

A HISTORY & REVIEW OF CURRENT EVIDENCE FOR COMPREHENSIVE TREATMENT INCLUDING MAT

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 **12** Every  minutes, a person in the United States dies from an opioid overdose.

U.S. SURGEON GENERAL, VIVEK MURTHY MD

- **AN ESTIMATED 20.8 MILLION PEOPLE IN OUR COUNTRY ARE LIVING WITH A SUBSTANCE USE DISORDER. THIS IS SIMILAR TO THE NUMBER OF PEOPLE WHO HAVE DIABETES, AND 1.5 TIMES THE NUMBER OF PEOPLE WHO HAVE ALL CANCERS COMBINED. THIS NUMBER DOES NOT INCLUDE THE MILLIONS OF PEOPLE WHO ARE MISUSING SUBSTANCES BUT MAY NOT YET HAVE A FULL-FLEDGED DISORDER. WE DON'T INVEST NEARLY THE SAME AMOUNT OF ATTENTION OR RESOURCES IN ADDRESSING SUBSTANCE USE DISORDERS THAT WE DO IN ADDRESSING DIABETES OR CANCER, DESPITE THE FACT THAT A SIMILAR NUMBER OF PEOPLE ARE IMPACTED. THAT HAS TO CHANGE.**

AGENDA

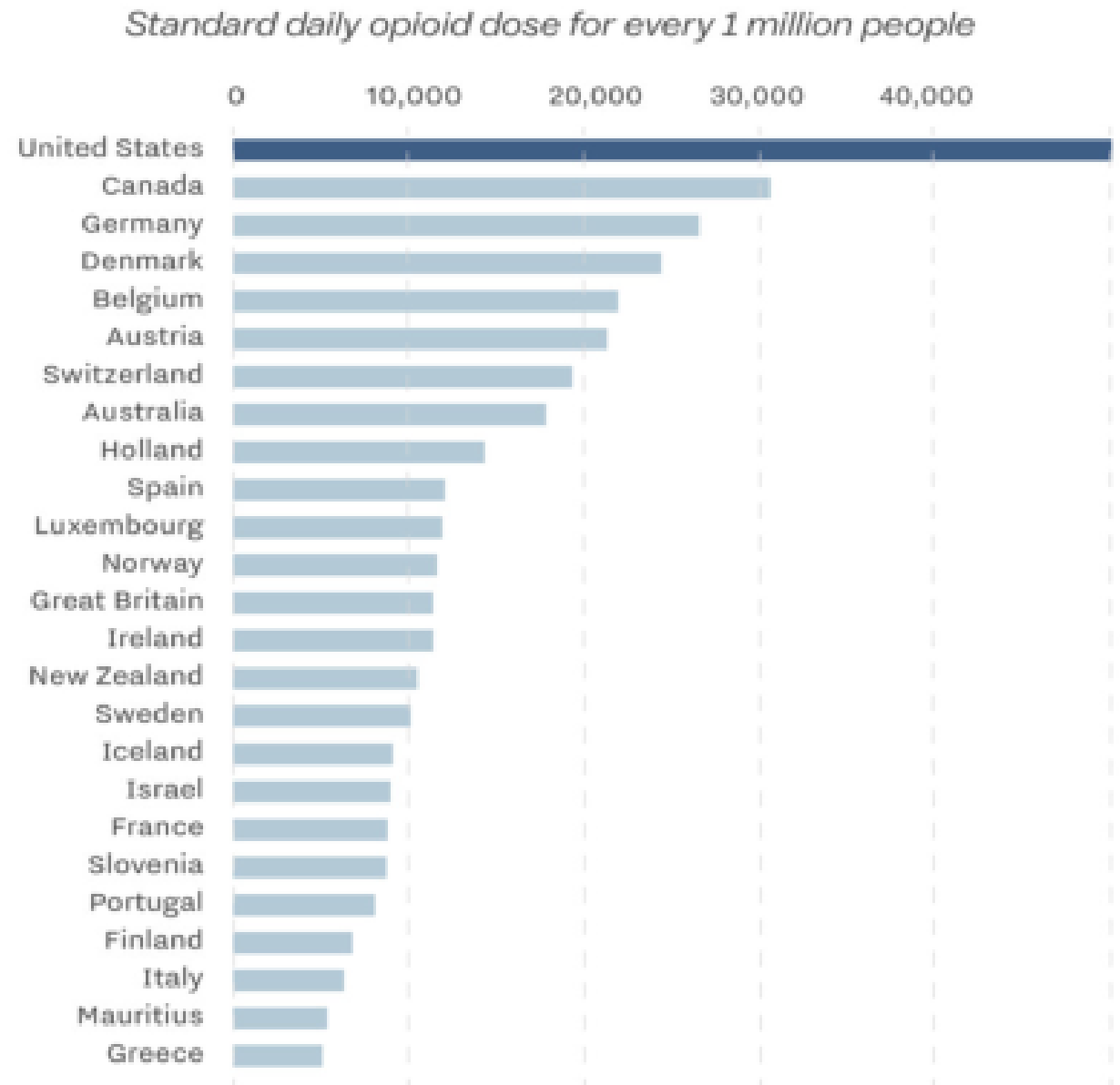
- The Issue in our Country
 - The Disease
- Medication-Assisted Treatment (MAT)
 - Medication *for* addiction treatment
 - History, evidence, indications and contraindications
- Comprehensive Integrated Addiction Treatment (For Opioids = COAT)
 - Best/evidence based practices - development and implementation of the current best practice model.

THE ISSUE

- Substance Use Disorder (SUD) is a **chronic, relapsing disease**, which has **significant economic, personal, and public health consequences**.
- Abuse of and addiction to alcohol, nicotine, and illicit and prescription drugs cost Americans more than **\$700 billion a year** in increased **health care costs, crime, and lost productivity**
- Nationally, **death rates** from Rx Opioid overdoses **QUADRUPLED** during 1999–2016
 - MMWR (CDC)
- CDC estimates over **42,000 people died in 2016** from overdoses involving opioid pain relievers.

THE ISSUE

- **AMERICANS CONSUME MORE OPIOIDS THAN ANY OTHER COUNTRY IN THE WORLD**

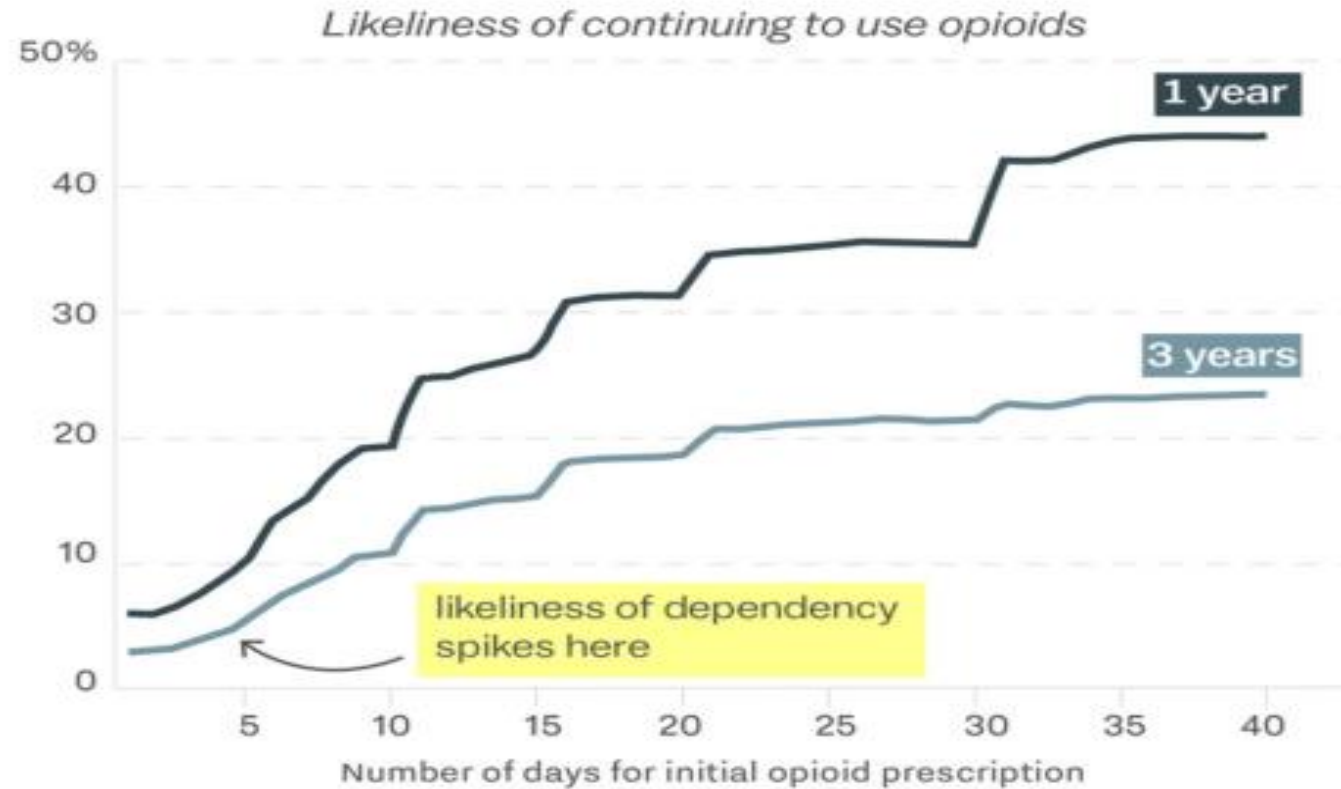


Source: United Nations International Narcotics Control Board
Credit: Sarah Frostenson

Vox

THE ISSUE

- **RISK OF CONTINUED OPIOID USE INCREASES AT 4-5 DAYS**



Source: Centers for Disease Control and Prevention


Credit: Sarah Frostenson


Vox


THE RESULT





On an average day in the U.S.:

 More than **650,000** opioid prescriptions dispensed¹

 **3,900** people initiate nonmedical use of prescription opioids²

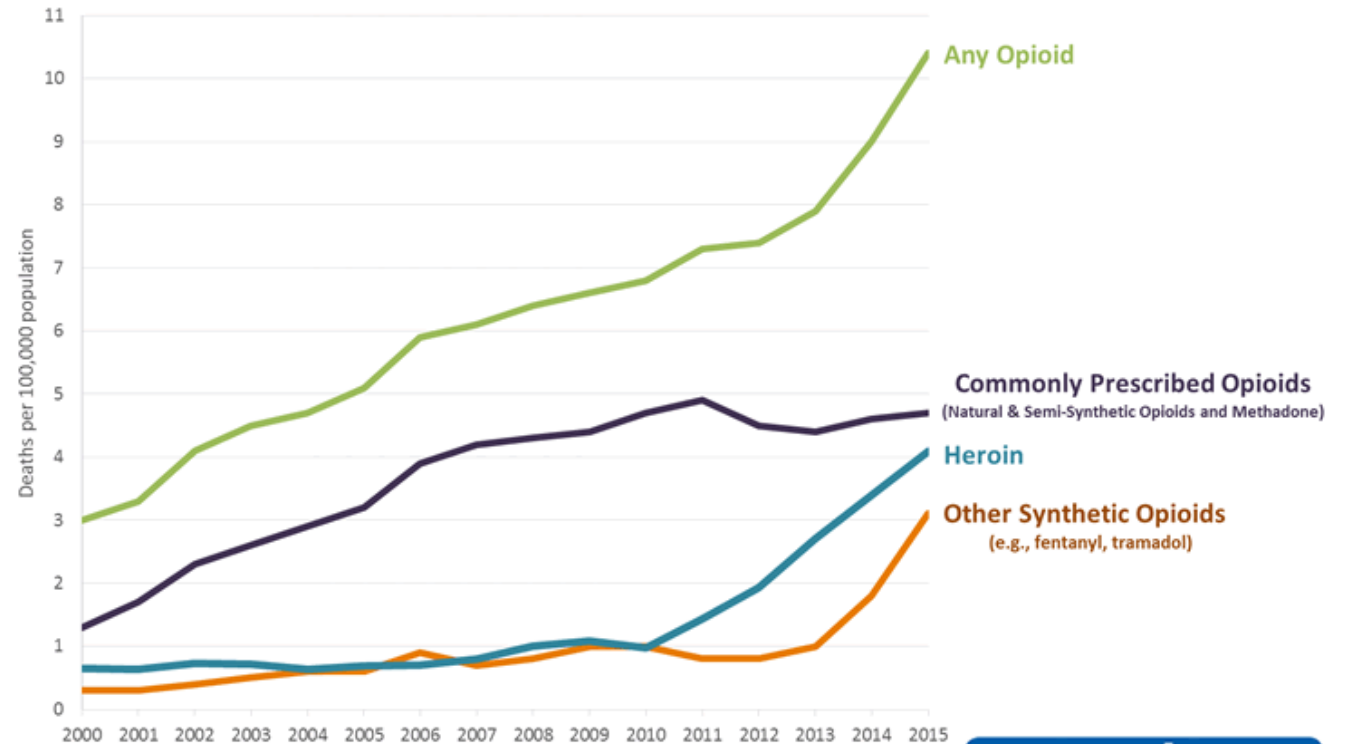
 **580** people initiate heroin use²

  **7** people die from an opioid-related overdose^{*3}

*Opioid-related overdoses include those involving prescription opioids and illicit opioids such as heroin

Source: IMS Health National Prescription Audit¹ / SAMHSA National Survey on Drug Use and Health² / CDC National Vital Statistics System³

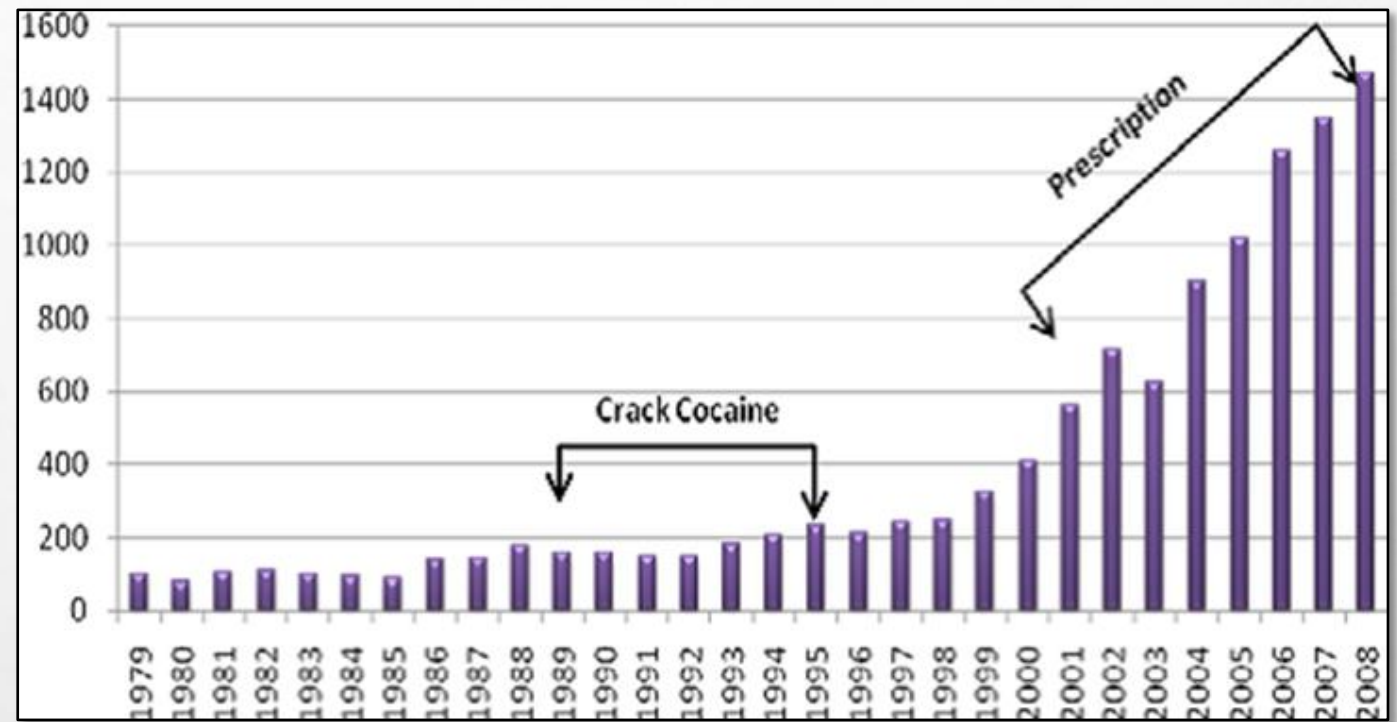
Overdose Deaths Involving Opioids, United States, 2000-2015



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/>.

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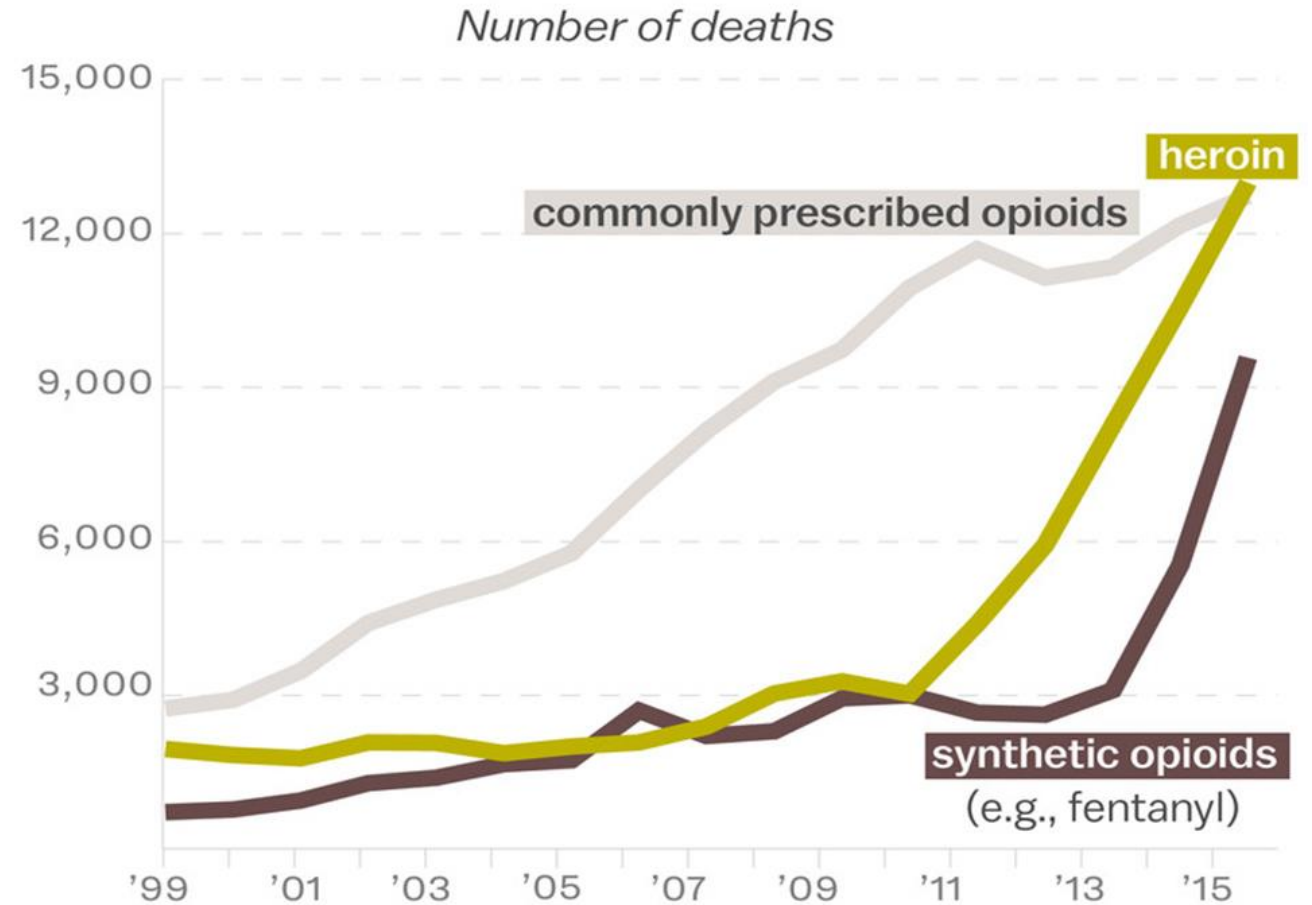
THE ISSUE - IN COMPARISON



- The current opioid epidemic is responsible for considerably more deaths than previous ones with **mortality rates currently 4-5 times higher** than the rates during the “black tar” **heroin epidemic** in the **mid-1970s** and more than **3 times** what they were during the peak years of **crack cocaine epidemic** of the **1990s**

SHIFT TO HEROIN & FENTANYL

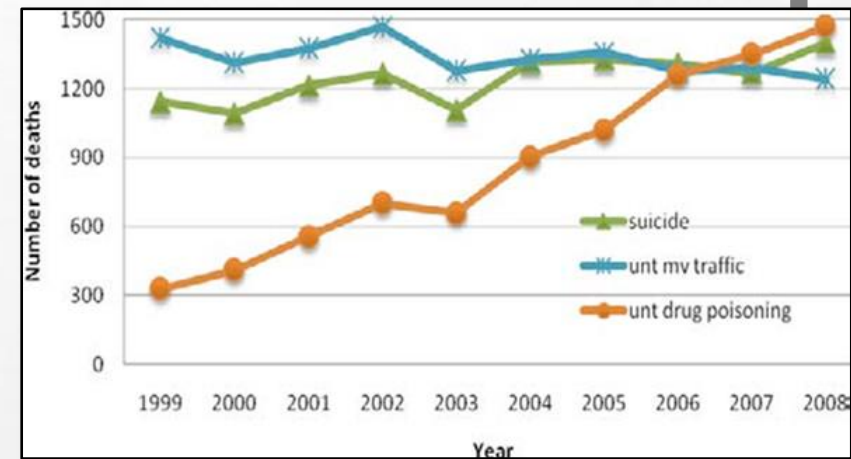
More drug overdose deaths now involve heroin than prescription painkillers



Source: CDC WONDER
Credit: Sarah Frostenson

Vox

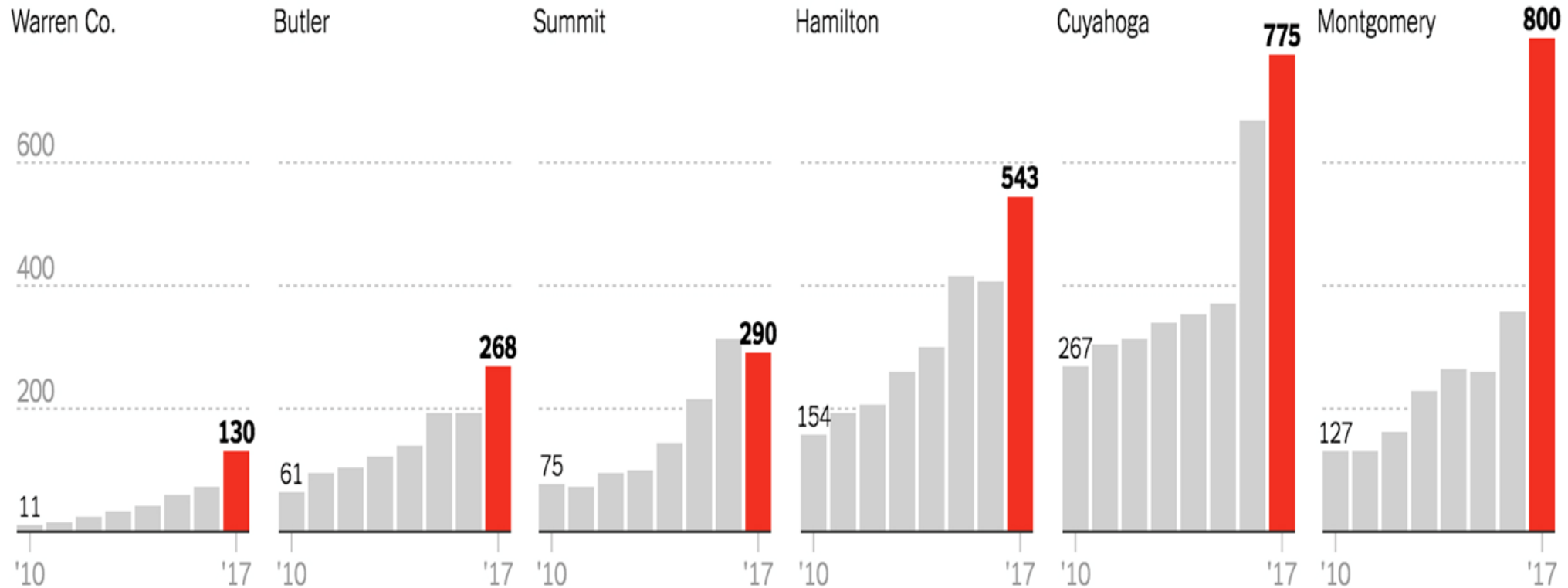
THE ISSUE – OUR REGION



- This disease is devastating our communities
 - 2007 - Unintentional drug poisoning became the **leading cause of injury death in Ohio**, surpassing motor vehicle crashes for the first time on record.
 - From **1999-2012**, Ohio's **death rate** due to unintentional drug poisonings **increased 440 percent**, and the increase in deaths has been driven largely by prescription drug overdoses.
 - Ohio's death rate has grown faster than the national rate, with southern Ohio being affected more than the rest of the state. On average, **nearly 6 people die each day in Ohio** due to drug-related poisoning.
 - Kentucky reported a **279% increase in heroin deaths** from **2010 to 2012**

WE CAN NOT FORGET ABOUT THE ISSUES OF ALCOHOL AND OTHER DRUGS

Drug overdose deaths in six Ohio counties, 2010 to 2017



Totals for 2017 assume that overdose deaths continue at the same rate through the remainder of the year.

Source: Butler County Coroner's Office; Cuyahoga County Medical Examiner's Office; Hamilton County Coroner; Montgomery County Alcohol, Drug Addiction & Mental Health Service; Montgomery County Sheriff's Office; Summit County Department of the Medical Examiner

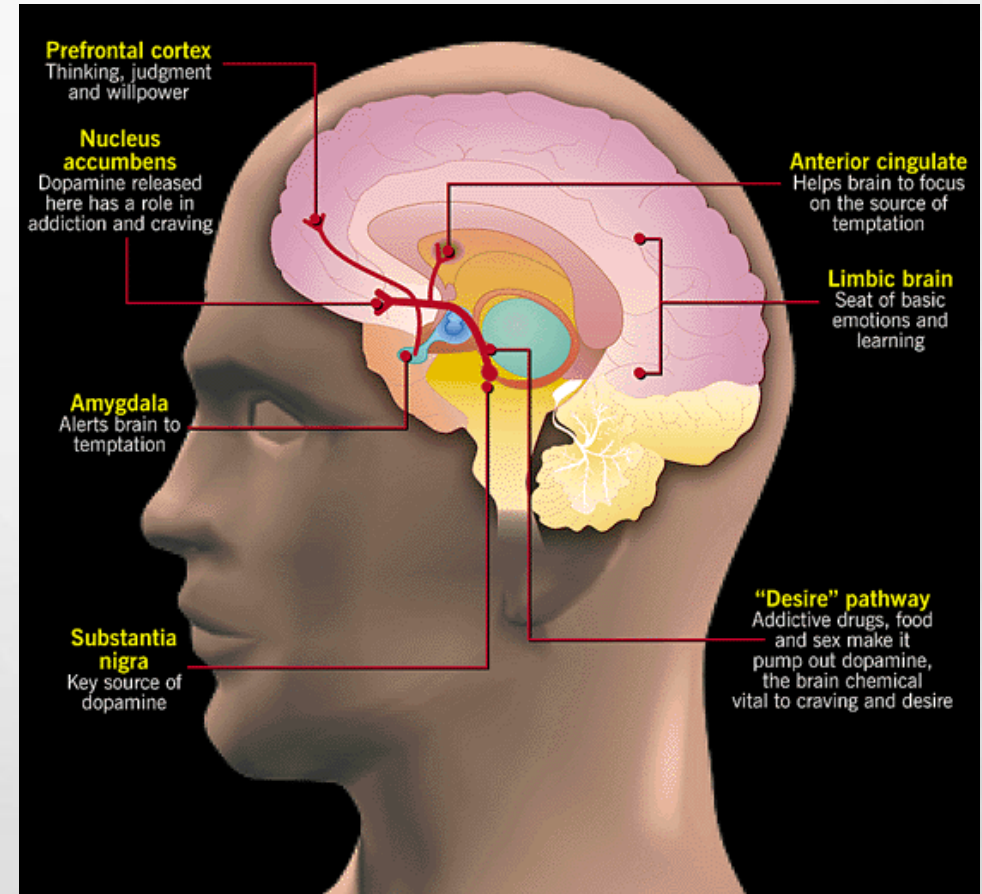
THE ISSUE – OHIO

THE DISEASE

- Definition of disease: Any deviation from or interruption of the normal structure or function of any body part, organ, or system that is manifested by a characteristic set of symptoms and signs and whose etiology, pathology, and prognosis may be known or unknown.
- ASAM definition of the disease of addiction: addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations.
- IT FITS THE DEFINITION; AND IT CAN BE FATAL WITHOUT TREATMENT.

THE DISEASE OF ADDICTION

- Addiction affects neurotransmission and interactions within reward structures of the brain, such that motivational hierarchies are altered and addictive behaviors supplant healthy, self-care related behaviors.
 - However, the neurobiology of addiction encompasses more than the neurochemistry of reward.
- The connections between the frontal cortex and circuits of reward, motivation and memory are fundamental in the manifestations of altered impulse control.
 - The frontal lobes are still maturing during adolescence, and early exposure to substance use is another significant factor in the development of addiction**
- Genetic factors account for about half of the likelihood that an individual will develop addiction. Environmental factors interact with the person's biology and affect the extent to which genetic factors exert their influence.



IMAGING EVIDENCE OF THE BRAIN DISEASE

Decreased Brain Metabolism in *Drug Abuse Patient*

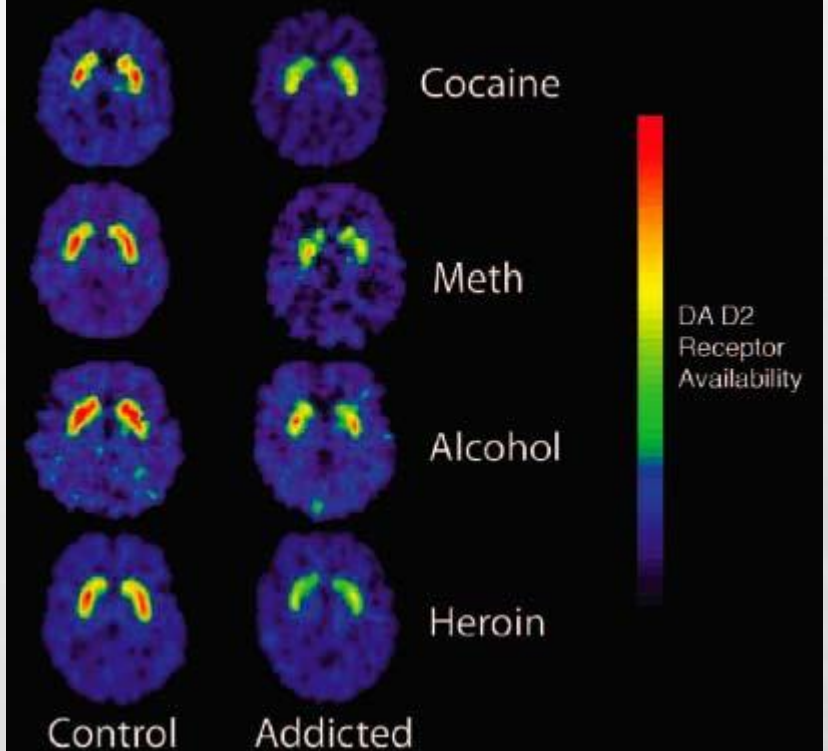


Decreased Heart Metabolism in *Heart Disease Patient*

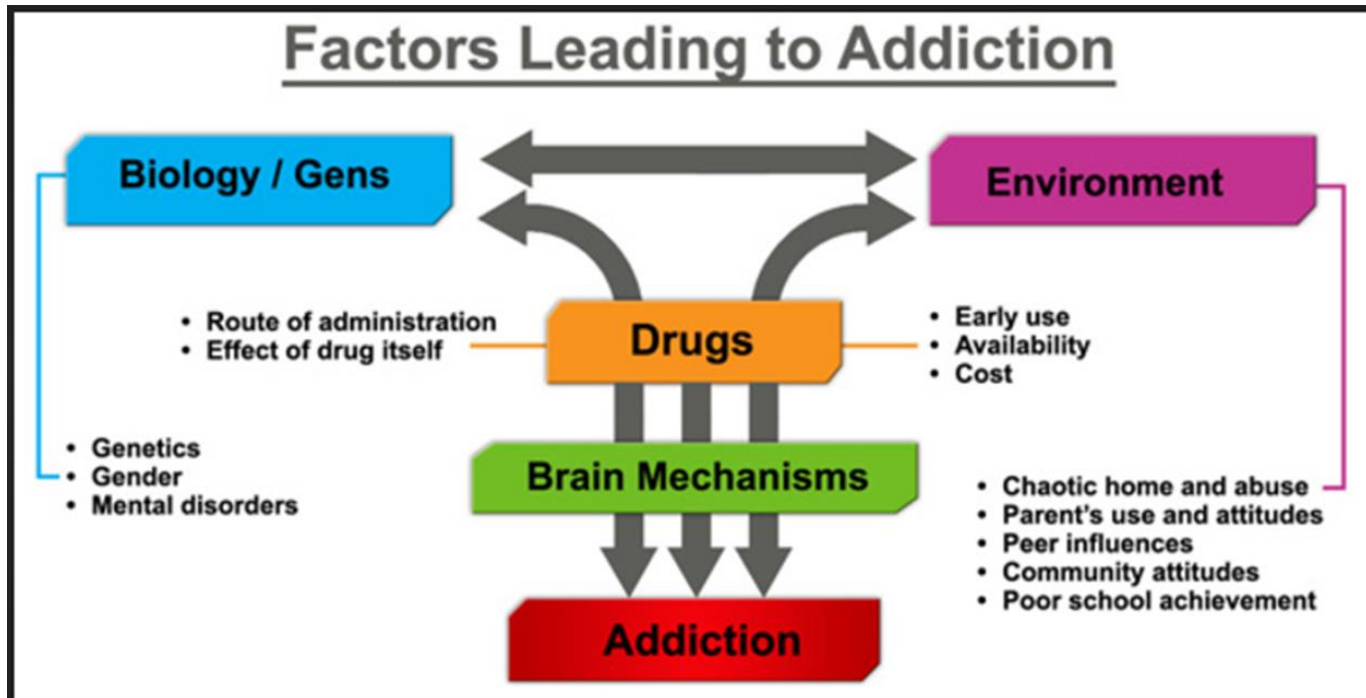


Sources: From the laboratories of Drs. N. Volkow and H. Schelbert

Dopamine D2 Receptors Are Lower in Addiction



DEVELOPMENT OF ADDICTION



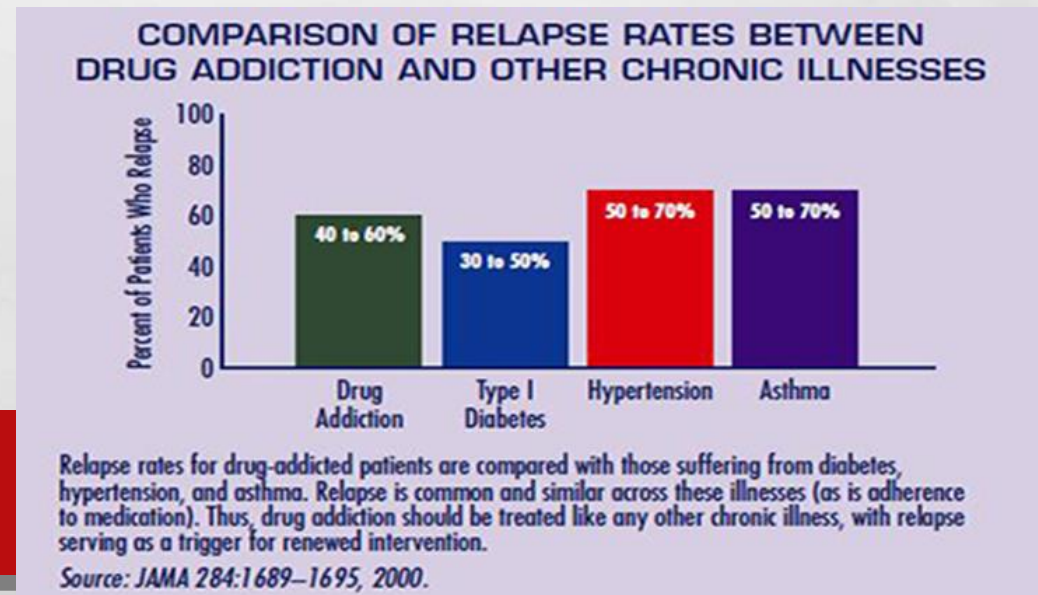
• **BIOLOGY (GENETICS)**

• **ENVIRONMENT**

• **EXPOSURE**

COMPARISON TO OTHER DISEASES

- WHO definition of diabetes type 2: Results from the body's ineffective use of insulin. This type of diabetes comprises the majority of people with diabetes around the world, and is largely the result of **excess body weight and physical inactivity with some predisposing genetic factors**.
 - The disease of addiction is also a state of dysfunction contributed to by **genetic factors (obviously not choice)** as well as **environmental ones such as abuse (mental or physical, again not a choice) and exposure (potentially a choice)**. Just like diabetes type 2, it is progressive without treatment and potentially life and limb threatening.
- The approximate rate of relapse of both diseases is also very similar →



SO WHAT ARE WE GOING TO DO BRAIN??



MULTI-FACETED SOLUTION

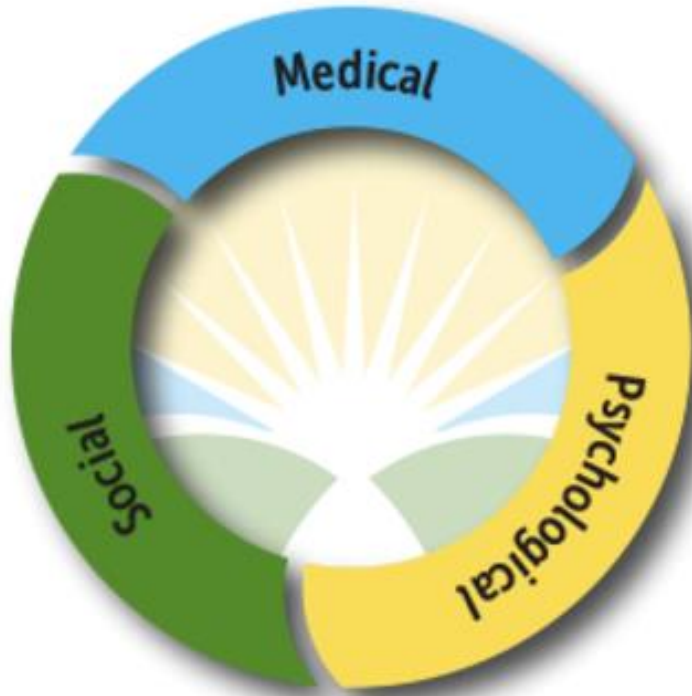
- Prevention: preventing youth drug use before it starts
- Treatment: creating better pathways to treatment and recovery
- Law enforcement: cracking down on drug trafficking
- Appropriate prescribing: encouraging appropriate use and availability of pain medication
- Harm reduction: saving lives by expanding access to naloxone, etc.

ASAM DEFINITION... AGAIN

- Chronic Relapsing Biopsychosocial Disease
- The Treatment for this Disease must address all Three components
 - Biological - Medical
 - Psychological
 - Social



TREATMENT



- **Medical** (addiction treatment)
 - Comprehensive assessment & intake – SAME DAY or NEXT DAY
 - Outpatient withdrawal management (and ongoing pharmacological management)
 - Medical stabilization services (general condition treatment until seen by or referred to PCP)
 - Care coordination and monitoring (ex: referrals to other physicians and monitoring of pdmps)
- **Psychological**
 - Clinical assessment (ASAM PLACEMENT CRITERIA)
 - Therapy (individual, group, and family, etc.)
- **Social**
 - Case management
 - Can include all of the following: crisis support, family services, legal services, vocational services, transportation, housing, etc.
 - Involving social support networks – AA, NA, Peer Support, etc

MEDICATION *FOR* ADDICTION TREATMENT - HISTORY

- Serious attempts to find medications for opioid addiction are traced to the early 1920's
- Investigation of over 150 compounds including: Metopon, Heroin("mistake"), Nalorphine, etc.
- 1929 – Porter Bill – Narcotic Farms for research; First in Lexington KY 1935
- 1948 - ARC (Addiction Research Center) CDAN – Committee on Drug Addiction and Narcotics
- 1962 - Dr. Vincent P. Dole, a specialist in metabolism at the Rockefeller University, became chair of the narcotics committee of the health research council of New York City. He read "the drug addict as a patient" by **Dr. Marie E. Nyswander (1956)**
 - Dr. Nyswander - a psychiatrist with extensive experience treating patients who were addicted to opioids.
 - She also believed that many would have to be maintained on opioids for extended periods to function *because a significant number of people who attempted abstinence without medication relapsed, in spite of detoxifications, hospitalizations, and psychotherapy*

MEDICATION *FOR* ADDICTION TREATMENT - HISTORY

- In 1965, the initial research project on methadone safety and efficacy was transferred to Manhattan General Hospital in New York City.
 - In general, the team found that patients' social functioning improved with time in treatment, as measured by elimination of illicit-opioid use and better outcomes
- Narcotic Addict Treatment Act of 1974, effectively limited methadone maintenance treatment to the context of the Opioid Treatment Program (OTP) (i.e., methadone clinic) setting.
- 1963 – Naltrexone first synthesized – Trials (mixed and approved in 1984 for OUD, 1995 for AUD)
- 1966 – Buprenorphine synthesized from thebaine
- 1996 – Approved for treatment of OUD in France; 2002 in US (DATA 2000)

MAT – EVIDENCE FOR AGONISTS

Methadone – full Mu agonist

- Fullerton CA, et al. Medication-assisted treatment with methadone: assessing the evidence. Psychiatric services in advance. November 18, 2013
 - Meta-analyses, systematic reviews, and individual studies of MMT from 1995- 2012.
 - **Nine studies** - High level of evidence for the positive impact of MMT on treatment retention and illicit opioid use, particularly at doses greater than 60 mg
 - Evidence suggests positive impacts on HIV risk behaviors, mortality, and criminality
 - MMT in pregnancy was associated with improved maternal and fetal outcomes

MAT – EVIDENCE FOR AGONISTS

Buprenorphine – partial Mu agonist (Suboxone, Zubsolv, Bunavail – Buprenorphine/Naloxone)

- Thomas CP, et al. Medication-assisted treatment with buprenorphine: assessing the evidence. Psychiatric services in advance. November 18, 2013
 - **Sixteen** adequately designed randomized controlled trials of BMT indicated a **high level of evidence for its positive impact on treatment retention and illicit opioid use.**
 - BMT was associated with less risk of adverse events than MMT.
 - BMT was also associated with improved maternal and fetal outcomes in pregnancy
 - Rates of NAS were similar for mothers treated with BMT and MMT during pregnancy, but symptoms were less severe with BMT. Latest studies show reduced LOS with BMT

MAT – EVIDENCE FOR AGONISTS

- Methadone and Buprenorphine - More studies/guidelines coming out frequently
 - D'Onofrio, et al JAMA 2015 - ED initiation of Buprenorphine
 - Increased attendance of outpatient treatment at 30 days
 - 78% in the buprenorphine group vs 37% patients in the referral group
 - The buprenorphine group also reported greater reductions in the average number of days of illicit opioid use
 - Dunlap, et al JAMA 2016 - JAMA Clinical Guidelines Synopsis: Clinical Management of Opioid Use Disorder
 - MAT is superior to withdrawal alone in multiple studies
 - Sordo, et al BMJ 2017 - Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies
 - Meta-analysis - 19 eligible cohorts, following 122,885 people treated with methadone over 1.3-13.9 years and 15831 people treated with buprenorphine over 1.1-4.5 years.
 - Retention in MMT and BMT is associated with substantial reductions in the risk for all cause and overdose mortality

MAT – EVIDENCE FOR AGONISTS

- Surgeon Generals Report
 - Abundant scientific data show that long-term use of maintenance medications successfully reduces substance use, risk of relapse and overdose, associated criminal behavior, and transmission of infectious disease, as well as helps patients return to a healthy, functional life.
 - Use of medications to treat addiction - controversial at times because of a longstanding misconception that methadone and buprenorphine are merely “substitute one addiction for another.”
 - This belief has reinforced scientifically unsound “abstinence-only” philosophies in many treatment centers and has severely limited the use of these medications.
- VA Clinical Practice Guideline For the Management of Substance Use Disorders
 - Strong recommendation for patients with OUD
 - Buprenorphine/naloxone or methadone in an opioid treatment program
 - For patients with OUD for whom opioid agonist treatment is contraindicated, unacceptable, unavailable, or discontinued and who have established abstinence for a sufficient period of time:
 - Extended-release injectable naltrexone (Vivitrol)

DETOX (Withdrawal management) VS MAINTENANCE

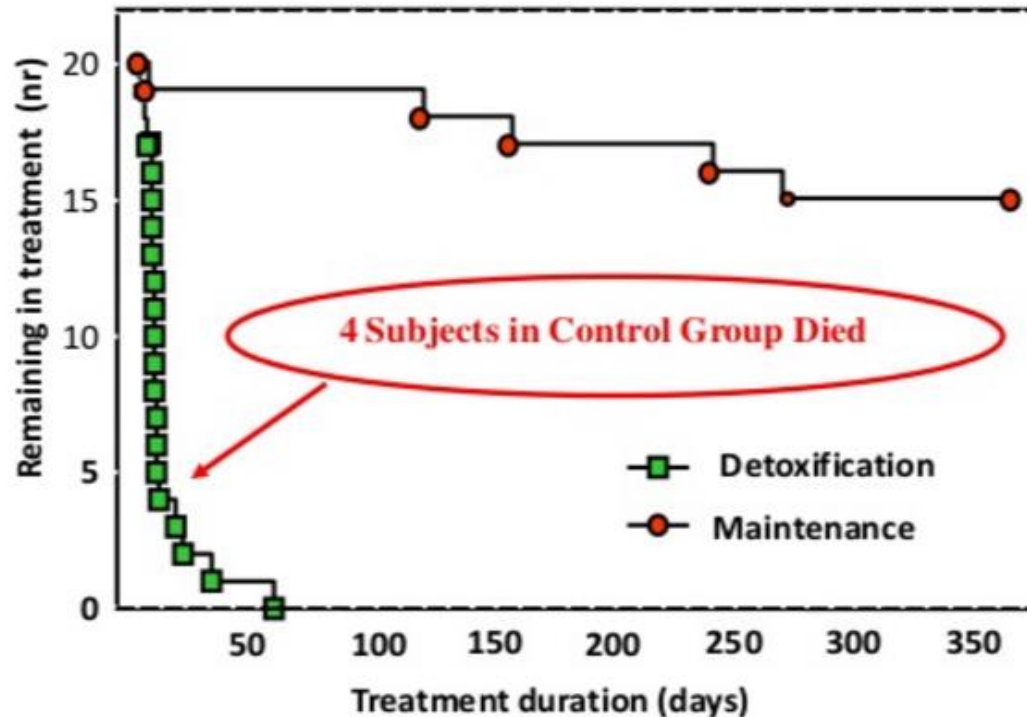
- There is NO GOOD EVIDENCE for Detoxification alone

Buprenorphine Treatment for Hospitalized, Opioid-Dependent Patients
A Randomized Clinical Trial

JAMA Internal Medicine August 2014 Volume 174, Number 8

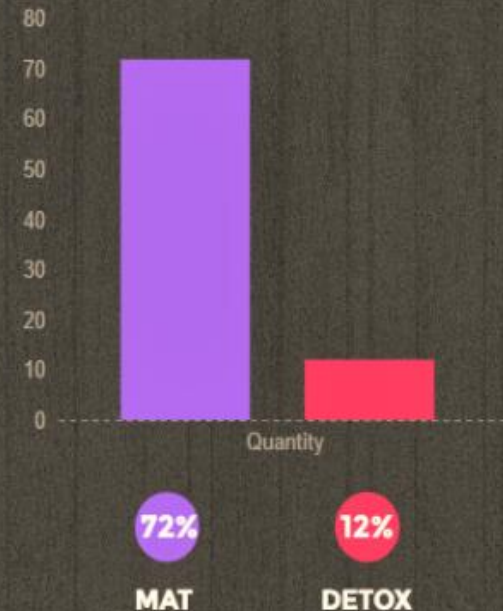
Buprenorphine vs. Placebo for Heroin Dependence

Kakko, Lancet 2003



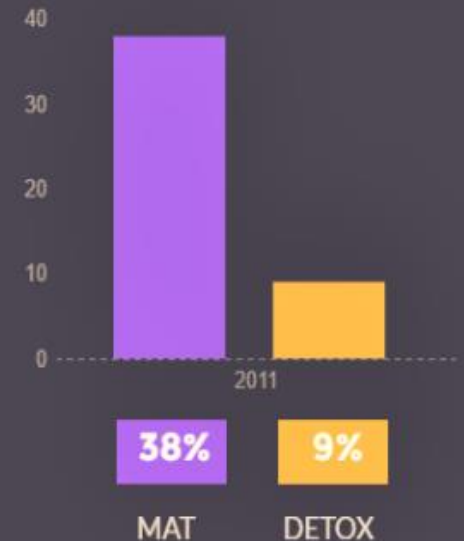
Rates of Treatment Continuation after discharge from Hospital

With detoxification alone and no continuation of MAT (medically assisted treatment), patients rarely ever continued their outpatient treatment plan



Cessation of Illicit Opioid Use

Rates of cessation of Illicit Opioid use at 6 month were much better with linkage to care and continuation of MAT than with detoxification alone



MAT – EVIDENCE FOR ANTAGONISTS

- Generally positive but sometimes mixed evidence
 - Generally recommended for “Highly Motivated Patients” – Revia (oral)
 - Extended-Release (Vivitrol) tends to have better compliance and abstinence rates
 - Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders – NEJM 2016, Lee J. et al
 - Time to relapse was significantly longer in the extended-release naltrexone group
 - 10.5 weeks versus 5.0 weeks
 - Several important secondary outcomes did not differ significantly between the groups: rates of cocaine, alcohol, and intravenous drug use and self-reported reincarceration
 - Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multi-centre, open-label, RCT. Joshua D Lee, et al 2017
 - In this population it is more difficult to initiate patients to XR-NTX than BUP-NX, and this negatively affected overall relapse. However, once initiated, both medications were equally safe and effective. Future work should focus on facilitating induction to XR-NTX and on improving treatment retention for both medications.

EVIDENCE FOR COAT – COMPREHENSIVE OPIOID ADDICTION TREATMENT

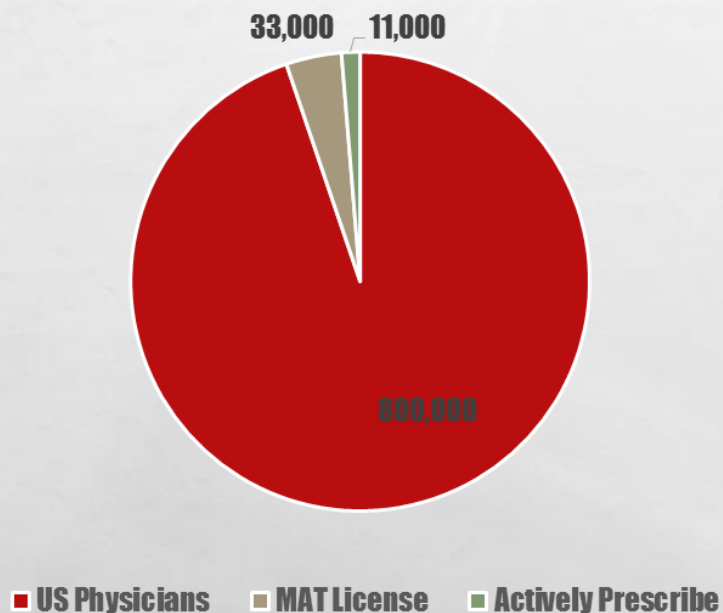
- EVERY RECOMMENDATION for MAT includes need for psychosocial interventions
 - ASAM, NIDA, SAMHSA, Surgeon General, VA Guidelines, etc
- Weiss, et al – Drug and Alcohol Dependence, 2014
 - Patients who had ever used heroin and received drug counseling in addition to buprenorphine/naloxone were more likely to be successful (abstinent or nearly abstinent)
- Lynch et al. Addiction Science & Clinical Practice, 2014
 - Patients receiving MAT (medically assisted treatment) plus addiction counseling had significantly lower total health care costs than patients with little or no addiction treatment (\$13,578 vs. \$31,055 = 56% reduction)
- JAM (Journal of Addiction Medicine) 2016 – A Systematic Review on the Use of Psychosocial Interventions in Conjunction With Medications for the Treatment of Opioid Addiction. Dugosh, et al.
 - Results generally support the efficacy of providing psychosocial interventions in combination with medications to treat opioid addictions, although the incremental utility varied across studies, outcomes, medications, and interventions.
 - Unclear as to the type of therapy that is superior and in what patient population

NO QUESTION THAT OPIOID AGONIST THERAPY *ALONE* REDUCES MORTALITY – HARM REDUCTION

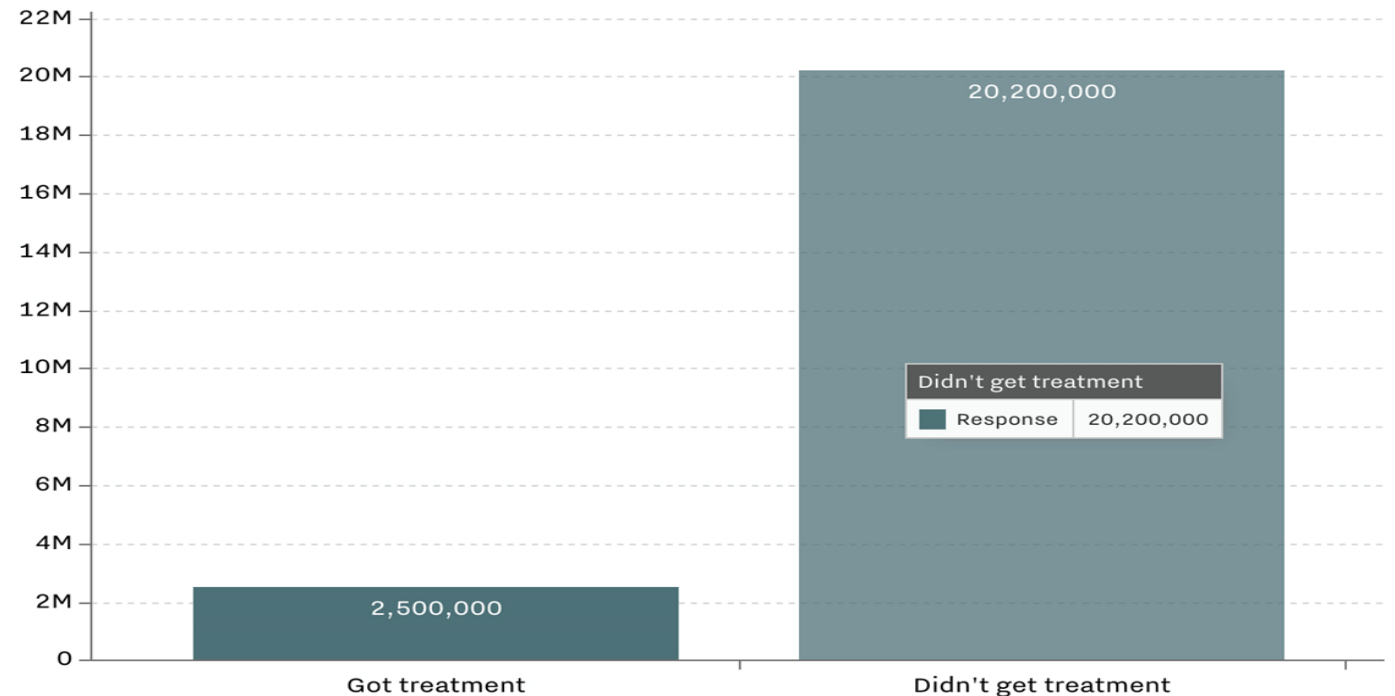
TREATMENT NEED

- Approx. 10-20% of patients with illicit drug use receive treatment
 - Estimated 5-10X increase in need for addiction treatment

MAT Providers



How many people who meet the definition of a drug use disorder got treatment?



TREATMENT IMPACT

- For every \$1.00 spent on treatment:
 - The costs of crime and lost productivity are reduced by \$7.46
 - The total societal and medical costs are estimated to be reduced by as much as \$18.54
- Patients with substance use disorder often use a disproportionate amount of healthcare in very inefficient ways.
 - Mean annual direct health care costs for opioid abusers were more than 8 times higher than for nonabusers (\$15,884 versus \$1,830, respectively) – White, 2010
- Reminder - patients receiving MAT (medically assisted treatment) plus addiction counseling had significantly lower total health care costs than patients with little or no addiction treatment (\$13,578 vs. \$31,055 = 56% reduction); As much as 90% reduction has been seen in other studies.

SUMMARY

- MAT works and it saves lives
 - Abstinence from opioids and mortality reduction
- COAT is best practice
 - Further research needed as to what type of psychosocial intervention is best
- We have a long way to go to turn the tide on opioid epidemic
 - Hope – new evidence coming out often
 - New medication and therapies are promising – Sublocade, Bridge, etc

LIST OF RESOURCES

- **ASAM - AMERICAN SOCIETY OF ADDICTION MEDICINE**
- **COPE - COALITION ON PHYSICIAN EDUCATION IN SUBSTANCE USE DISORDERS**
- **SAMHSA – SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION**
- **NIDA – NATIONAL INSTITUTE ON DRUG ABUSE**
- **HAMILTON COUNTY AREA– INJECTHOPE.COM**
- **SURGEON GENERALS REPORT ON ALCOHOL, DRUGS, AND HEALTH**
- **VA CLINICAL PRACTICE GUIDELINE ON SUBSTANCE USE DISORDER TREATMENT**
- **MULTIPLE ARTICLES AS REFERENCED IN THE PRESENTATION**