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Understanding Opioid Use Disorder and the Treatment Armamentarium

Edwin Salsitz, Mount Sinai Beth Israel

Lisa Alexander, PA Education Association & George Washington School of Medicine and Health Services

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Understanding Opioid Use Disorder and the Treatment Armamentarium:

Neurobiology, Vulnerability, Stigma, Terminology

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No Disclosures

PAPAVER SOMNIFERUM

Drs. Dole, Nyswander, and Kreek

Courtesy Dr. Vincent Dole

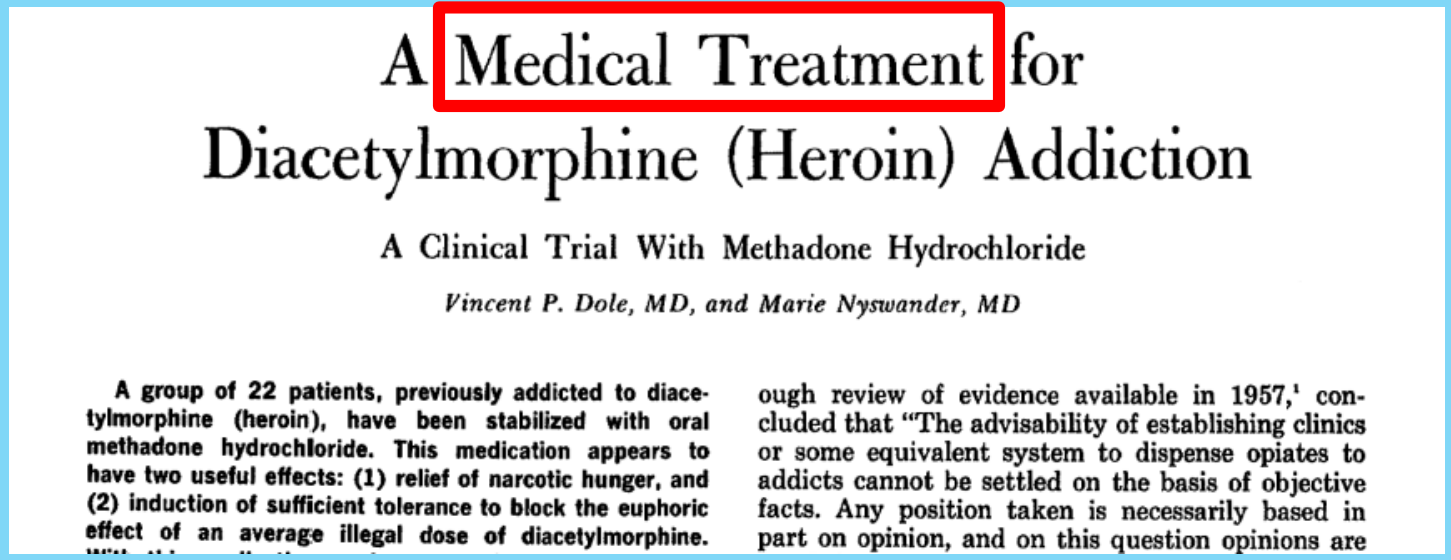
Dr. Vincent Dole and Dr. Marie Nyswander
Methadone Pioneers

Mary Jeanne Kreek, M.D.
Addiction Laboratory Rockefeller University

… “their Brain Lacks Something that Heroin Provides” V.D.

… “they Function Better on Heroin, than off Heroin” M.N

Initial Methadone Publication



A Medical Treatment for Diacetylmorphine (Heroin) Addiction

A Clinical Trial With Methadone Hydrochloride

Vincent P. Dole, MD, and Marie Nyswander, MD

A group of 22 patients, previously addicted to diacetylmorphine (heroin), have been stabilized with oral methadone hydrochloride. This medication appears to have two useful effects: (1) relief of narcotic hunger, and (2) induction of sufficient tolerance to block the euphoric effect of an average illegal dose of diacetylmorphine.

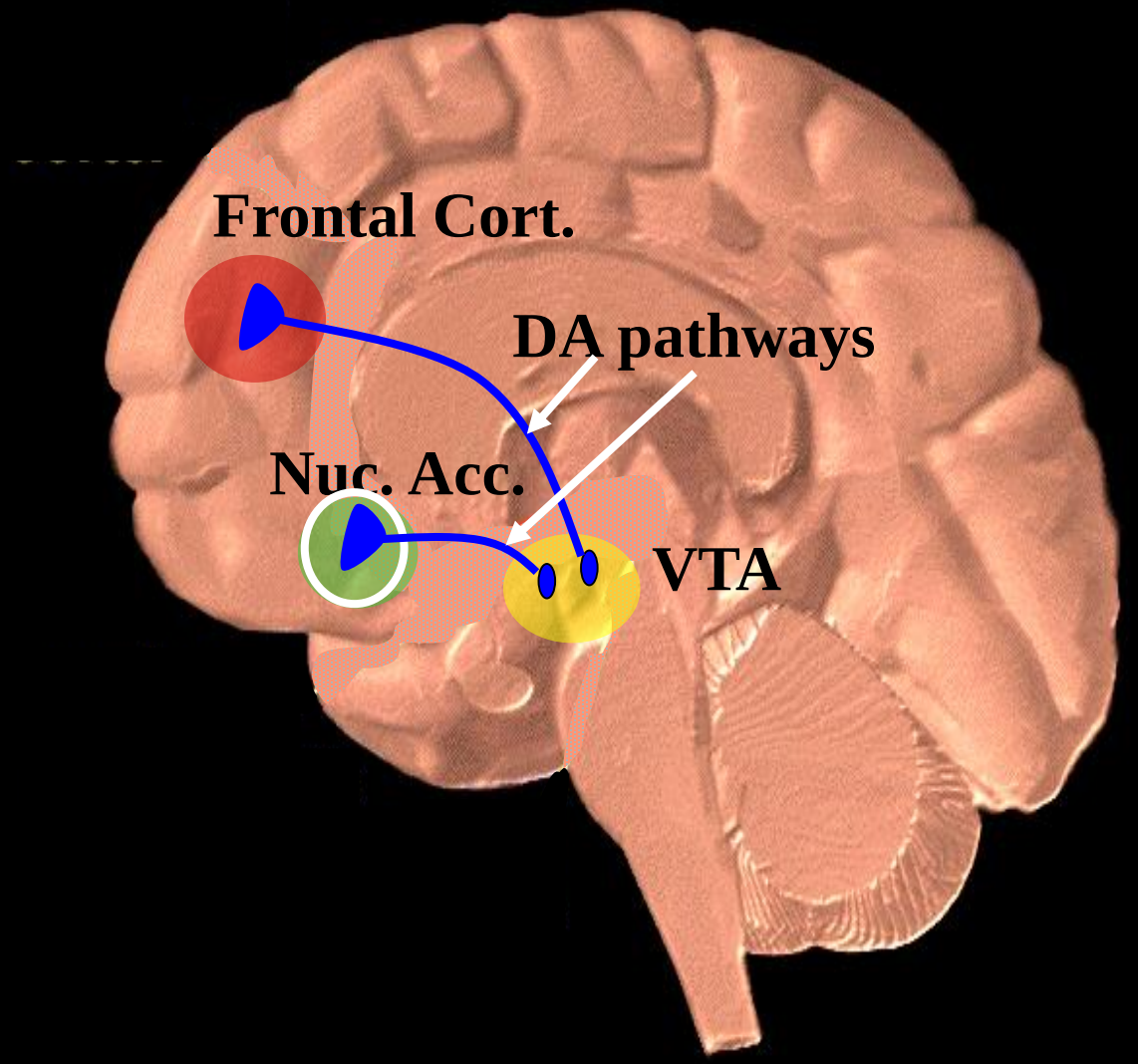
ough review of evidence available in 1957,[1] concluded that "The advisability of establishing clinics or some equivalent system to dispense opiates to addicts cannot be settled on the basis of objective facts. Any position taken is necessarily based in part on opinion, and on this question opinions are

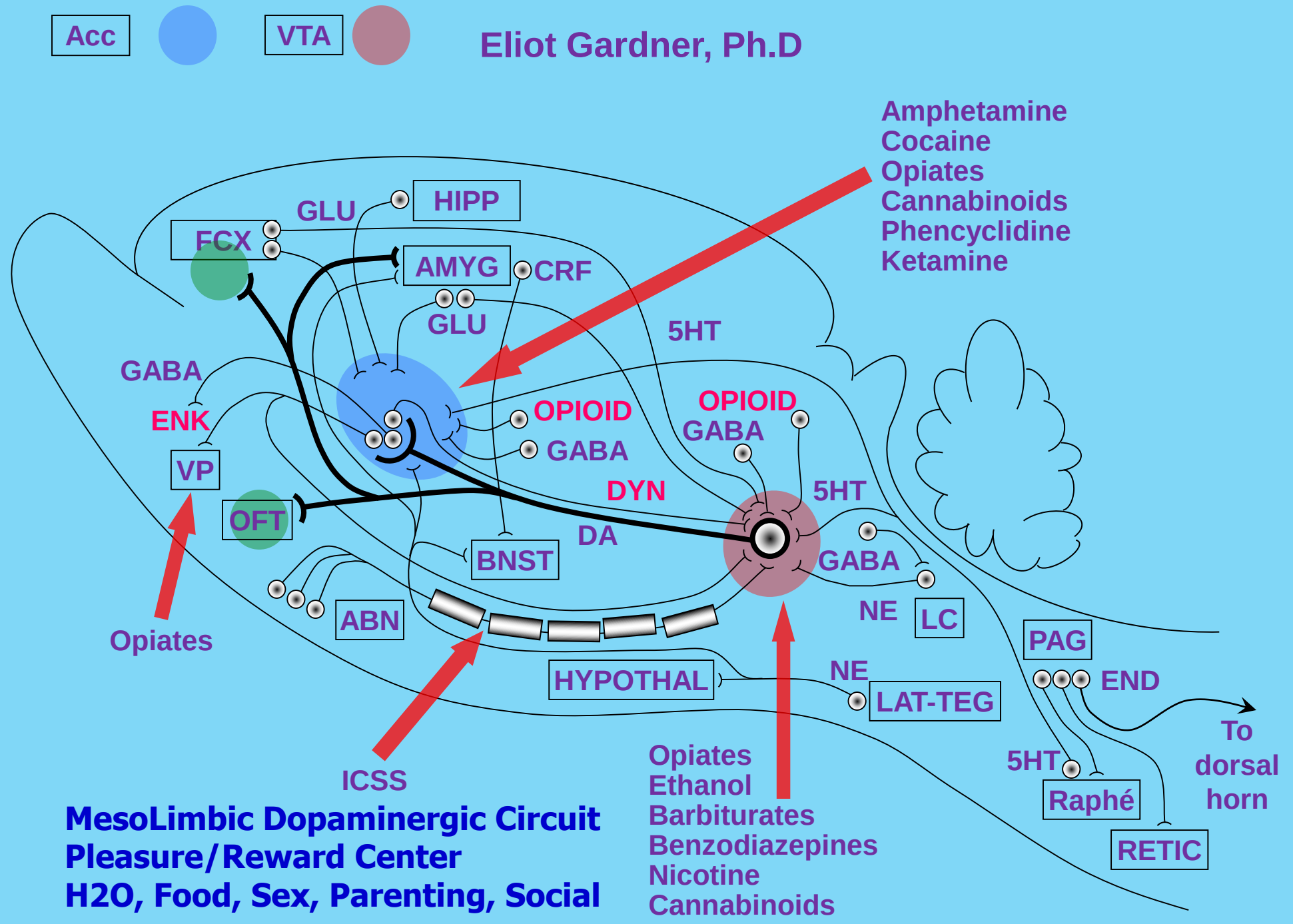
JAMA Classics: Celebrating 125 Years
Methadone Maintenance 4 Decades Later
Thousands of Lives Saved But Still Controversial
Commentary by Herbert D. Kleber, MD
JAMA. 2008;300(19):2303-2305

JAMA. 1965;193(8):646-650

From the Rockefeller Institute, and Manhattan General Division of Beth Israel Hospital, New York.
Reprint requests to Rockefeller Institute, New York 10021 (Dr. Dole).

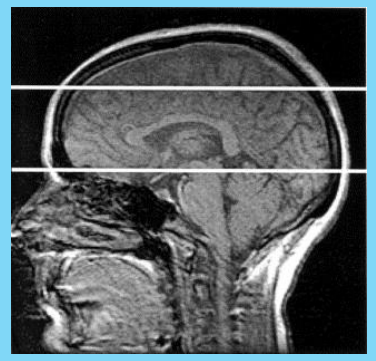
Reward Pathways

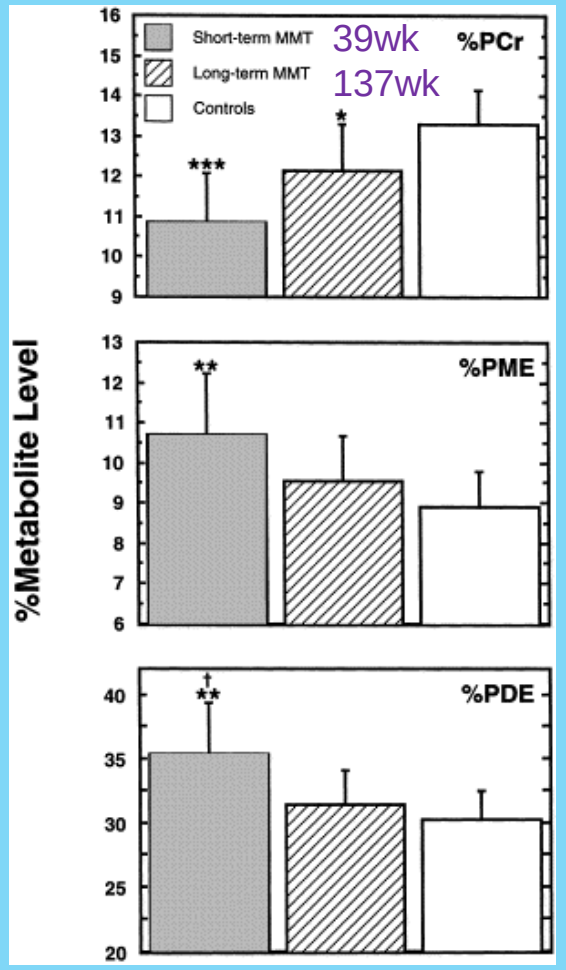



Acc
VTA
Eliot Gardner, Ph.D
Amphetamine
Cocaine
Opiates
Cannabinoids
Phencyclidine
Ketamine
HIPP
GLU
FCX
AMYG
CRF
GLU
5HT
GABA
ENK
VP
OPIOID
GABA
OPIOID
GABA
DYN
5HT
OFT
DA
BNST
GABA
ABN
NE
LC
Opiates
PAG
HYPOTHAL
NE
END
LAT-TEG
To
dorsal
horn
5HT
Raphé
RETIC
ICSS
Opiates
Ethanol
Barbiturates
Benzodiazepines
Nicotine
Cannabinoids
MesoLimbic Dopaminergic Circuit
Pleasure/Reward Center
H2O, Food, Sex, Parenting, Social

Methadone: Effectiveness/MOA

Cerebral phosphorus metabolite abnormalities in opiate-dependent polydrug abusers in **methadone maintenance**





Psychiatry Research: Neuroimaging
Volume 90, Issue 3 ,
30 June 1999, Pages
143-152
Kaufman,M

Phosphorous MR Spectroscopy

Fig. 3. Metabolite levels in control subjects (*n*=16) and in short- (*n*=7) and long-term (*n*=8) methadone maintenance treatment (MMT) subgroups. Shown are means±S.D. of percent metabolite measures.

Methadone: Effectiveness/MOA

From these data, we conclude that polydrug abusers in MMT have 31P-MRS results consistent with abnormal brain metabolism and phospholipid balance. **The nearly normal metabolite profile in long-term MMT subjects suggests that prolonged MMT may be associated with improved neurochemistry.**

Psychiatry Research: Neuroimaging
Volume 90, Issue 3 , 30 June 1999, Pages 143-152

N=25
Mean=54mos
MMTP

Normalize & Stabilize the Brain, so that Rehabilitation Can Proceed.

V.Dole

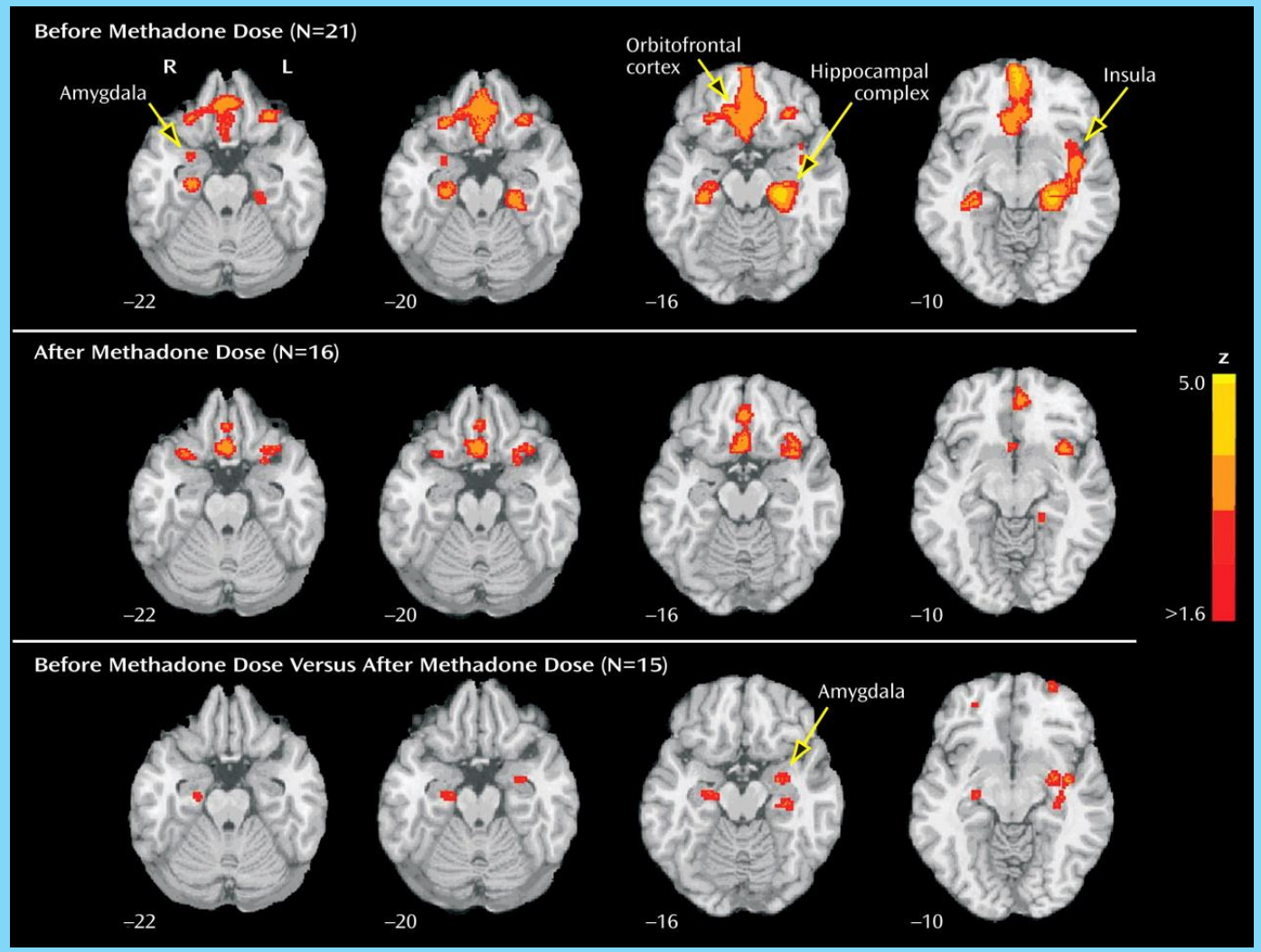


Figure 1. Activation Maps of Brain fMRI Response to Heroin-Related Stimuli in Methadone Maintenance Patients Before and After Daily Methadone Dose.

Am J Psychiatry 2008; 165:390-394

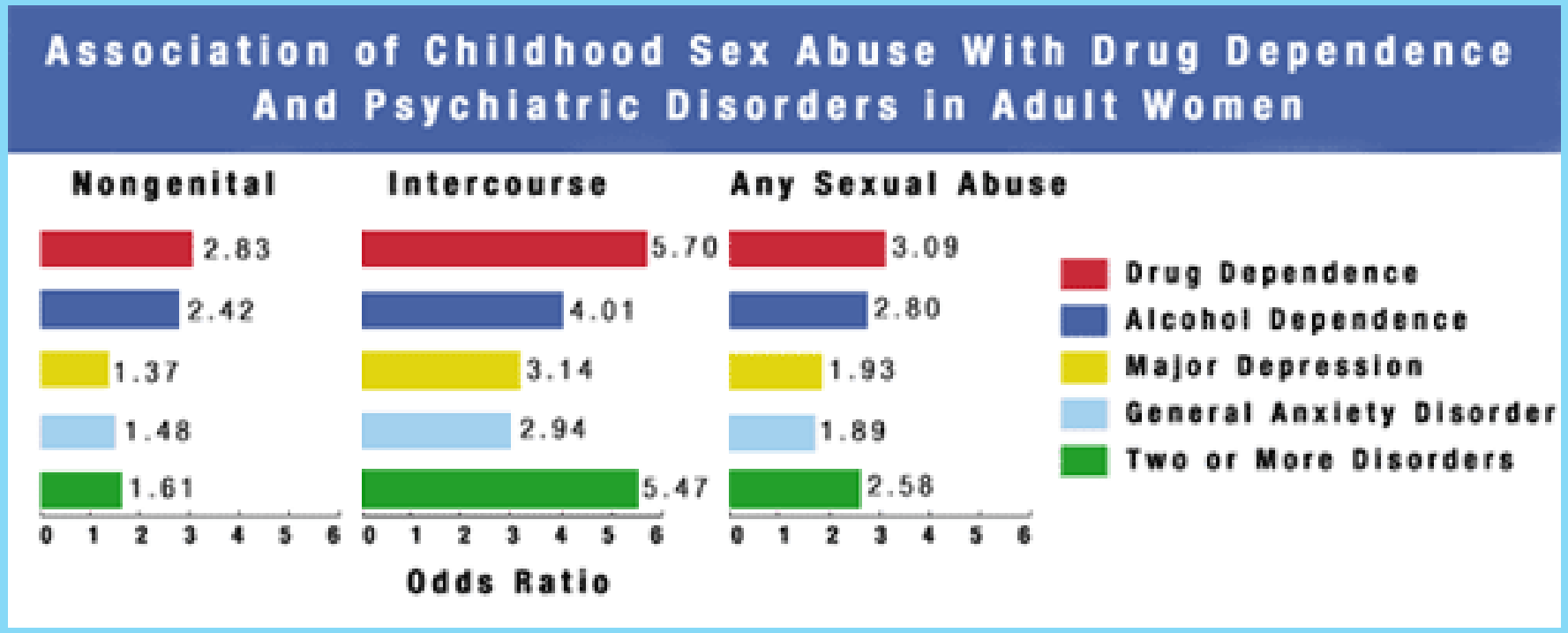
Vulnerability to Addiction

- **Genetic**
- **Environmental**
- **Cultural**
- **Stress**
- ***Social Determinants/Syndemics***
- ***Exaggerated Response***
- **Spotlight Euphoria**
- **Geriatrics**
- **Adolescents**
- **Privileged Upbringing**
- **Availability**

“Exaggerated Response”

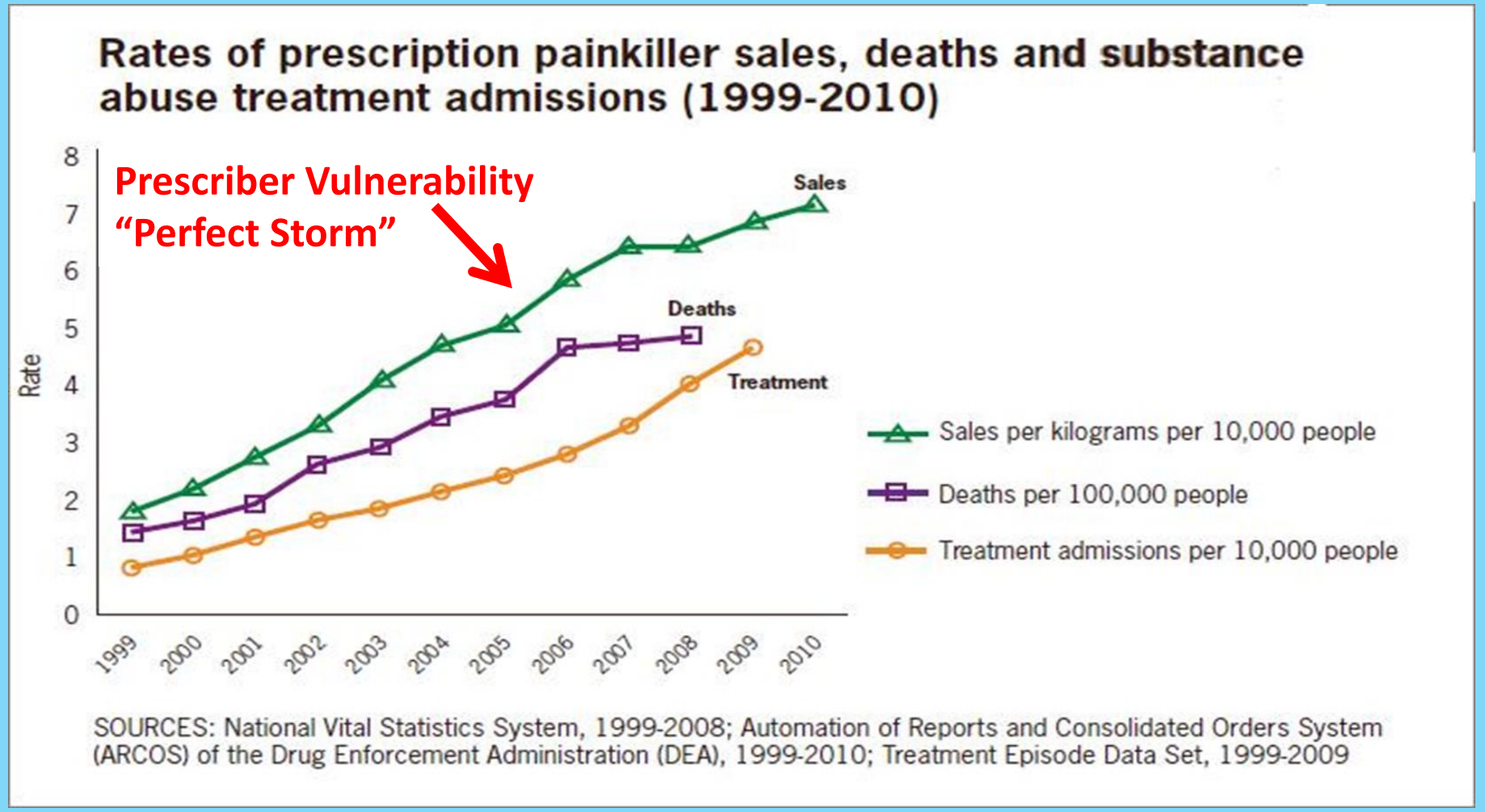
What Did It Feel Like The First Few Times You Used Opioids?

- “All My Problems Disappeared”
- “Felt Like There Was Sunshine on My Face”
- “Felt Like I Was Under a Warm Blanket”
- “Thought This is How Normal People Feel”
- “Forgot About All the Abuse”
- “Felt Like the World Was at Peace”
- “Totally Relaxed” “Not Shy”
- “Looking at a Beautiful Sunset”
- “I Was Energized!!”
- Liking an Opioid is Itself a Vulnerability

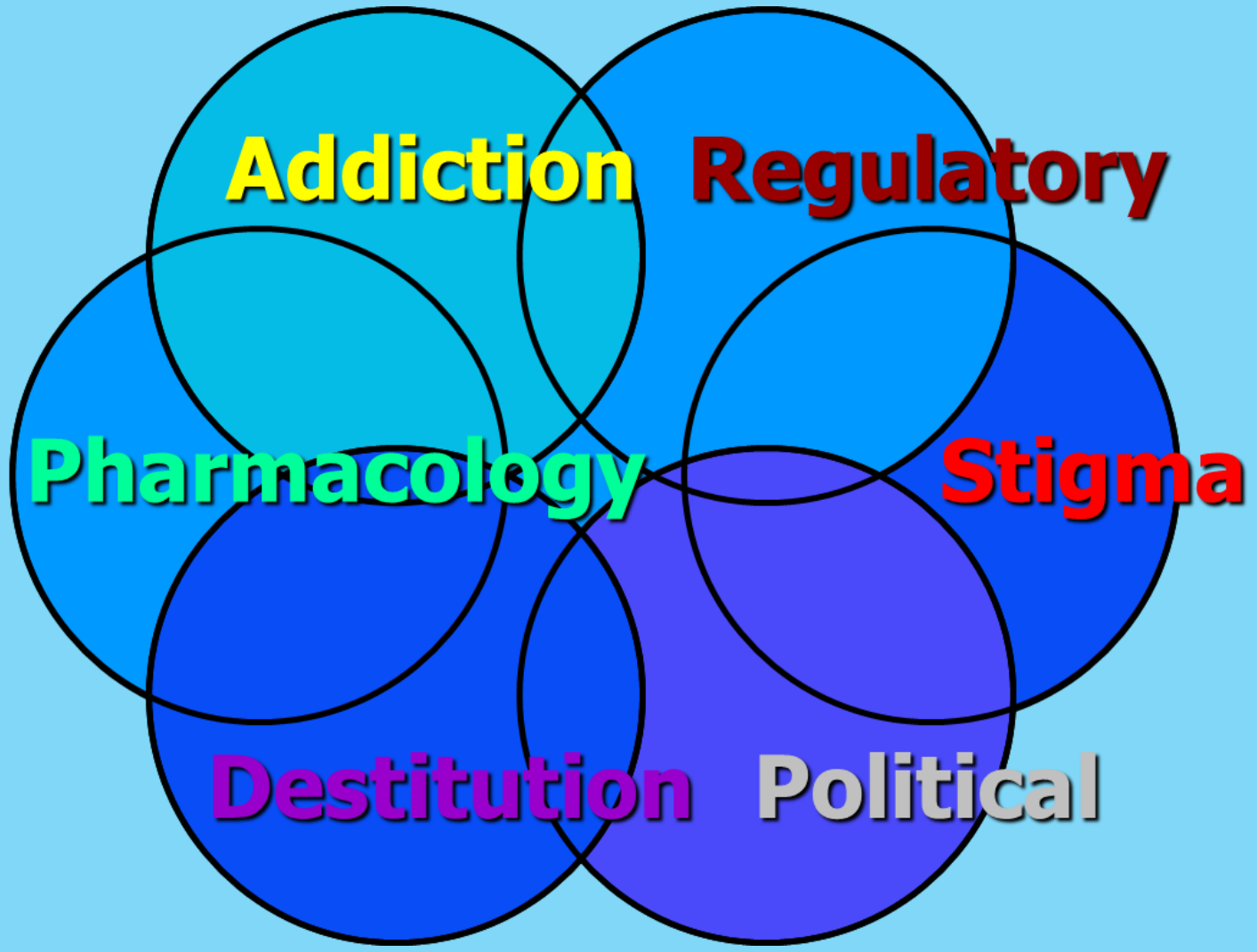


Kendler, et. Arch Gen Psychiatry. 2000;57(10):953-959.

Rates of Opioid Overdose Deaths, Sales, and Treatment Admissions, United States, 1999–2010



Opioid Agonist Therapy



STIGMA--METHADONE

- “My Wife’s Opinion Is that Methadone Maintenance Treatment Is As Close To **Evil** As You Can Get, Without Killing Someone.”

A “successful” methadone patient quoting his wife’s attitude toward methadone maintenance treatment.

Duration Barriers: Stigma

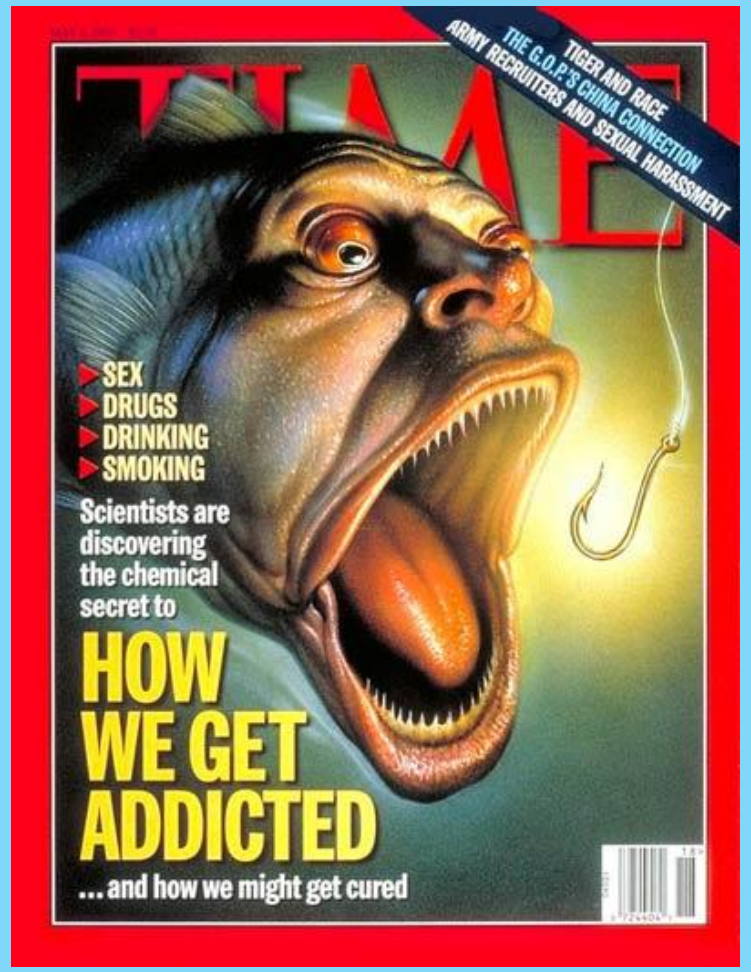
SM: You must be excited to see him when he comes back?

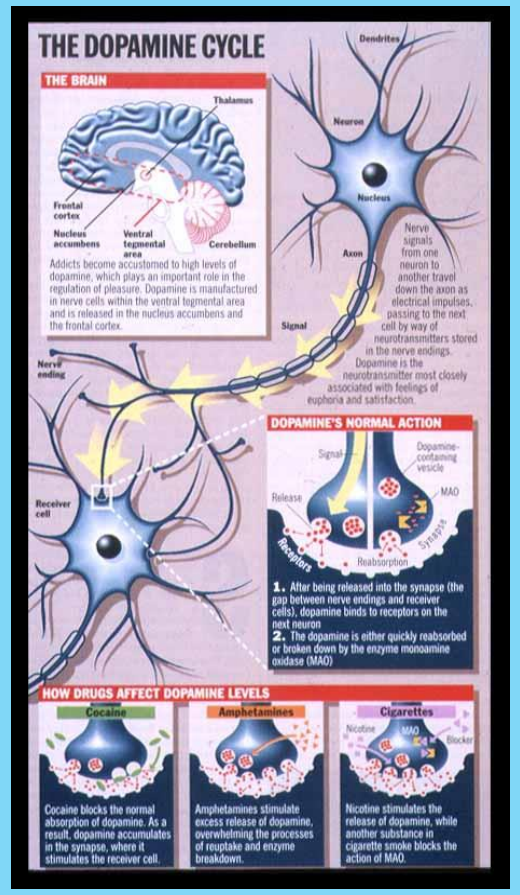
Mrs. Claus: By the time he stumbles in at 6AM, Chris has eaten roughly 2 Billion cookies, so he pukes for a solid day! She continues-

THEN HE SPENDS A WEEK IN A **METHADONE CLINIC** TO COME DOWN FROM THE SUGAR HIGH.

Aidy Bryant, Seth Meyers. SNL, 12/8/12

OAT Barriers: Terminology





05/1997

OAT Barriers: Terminology

A Way Out for Junkies?

In trials going on nationwide, buprenorphine seems to block the cravings of heroin withdrawal

By JOHN CLOUD

WHEN TED C., A HEROIN JUNKIE AND former baseball umpire, heard about an experimental new treatment for his addiction, he was skeptical. Doctors told him that a simple pill called buprenorphine could eradicate his enormous craving for the narcotic, which he had been snorting daily for several years. It sounded too good to be true—junkies live in fear of the agony that arrives when a hit wears off—so Ted bought an extra bag of heroin the night before he took buprenorphine for the first time. Just in case.

But this time there was no pain. "I went to the clinic, took the pill and went home. I used the last of the bag and haven't touched heroin since," he says. That was April, and today he still takes the tablets—one a day keeps the craving away—but he expects to stop using the drug in a few months. "There was no struggle," he says. "There is no downside to the drug."

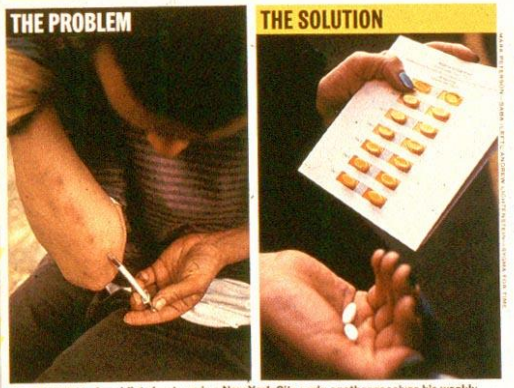
Testimonials such as Ted's have researchers across the U.S. claiming a breakthrough in the treatment of heroin addiction. Today most addicts who want to kick the drug are sent to clinics that administer methadone. But that cure is nearly as troublesome as the disease it treats. Methadone produces its own high and is so addictive that it has its own black market. To receive it legally, addicts must report every day to authorized clinics, something many are loath to do. Before buprenorphine, Ted tried methadone and found the experience a lot like taking heroin—only he had to get his fix in front of a mangy group of drug pushers and criminals. The scene made him feel closer to drugs, not free of them.

Buprenorphine is an opiate too, but it creates only a passing flicker of a high, if that—and it is not addictive. Consequently, the FDA is expected to approve the drug by spring, which would allow physicians to dispense it from the privacy of their offices. For many, that will be not a moment too soon. During the 1990s, heroin addiction has spread to groups ill-served by existing treatment networks: professionals like Ted and middle-class, often suburban, teens. The majority of addicts are still poor, city-dwelling adults, but teens account for more than a fifth of those who say they have taken heroin in the past year, double the proportion in the early '90s. Researchers believe more kids are using it because it is now sold in purer form—pure enough to snort or smoke. Like Ted, most teens will not inject, but they don't mind taking a puff or a sniff. (Injecting heroin is the quickest way to experience its rush, but the drug still packs a punch when snorted or smoked.)

For suburban kids, treatment options are sparse. Federally funded methadone clinics are off limits to those younger than 21. Even at private clinics, doctors are reluctant to prescribe methadone for all but the most hard-core addicts. "Methadone itself is a terribly shackling drug, and putting young or short-time users ... on methadone is criminal," says Paul Earley, an addiction specialist at the Ridgeview Institute, outside Atlanta.

In the fight against addiction, breakthrough promises have been made and broken many times; methadone was once considered a miracle drug, and heroin itself was developed to cure addictions. But researchers say buprenorphine could be the answer. Like heroin and methadone, it bonds to certain receptors in the brain, blocking the pain they transmit and convincing the brain that the cravings have been satisfied. Yet somehow it does that without creating cravings for itself. Even long-term junkies who try buprenorphine simply do not want heroin anymore.

So why has buprenorphine not replaced methadone? Although the drug has been rumored since the 1970s to work well for addicts—and has been used in France for more than a year—scientists only recently began the costly clinical trials needed for government approval. Conducted at 12 hospitals around the U.S. and coordinated jointly by the government and drugmaker Reckitt & Colman, the trials have gone extremely well—so well that clinicians stopped giving placebos to control groups. "We could not morally go on giving placebos to people who needed the drug," says Dr. John Rotrosen, one of the study's administrators.



GETTING WELL: An addict shoots up in a New York City park; another receives his weekly dosage of buprenorphine, an experimental antidote that erases cravings for the opiate

The inevitable catch? No one is sure how long patients will have to take buprenorphine before they can be free of it. Doctors say most heroin addicts are addicted for life, even if they stop using it—a warning Ted C. might well heed. What's more, buprenorphine will probably cost more than methadone, ruling it out for poor junkies without government aid. Still, it could be a lifeline for many of the estimated half-million American addicts. Predicts Rotrosen: "It will fundamentally change the way heroin is treated in the U.S." —*Reported by Edward Barnes/New York, Greg Fulton/Atlanta and Chandrani Ghosh/Washington*

1998

OAT: Terminology

- OST: Opioid Substitution Therapy
- Commonly Used in Europe and Australia
- Leads To:

  “Substituting One Addiction For Another”

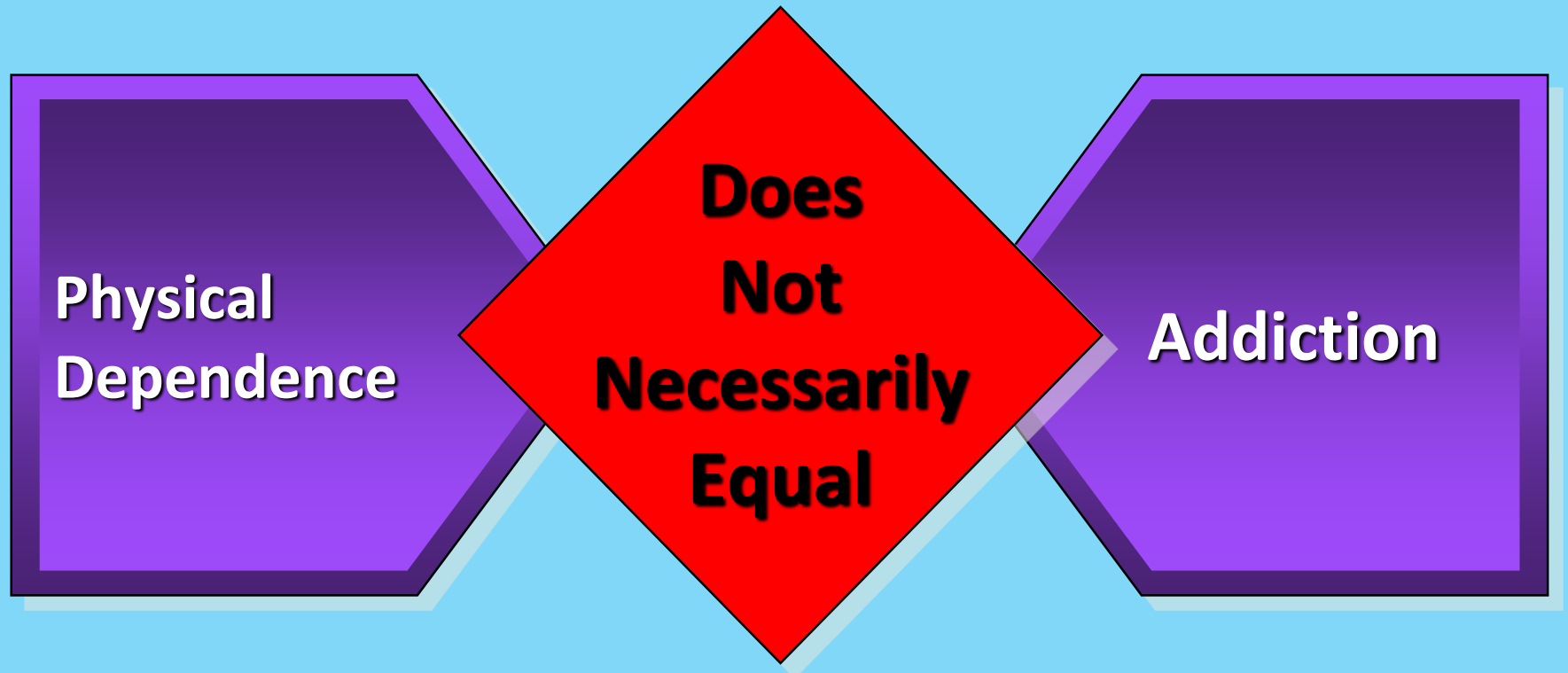
  “Substituting One Drug For Another”

MAT: A Misnomer For Many Patients

Why Not Call It: “Treatment for OUD” or

“Pharmacotherapy for OUD”

OAT: Terminology



Courtesy A.W.

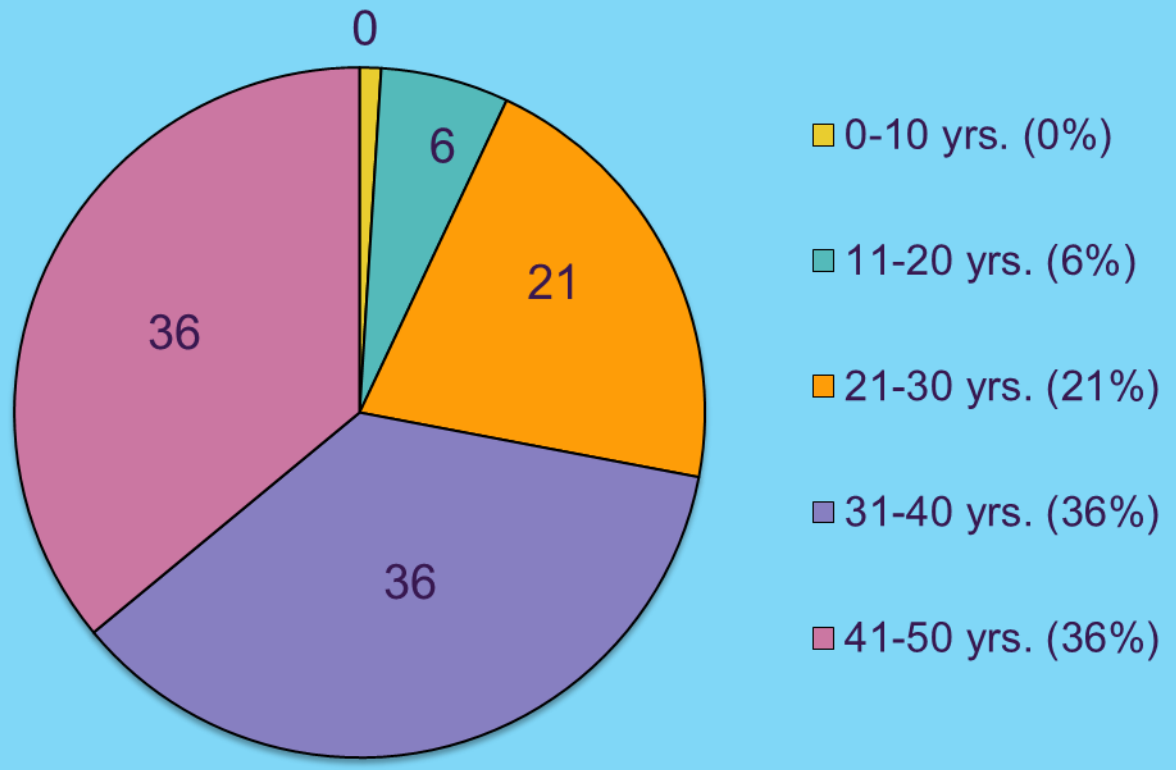
Opioid Agonist Therapy:
The Duration Dilemma

Based on 55 Years of Evidence,

With Consistently High Relapse Rates,

Indefinite Effective Treatment is the Safest Option

Methadone Medical Maintenance
Total Years on Methadone



Courtesy A.W.

MEDICATION "ASSISTED" TREATMENT
"ADDICTION PHARMACOTHERAPY"

"**All** Treatments Work For **Some** People/Patients"

"**No One** Treatment Works for **All** People/Patients"

Alan I. Leshner, Ph.D
Former Director NIDA

Why Is This So Important?

Actor Philip Seymour Hoffman, **46 yo**, who was found dead February 2, 2014 on the bathroom floor of his New York apartment with a syringe in his left arm, died of acute mixed drug intoxication, **including heroin**, cocaine, benzodiazepines and amphetamine, the New York medical examiner's office said Friday.

3 Children: 11, 8, 6, yo.

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The Evidence for Medication-Assisted Treatment of Opioid Use Disorder

Lisa Mustone Alexander EdD, MPH, PA-C

President

Physician Assistant Education Association

Objectives for Medication-Assisted Treatment

- Suppress signs and symptoms of opioid withdrawal
- Extinguish opioid-drug craving
- Block the reinforcing effects of illicit opioids (“blockade”)
- Treatment of OUD is part of a continuum of care that includes prevention, screening, treatment, and follow-up care

Basic Overview/Pharmacology

Methadone

- Daily dosing in supervised settings
- On WHO's essential medicines list
- Synthetic opioid with long half-life

****

Buprenorphine

- Partial opioid receptor agonist; ceiling effect
- Combined with naloxone antagonist
- Available through treatment programs and in outpatient settings
- Requires special training to prescribe—DATA 2000 Waivers

****

Naltrexone

- Full opioid receptor antagonist
- Available through treatment programs and outpatient offices
- No special training to prescribe

Evidence for Use

Evidence for efficacy, effectiveness, and safety in OUD and other disorders

PubMed September 2018

- Methadone Maintenance Treatment
  - 633 studies (1972)
- Buprenorphine AND opioid use disorder
  - 185 studies (1978)
- Naltrexone AND opioid use disorder
  - 104 studies (1981)

Limits: “Clinical Trial” and “Humans”

Methadone

Systematic reviews demonstrate:

- Improved retention in treatment
- Reduced levels of criminality
- Reduced rates of injection drug use and blood-borne infections
- Reduced overall mortality

Innov Clin Neurosci. 2017; 14(7-8): 8-19
Cochrane Database of Systematic Reviews 2009, Issue 3, Art. No. CD002209
Proposal for the Inclusion of Methadone in the WHO Model List of Essential Medicines, 2004
Cochrane Database of Systematic Reviews 2003, Issue 3, Art. No. CD002208

Buprenorphine

Systematic reviews demonstrate:

- Increases time in treatment
- Reduces illicit opiate use
- Reduces use of other illicit substances

The Journal of Substance Abuse Treatment 2015; 48: 62-69
Cochrane Database of Systematic Reviews 2014, Issue 2, Art. No. CD002207

Naltrexone

Systematic reviews demonstrate:

- Assists in maintaining abstinence from illicit opioids
- Significantly reduces cravings for opioids

The Lancet 2018; 391: 309-318
JAMA Psychiatry 2017; 74: 1197-1205
CNS Drugs 2013; 27: 851-861

OUD Treatment Risks

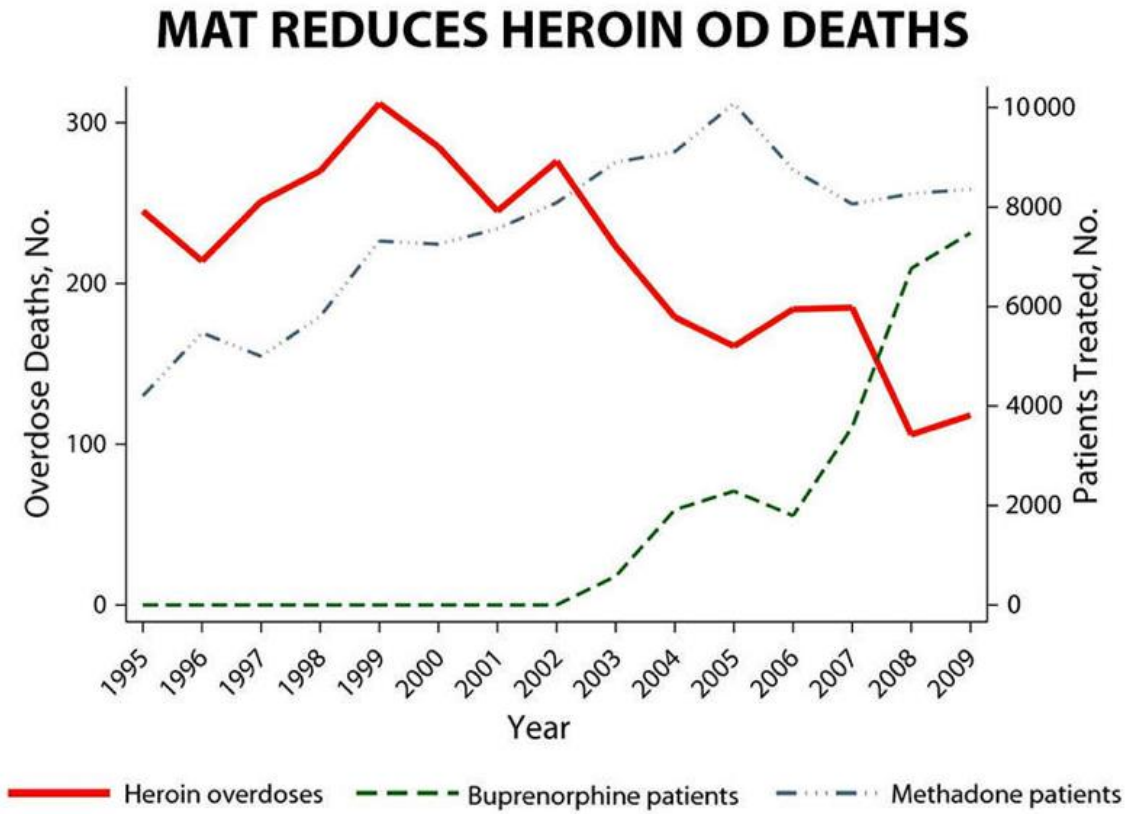
- The primary risk for mortality with methadone treatment is during the first four weeks after induction and the first four weeks after cessation
- The most lethal adverse reaction to methadone is QT-prolongation and the risk for fatal arrhythmia
- The ceiling effect of buprenorphine obviates the risk of respiratory depression after induction however, risk of mortality increases after cessation (due to loss of tolerance)
- Diversion risk is reduced
  - By directly observed treatment in OTPs
  - Combining buprenorphine with naloxone or using the extended release IM formulation or implant

Summary

- When used in appropriately selected patients, all three medications approved for the treatment of opioid use disorder are effective at:
    - Preventing relapse to illicit opioid use
    - Increasing retention in treatment

Harvard Review of Psychiatry 2015; 23: 63-75

Summary



Schwarzt R, et al. Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995-2009. Am J Public Health. 2013 May;103(5):917-22.

Selected References

Ali S, Tahir B, Jabeen S, Malik M. Methadone Treatment of Opiate Addiction: A Systematic Review of Comparative Studies. *Innov Clin Neurosci.* 2017; 14(7-8): 8-19

Burma NE, Kwok CHT, Trang T. Therapies and Mechanisms of Opioid Withdrawal. *Pain Management* 2017; 7: 455-459

Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone Maintenance at Different Dosages for Opioid Dependence. *Cochrane Database of Systematic Reviews* 2003, Issue 3, Art. No. CD002208

Lee JD, Nunes EV, Novo P, Bachrach K, Bailey GL, Bhatt S, Farkas S, Fishman M, Gautheir P, Hodgkins CC, King J, Lindblad R, Liu D, Matthews AB, May J, Peavy KM, Ross S, Salazar D, Schkolnik P, Shmueli-Blumberg D, Stablein D, Subramaniam G, Rotrosen J. *Comparative Effectiveness of Extended-release Naltrexone Versus Buprenorphine-Naloxone for Opioid Relapse Prevention (X:BOT): A Multicentre, Open-label, Randomized Controlled Trial. The Lancet* 2018; 391: 309-318

Lett S. Treatment of the opium neurosis. *JAMA* 189; 17(2): 828-833

Mattick RP, Breen C, Kimber J, Davoli M. Methadone Maintenance Therapy Versus No Opioid Replacement Therapy for Opioid Dependence. *Cochrane Database of Systematic Reviews* 2009, Issue 3, Art. No. CD002209

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

Moosavysadeh A, Ghaffari F, Mosavat SH, Zargaran A, Mokri A, Faghihzadeh S, Naseri M. *J Integr Med*. 2018; 16(2): 77–83.

National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. *JAMA* 1998; 280(22): 1936-43

Potter JS, Dreifuss JA, Marino EN, Provost SE, Dodd DR, Rice LS, Fitzmaurice GM, Griffin ML, Weiss RD. The Multi-Site Prescription Opioid Addiction Study: 18-month Outcomes. *The Journal of Substance Abuse Treatment* 2015; 48: 62-69

Proposal for the Inclusion of Methadone in the WHO Model List of Essential Medicines, 2004

Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ* 2017; 357: j1550

Syed YY, Keating GM. Extended-Release Intramuscular Naltrexone (Vivitrol): A Review of Its Use in the Prevention of Relapse to Opioid Dependence in Detoxified Patients. *CNS Drugs* 2013; 27: 851-861

Tanum L, Klemmetsby K, Latif Z, Benth JS, Opheim A, Sharma-Haase K, Krajci P, Kunøe N. Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. *JAMA Psychiatry* 2017; 74: 1197-1205

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