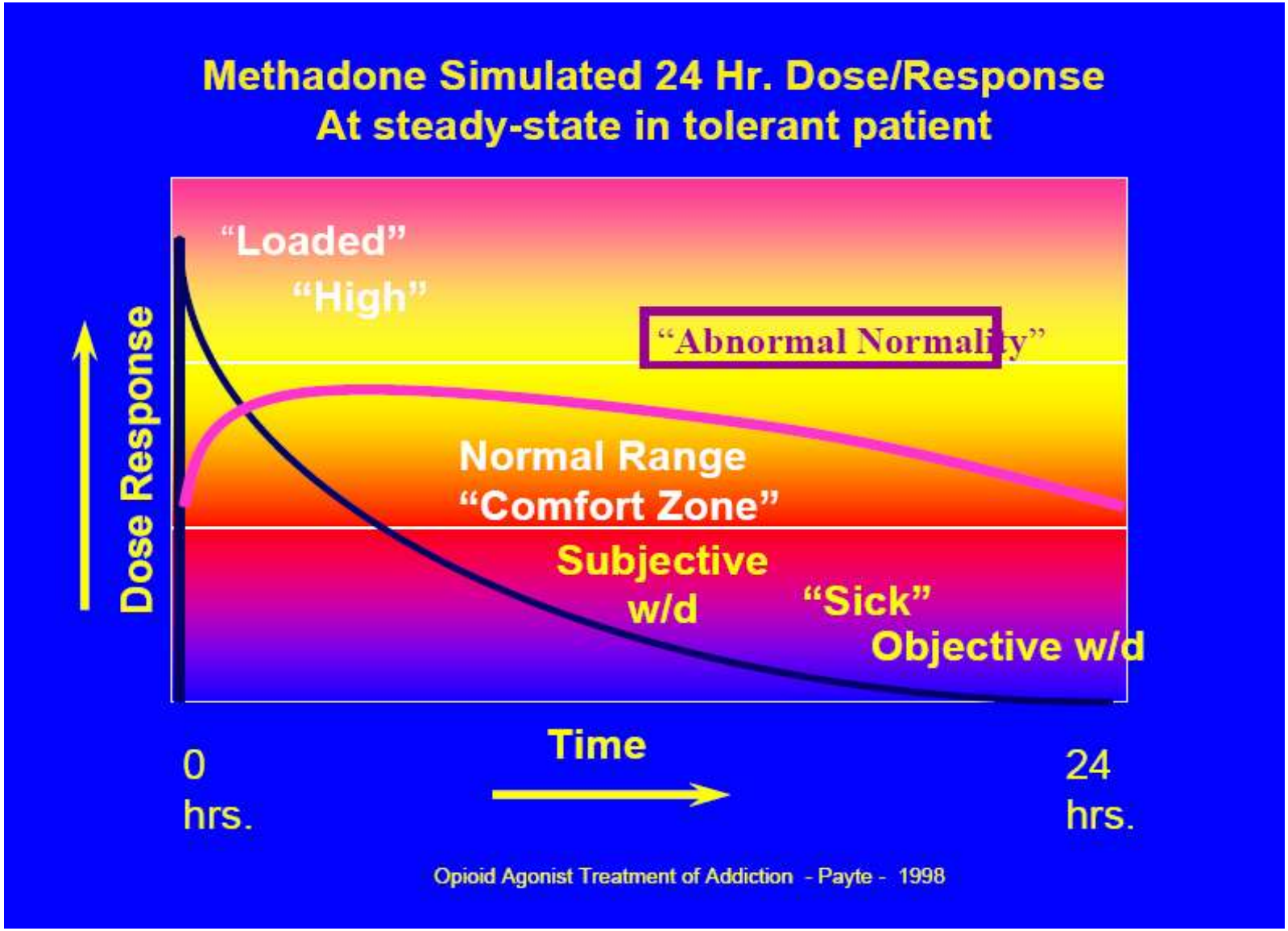






Methadone - Pharmacokinetics

- *Mu* opiate receptor agonist
- Onset of analgesia is in 30 minutes and peaks about 4 hours
- Highly protein bound (90%) as well as stored unchanged in liver and released 2-3 hours after taken (booster effect)
- Half-life of 15-40 hours
- Suppress withdrawal symptoms > 1 day


Methadone Simulated 24 Hr. Dose/Response
At steady-state in tolerant patient
"Loaded"
"High"
"Abnormal Normality"
Normal Range
"Comfort Zone"
Subjective
w/d
"Sick"
Objective w/d
Dose Response
Time
0
hrs.
24
hrs.
Opioid Agonist Treatment of Addiction - Payte - 1998

Methadone - Pharmacokinetics

Metabolism effected by multiple factors

- Chronic liver and kidney disease
  - lower doses needed in cirrhosis but higher doses needed in chronic Hepatitis C
- Pregnancy
- Numerous drug interactions
  - rifampin,
  - phenytoin,
  - alcohol,
  - cocaine,
  - phenobarbital,
  - diazepam,
  - cimetidine,
  - estrogens,
  - antiviral agents,
  - nicotine,
  - antidepressants...

Drugs Contraindicated with Methadone

Partial/mixed opioid agonists	Opioid Antagonists	Tramadol
• Buprenorphine • butorphanol • nalbuphine • pentazocine	• Naltrexone • naloxone • nalmefene	

Immune System

Heroin	Methadone
↑ Total lymphocytes	normal
↑ T-lymphocytes	normal
↑ CD-4	normal
↑ CD-8	normal
↕ Natural killer cell	normal

Opioid Side Effects

- Sedation
- Altered Cognitive Function
- Dysphoria
- Urinary Retention
- Sleep Disturbances
- Constipation
- Sweating

***30% - 50% STOP MEDICATION**

Methadone Side Effects

- Minimal sedation once tolerance achieved
- Constipation
- Increased Appetite/Weight Gain
- Lowered Libido; May decrease gonadal hormone levels
- Exhaustively studied in all other organ systems with no evidence of chronic harm

Treatment of Adverse effects

Opioid Bowel dysfunction/constipation

- Regular regimen of senna, docusate
- Fiber and bulk laxatives
- Exercise and increased fluids
- Lactulose; Miralax (polyethylene glycol)
- Opioid antagonists
  - *Naloxegol/Movantick*
- Prostaglandins (stimulants)
  - *lubiprostone/Amitiza*
  - *misoprostol/Cytotec*

Treatment of Adverse effects

Sexual Dysfunction

- Testosterone, if indicated
- ?Dopamine agonists
- Methadone dose adjustments
- Viagra, Cialis, Levitra

Blood Level

- 150 ng/ml-600ng/ml

- No mathematical correlation between the dose and the blood level!

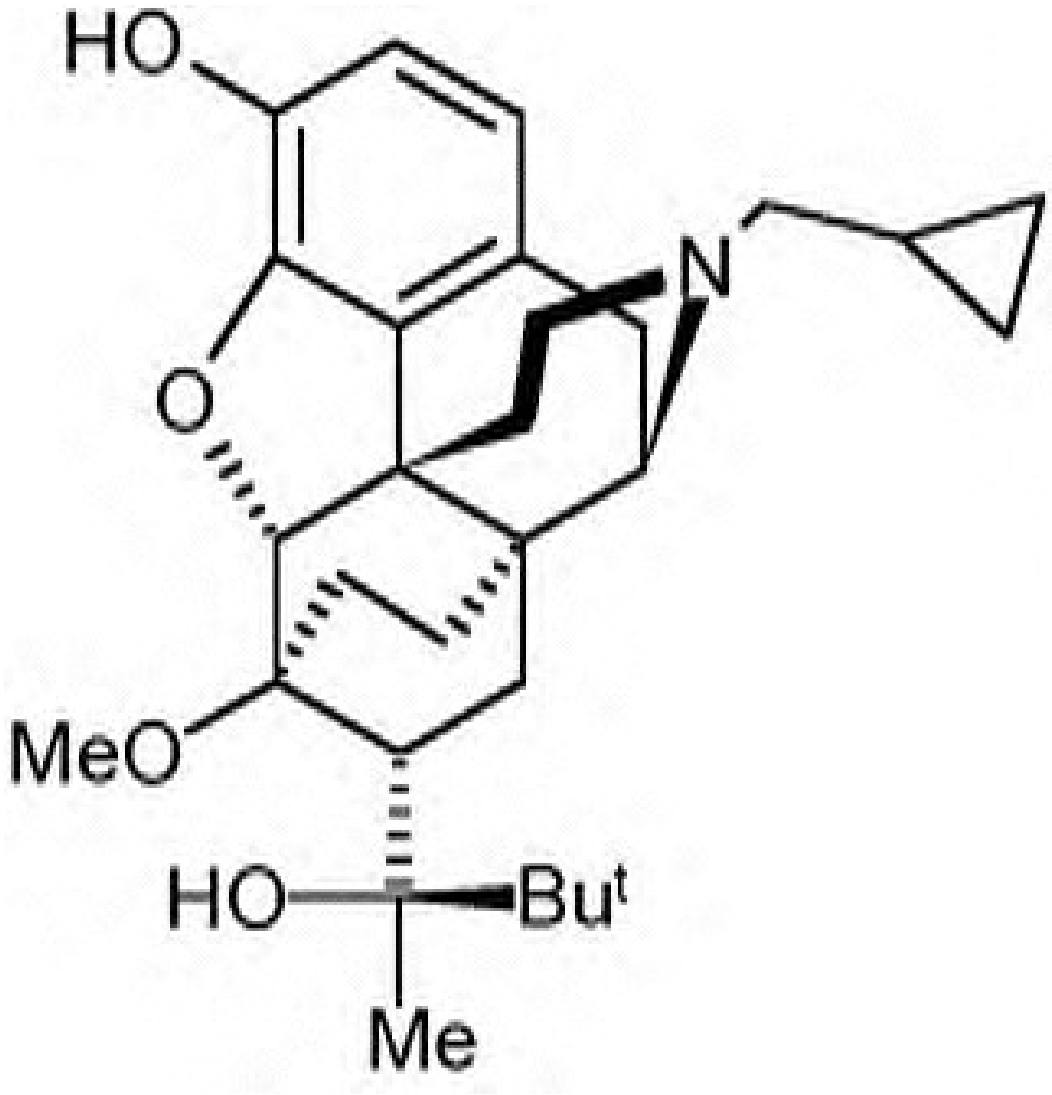
Medical Dispensing

Methadone Liquid Dispensing

Methadone Take-Home Box

Treatment of Opioid Dependency with Buprenorphine

Buprenorphine



CSAT

The Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration (SAMHSA) was created in October 1992 by Congress to expand the availability of effective treatment and recovery services for individuals with alcohol and drug problems and to coordinate national policy for medication assisted treatments.

Buprenorphine Legal Status

- Drug Addiction Treatment Act of 2000
  - allows qualified physicians to prescribe Schedule III-V drugs for treatment of opiate dependence

- Registered qualified physicians can treat up to 100 opiate dependent patients at one time with buprenorphine.
- Number now essentially not limited and providers no longer need an “X” number to prescribe.

Affinity and Dissociation

AFFINITY

Strength with which a drug binds to its receptor

(Strength of binding is not related to activation or efficacy at the receptor)

DISSOCIATION

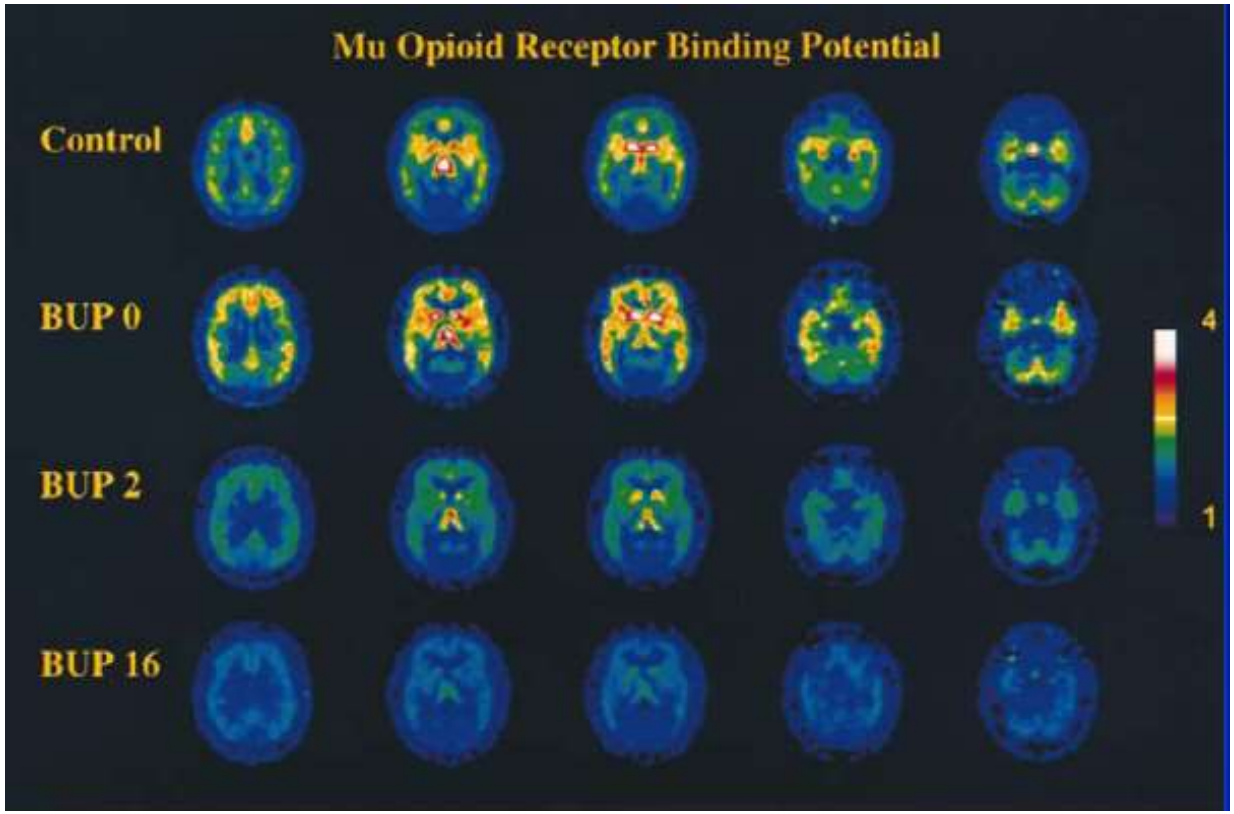
Speed (slow or fast) of disengagement or uncoupling of drug from the receptor

Affinity and Dissociation

Buprenorphine

- high affinity for *mu* opioid receptor
  - competes with other opioids and blocks their effects or displace them
- antagonist at kappa receptor
- slow dissociation from *mu* opioid receptor
  - prolonged therapeutic effect for opioid dependence treatment

Buprenorphine Binding mu Receptors



Buprenorphine blocks opioid full mu agonist binding

Zubieta et al [U Mich] Neuropsychopharmacology 23:326-334, 2000

Bioavailability

- Good parenteral bioavailability
- Poor oral bioavailability
- Fair sublingual bioavailability
- For opioid dependence treatment:
  - Early clinical trials used an alcohol-based solution
  - FDA approval for tablets that are held under tongue

Bioavailability

- Considerable variability between patients in bioavailability of tablets

- Tablets about 50-70% bioavailable relative to solution (much research prior to approval used solution)

Combination of Buprenorphine plus Naloxone

Sublingual buprenorphine has good bioavailabity, while sublingual naloxone has relatively poor bioavailability.

Combination ratio is 4 to 1 (buprenorphine to naloxone).

Suboxone (2/0.5 and 8/2 mg tablets)

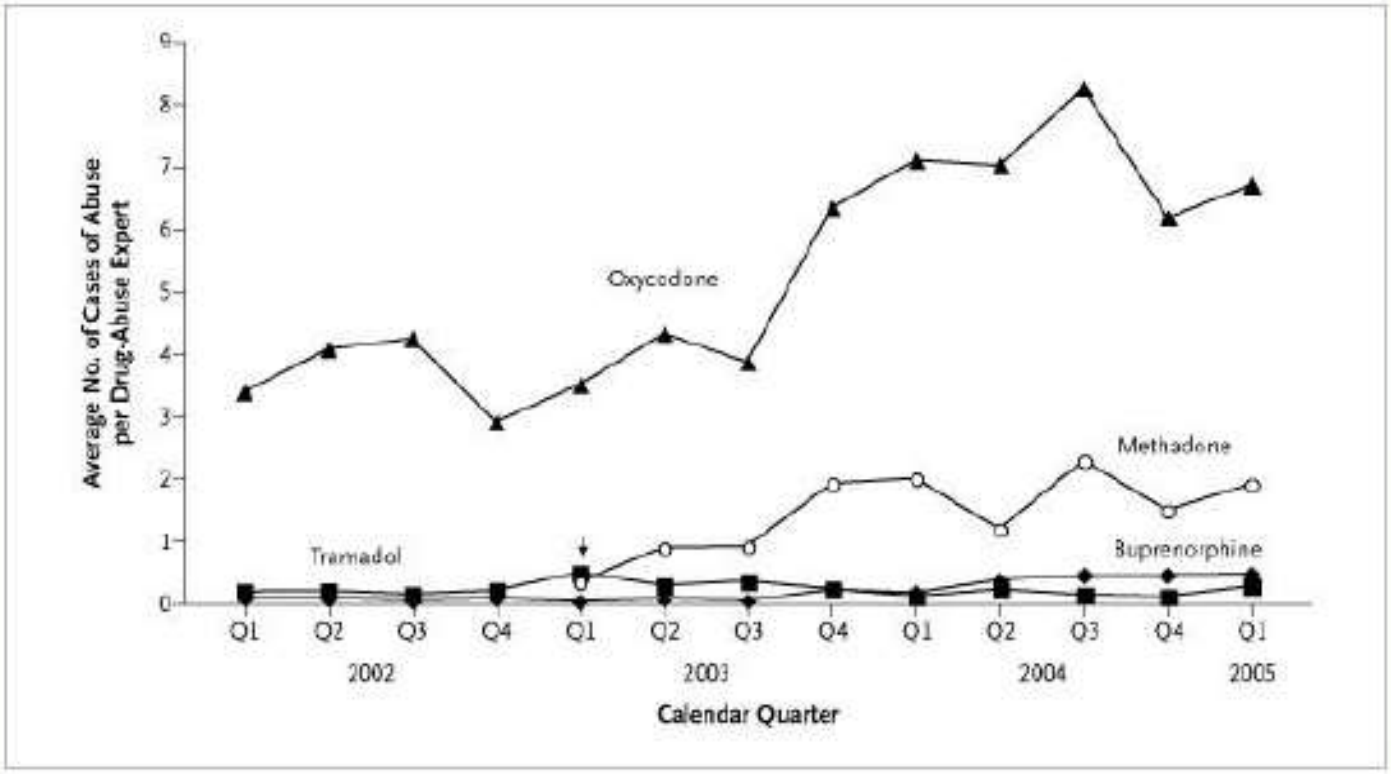
Subutex (2 and 9 mg tablets)

Sublingual naloxone has a bitter taste

Abuse Potential

- Buprenorphine is abusable
  - (epidemiological, human laboratory studies show)
- Diversion and illicit use of analgesic form (by injection)
- “Relatively” low abuse potential compared to other pure agonist opioids

Average Number of Cases of Abuse of Buprenorphine Products, Methadone, Tramadol, and Oxycodone per Drug-Abuse Expert



Cicero, T. J. et al. N Engl J Med 2005;353:1863-1865

The NEW ENGLAND JOURNAL of MEDICINE

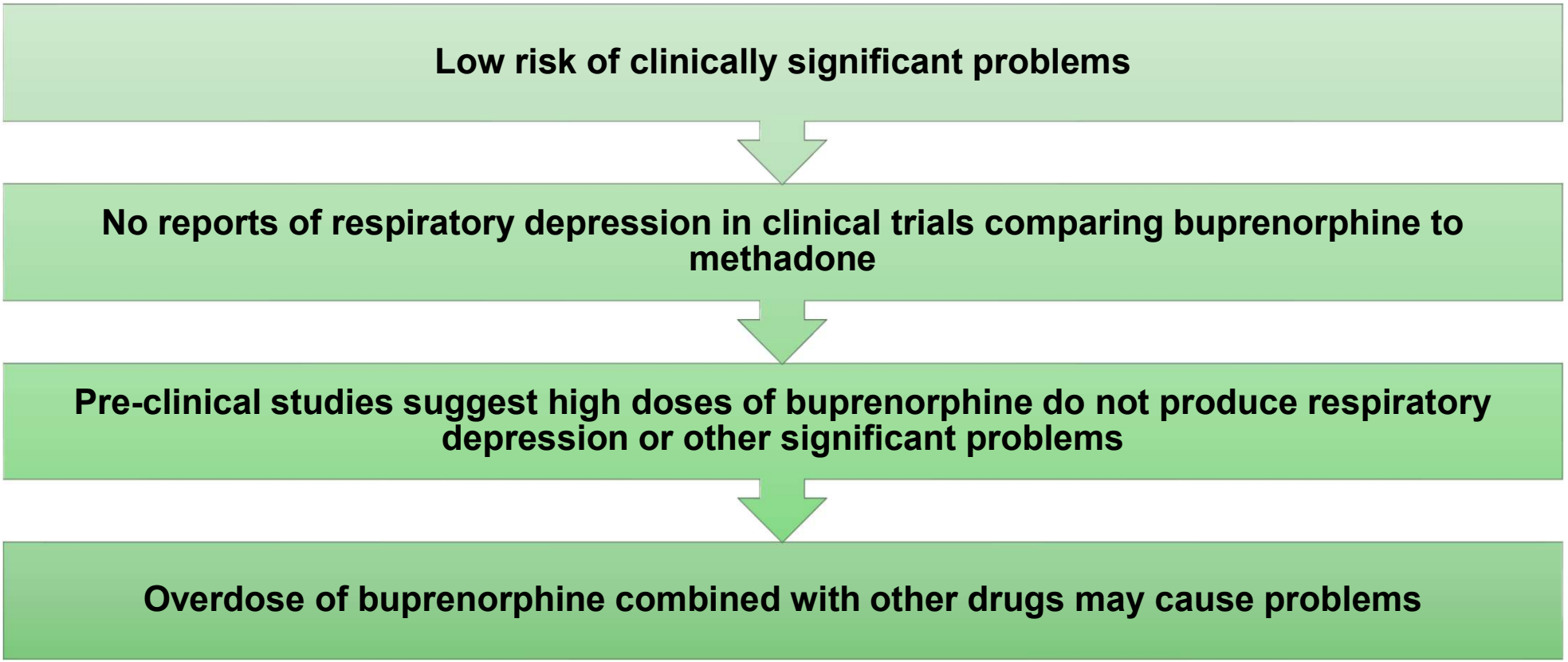
Overview to Safety

Highly safe medication (acute and chronic dosing)

Primary side effects: like other *mu* agonist opioids (e.g., nausea, constipation) but may be less severe

No evidence of significant disruption in cognitive or psychomotor performance with buprenorphine maintenance

Overdose with Buprenorphine



Benzodiazepines and Other Sedating Drugs

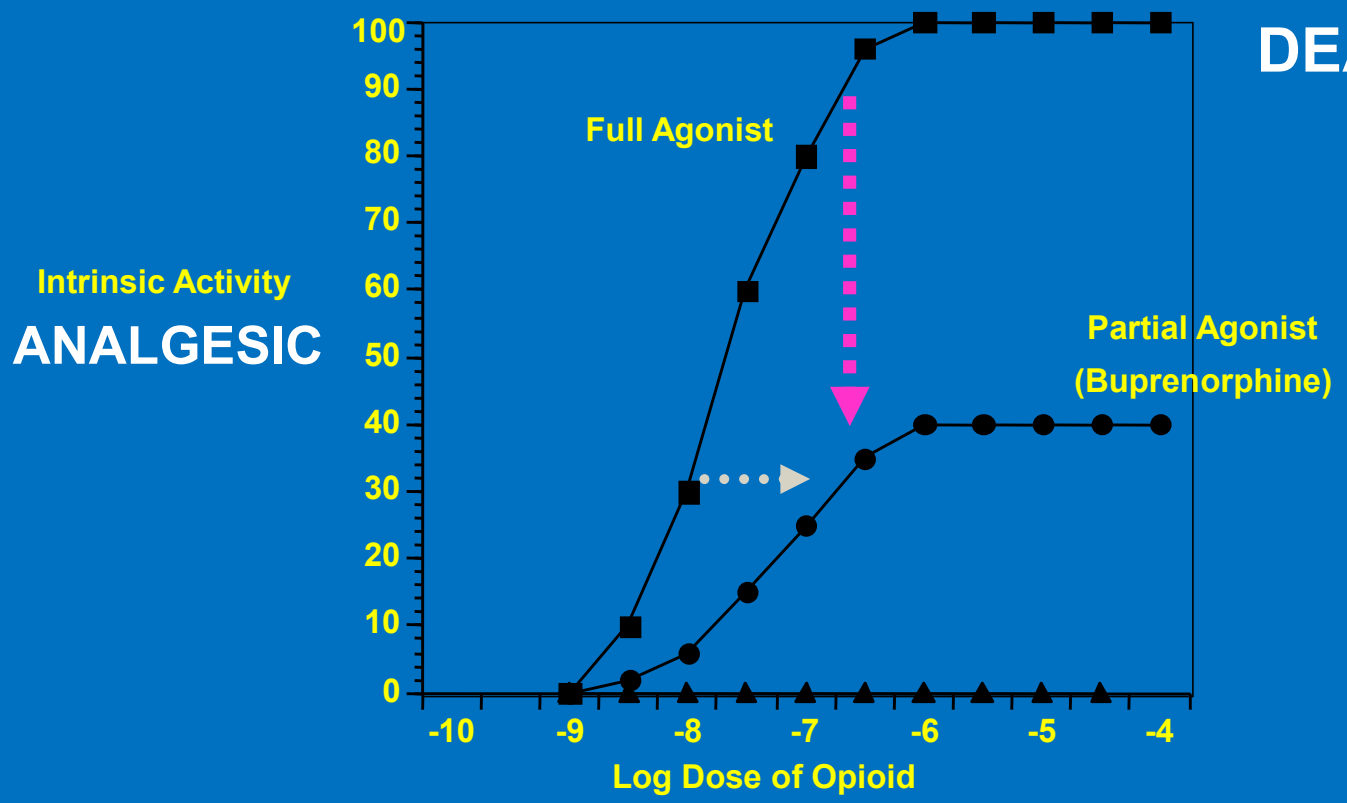
- Reports of deaths when buprenorphine injected along with benzodiazepines
  - Primarily reported from France where tablets available
  - Appears patients dissolve and inject tablets with benzodiazepines, typically Rohypnol
- Probably possible for this to occur with other sedatives as well

Precipitated Withdrawal

Occurs with administration of an opioid antagonist to a person who has *mu* agonist opioids in their system

Is qualitatively similar to spontaneous withdrawal but faster onset and duration depends upon half life of antagonist

Intrinsic Activity: Full Agonist and the effect of adding a Partial Agonist (Buprenorphine)



Precipitated Withdrawal (continued)

While the most common situation is for an antagonist such as naloxone or naltrexone to precipitate withdrawal, partial agonists such as buprenorphine can precipitate withdrawal under certain circumstances, such as if the patient has another opioid agonist “on board”.

A partial agonist displaces a full agonist, but only partially activates the receptor (a net decrease in activation)

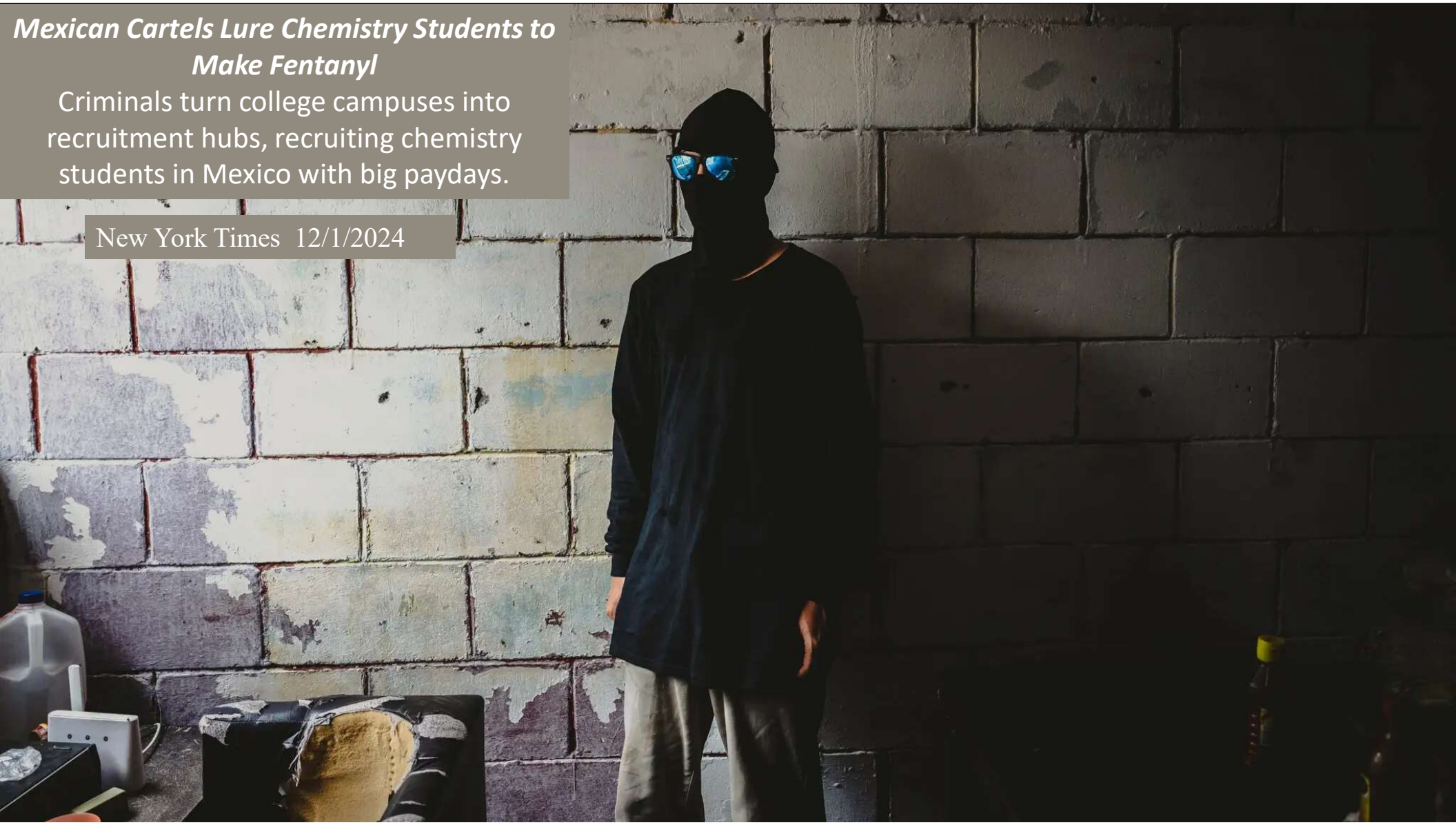
Semi-synthetic Opioids

- Carfentanyl
  - 100x more potent than fentanyl
- Nitazenes
  - 10x more potent than fentanyl
  - Created by CIBA in Switzerland
  - Very potent and long-acting metabolites
- More coming down the pike

Mexican Cartels Lure Chemistry Students to Make Fentanyl

Criminals turn college campuses into recruitment hubs, recruiting chemistry students in Mexico with big paydays.

New York Times 12/1/2024



'This Is What Makes Us Rich': Inside a Sinaloa Cartel Fentanyl Lab

New York Times reporters witnessed the dangerous fentanyl production process inside a secret lab in Culiacán run by Mexico's most powerful criminal syndicate.

New York Times 12/19/2024

How Mexican Cartels Test Fentanyl on Vulnerable People and Animals

A global crackdown on fentanyl has led cartels to innovate production methods and test their risky formulas on people, as well as rabbits and chickens.

- New York Times 12/26/2024

Factors Promoting Successful Treatment

Addiction is a complex biopsychosocial disorder and must be addressed at all levels

Retention in treatment is consistently related to improved outcome

Engagement strategies improve retention

Co-existing psychiatric disorders are very common and *must be addressed*

Upcoming Lunch talks

Stimulants such as methamphetamine, cocaine

Hallucinogen-assisted therapy of drug disorders

Medication-assisted therapy not using agonists

Thank you for attending!

Please reach out with any questions you may have.

MinnesotaASAM@acentra.com

https://mhcp.acentra.com/