

Addiction 101: Understanding the Neurobiology of Addiction

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Family Medicine

Hospice and Palliative Medicine

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Special Thanks to:

- Nicole T. Labor, DO, BCFP, BCABAM
- Medical Director, OneEighty, Wooster, OH
- Fellowship Director of Addiction Medicine, SummaHealth, Akron, OH
- Associate Clinical Professor of psychiatry and family and community medicine, NEOMED

Objectives

- Define addiction and chemical dependence
- Understand the neurobiology of addiction
- Understand the most recent data on the Ohio opioid epidemic and its implications
- Understand how the Pandemic has effected the opioid epidemic
- Understand the criteria of Substance Use Disorder (SUD) and its evidence based treatment
- Understand treatment of addiction

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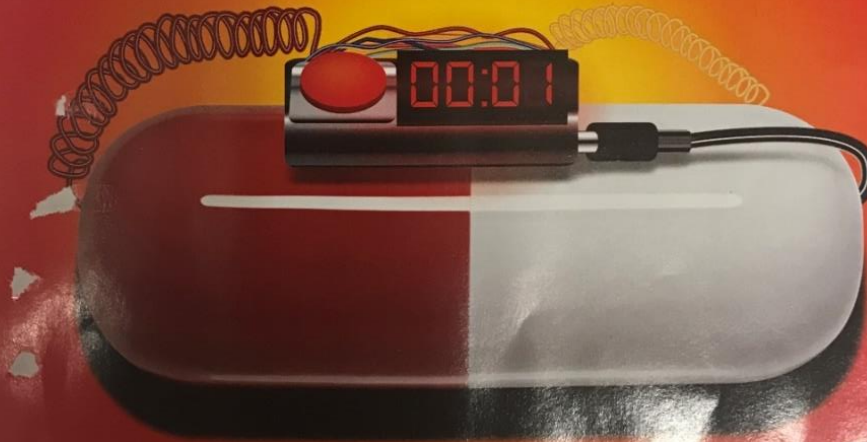
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OPIOID CRISIS

How physicians can help patients, community



Law enforcement's
view of the epidemic

A patient's path
to recovery

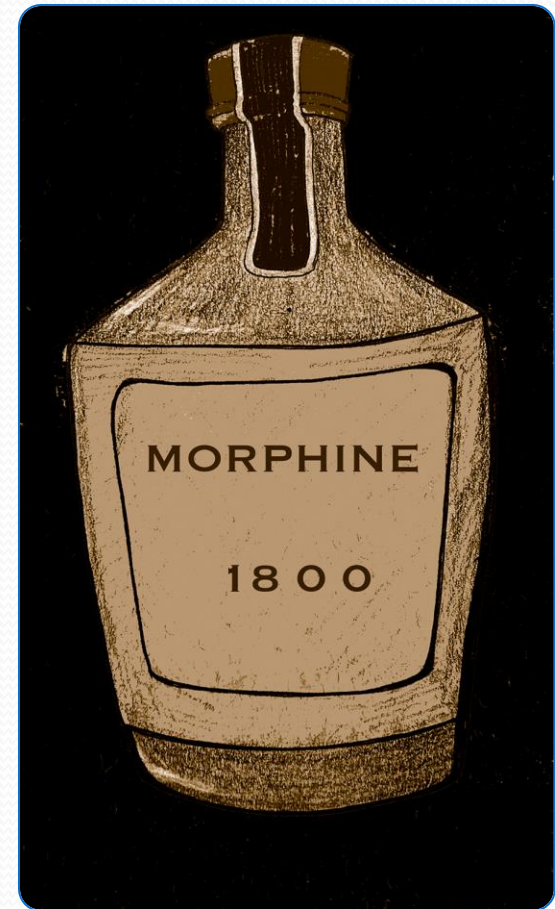
A doctor's
approach



Addiction: It Isn't a New Phenomenon


Prior “Opioid” Epidemics

1. Late 1800s: Morphine
 - Mainly middle class
 - Female > Male
2. Early 1900s: Heroin (pharmaceutical grade)
 - First generation Italians, Jews, Irish
 - Male > Female
3. 1950s-1970s- Heroin (illicit)
 - African American/Latinos
 - Male > Female




Other addiction epidemics

Crack cocaine: In 1985, cocaine-related hospital emergencies rose by 12 percent, from 23,500 to 26,300. In 1986, these incidents increased 110 percent, from 26,300 to 55,200. Between 1984 and 1987, cocaine incidents increased to 94,000.



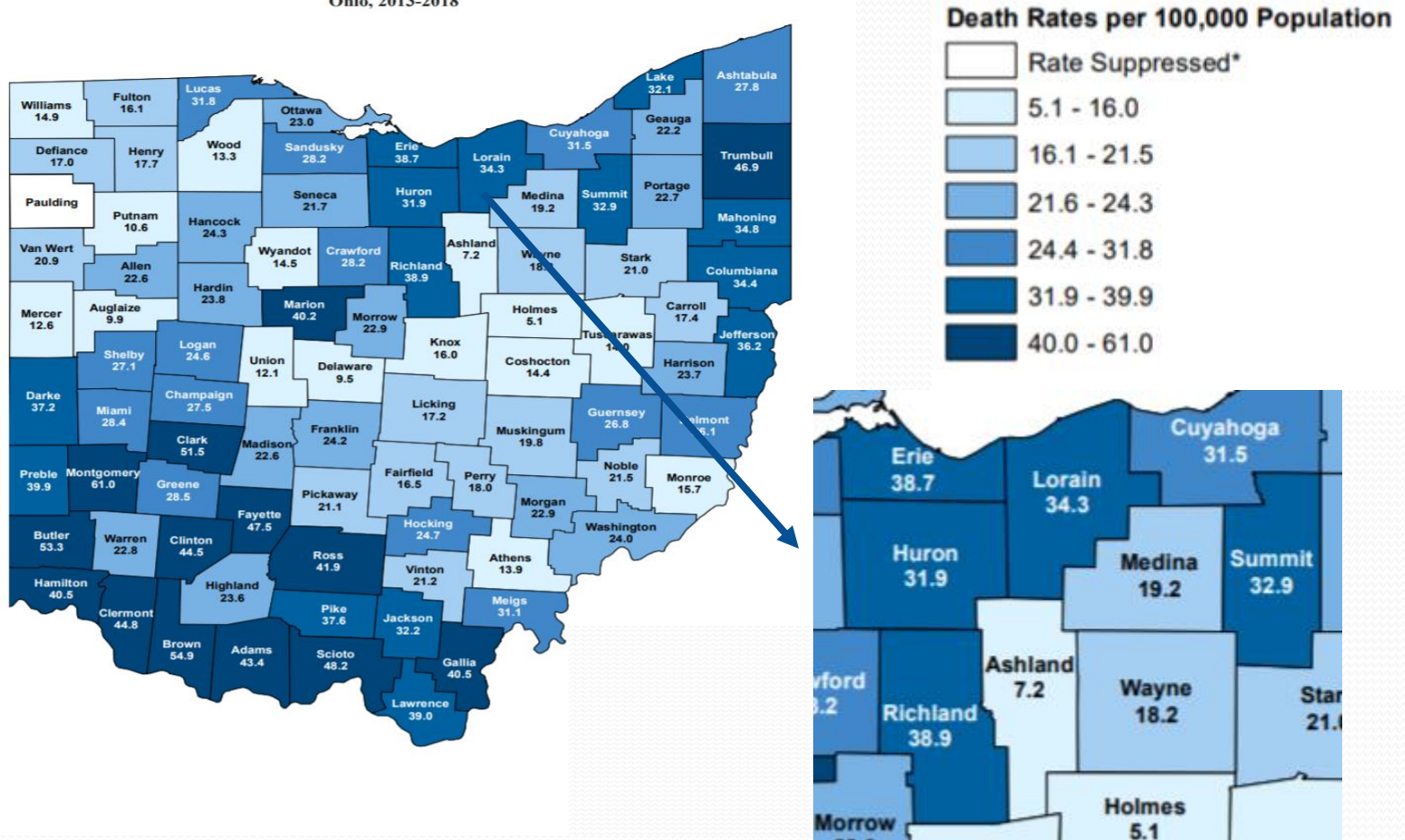
Methamphetamine: The **Combat Methamphetamine Epidemic Act of 2005 (CMEA)** is federal legislation enacted in the United States on March 9, 2006, to regulate, among other things, retail over-the-counter sales of following products because of their use in the manufacture of illegal drugs: ephedrine, pseudoephedrine, phenapropanolamine



Bath Salts: In October 2011, the DEA used its administrative powers to institute an emergency but temporary one-year ban on the three basic bath-salt chemicals, declaring them Schedule 1 substances. Possession can now lead to a four-year federal felony sentence.

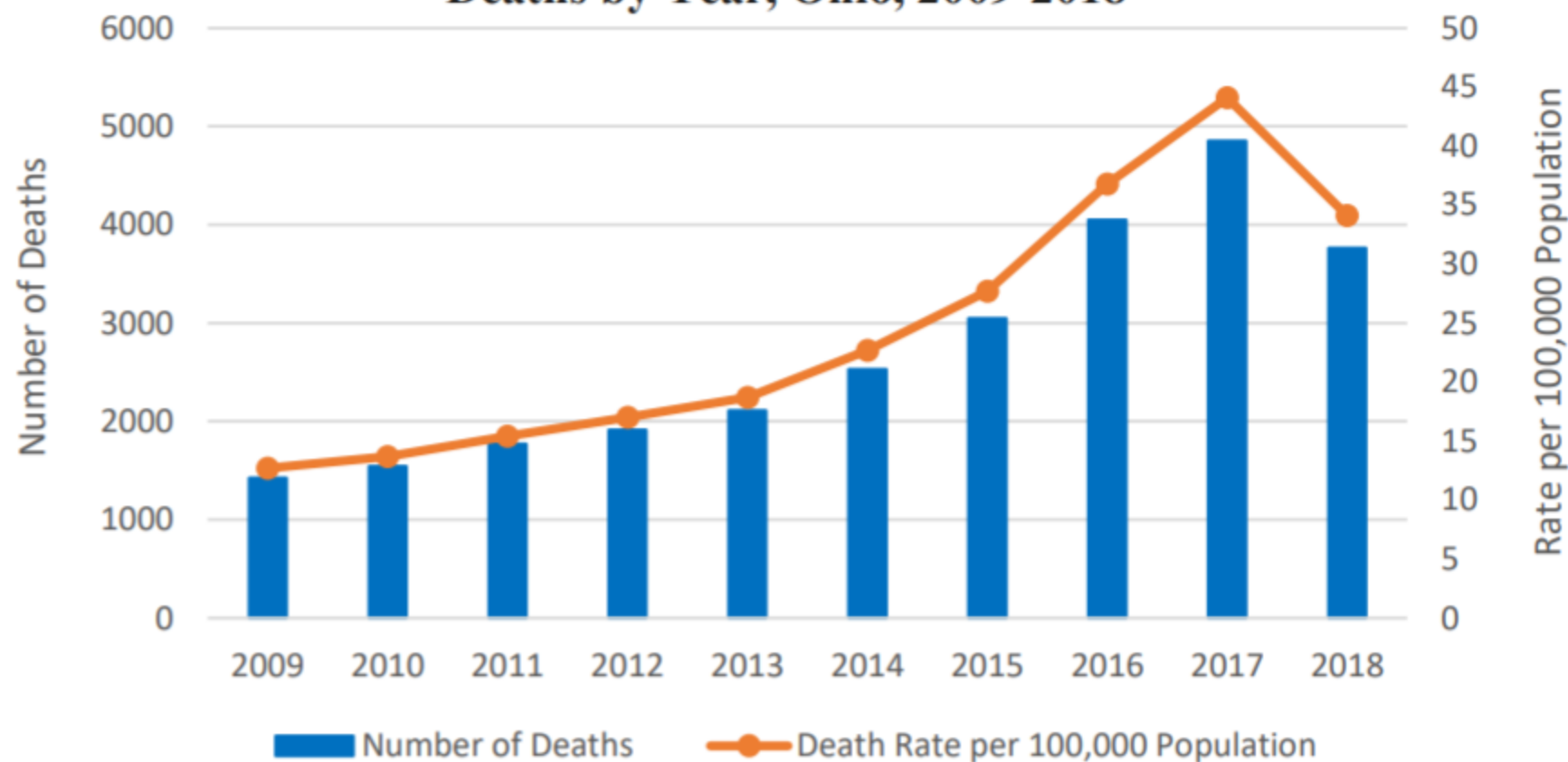
ODH annual opioid epidemic update for 2018

Figure 12. Average Age-Adjusted Rate of Unintentional Drug Overdose Deaths by County, Ohio, 2013-2018



<https://www.odh.ohio.gov/-/media/ODH/ASSETS/Files/health/injury-prevention/doverdose18/ODH-2017-Ohio-Drug-Overdose-Report.pdf?la=en>

Figure 1. Number and Age-Adjusted Rate of Unintentional Drug Overdose Deaths by Year, Ohio, 2009-2018



Ohio's opioid overdose deaths

- In 2007, unintentional drug poisoning became the leading cause of injury death in Ohio, surpassing motor vehicle crashes for the first time on record. This trend has continued through 2018.
- In 2018, 3,764 people died of unintentional drug overdoses, a decrease of 1,090 compared to 2017 and the lowest number of deaths since 2015.
- Fentanyl was involved in nearly 73% of overdose deaths in 2018, often in combination with other drugs. That percentage was up from 71% in 2017, 58% in 2016, and nearly 38% in 2015.
- In 2018, fentanyl was involved in nearly 80% of all heroin-related overdose deaths, 74% of all cocaine-related overdose deaths, and 67% of all psychostimulant/methamphetamine-related overdose deaths. Carfentanil was involved in 75 fentanyl-related overdose deaths in 2018 compared to 1,010 in 2017.
- The number of overdose deaths involving natural and semi-synthetic opioids (e.g., oxycodone and hydrocodone) declined 42% from 2017 to 2018.

Figure 10. Number of Unintentional Drug Overdose Deaths Involving Select Drugs by Year, Ohio, 2009-2018

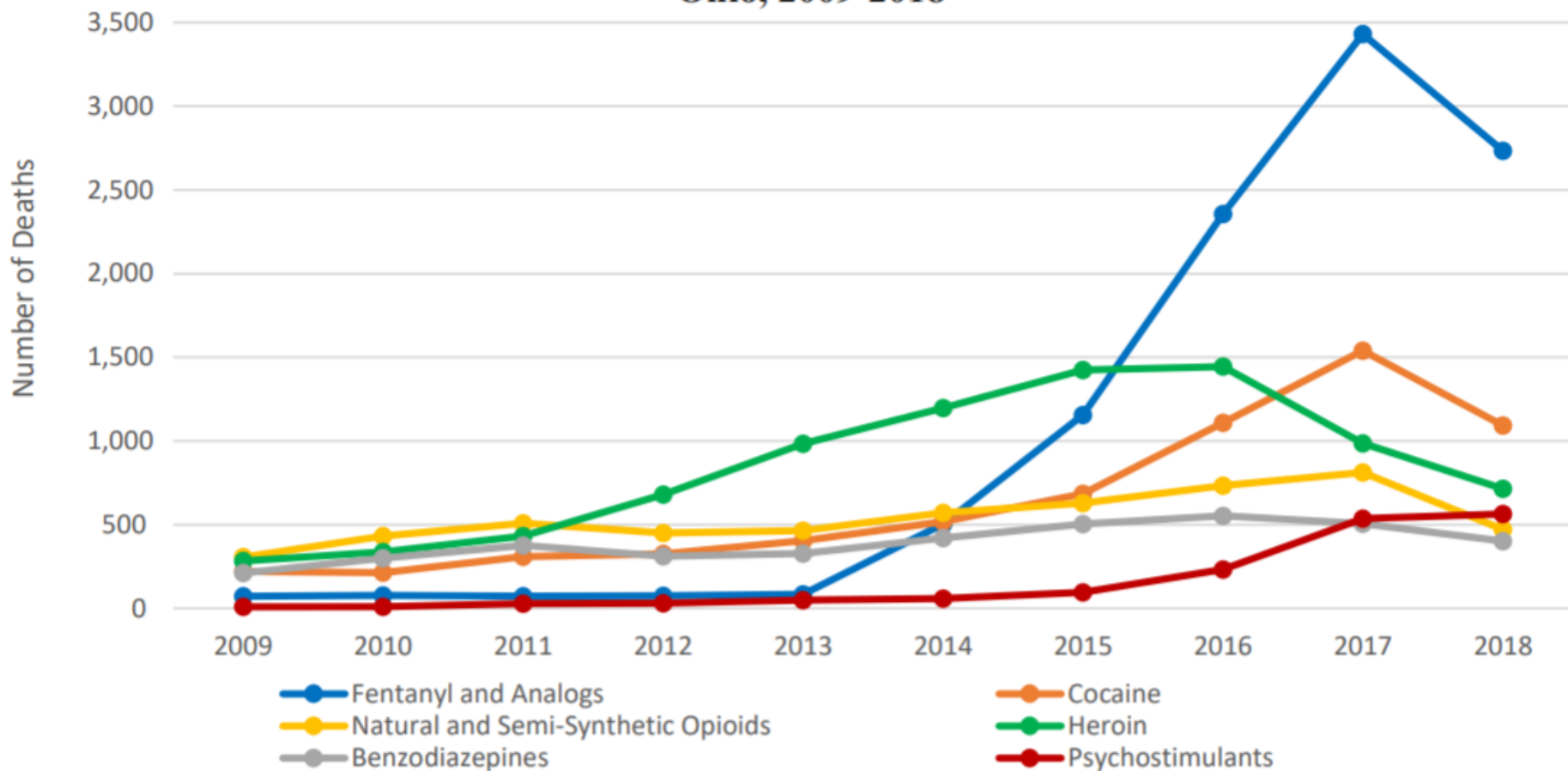
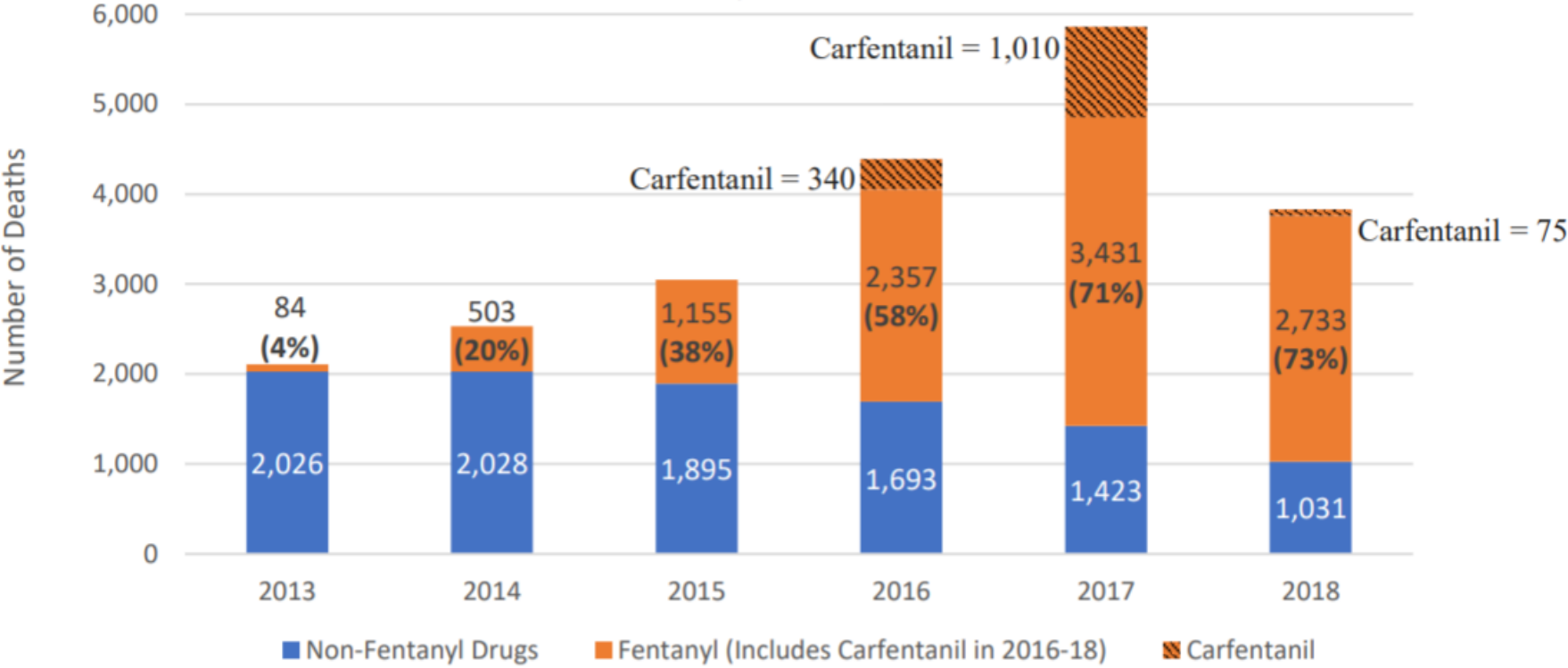


Figure 8. Number and Percentage of Fentanyl-Related Unintentional Drug Overdose Deaths by Year, Ohio, 2013-2018



US overdose deaths appear to rise amid coronavirus pandemic

By MIKE STOBBE and ADRIAN SAINZ October 20, 2020



Drug epidemic and the Pandemic

- Experts blame the pandemic, which has left people stressed and isolated, disrupted treatment and recovery programs, and contributed to an increasingly dangerous illicit drug supply.
- Dr. Mark Tyndall, a University of British Columbia medical professor who researches overdose deaths, said the pandemic interfered with heroin importation. Meanwhile, meth and fentanyl have continued to proliferate.
- “On the whole, COVID had further deteriorated the illegal drug supply. Made it even deadlier,” Tyndall said. “That’s one reason why things are worse. The risk of you injecting poison is higher than it was before COVID.”
- As stay-at-home orders and other measures were put in place, counseling sessions moved online.
- “It’s not the same as being in a place with that depth of connection that we have from in-person engagement, because connectedness is one of the drivers of recovery,” said Robert Pack, of East Tennessee State University.
- “Being surrounded by good people, sober people, is the most important thing for a drug addict in recovery,” Wyatt said. “When that’s gone, trouble is going to happen.”

<https://apnews.com/article/virus-outbreak-technology-pandemics-kentucky-22e4c7213a3f5a857cd50b8489325d9a>

Chemical Dependence prevalence

- 10-14% lifetime prevalence
- 15-18% Primary care outpatients
- 25% primary care inpatient
- 40% trauma inpatient
- 40-70% psychiatric inpatient – not because psychiatric illness causes addiction, but because of shared genetics

Addiction morbidity and mortality: *an unspeakable toll*

- Smoking kills 33% and maims 33% of users
- Other addictions:
 - Up to a 700% increased annual mortality risk
 - 50% divorces, 70% domestic violence, > 70% of child abuse/neglect
 - Physical trauma
- Not to mention the morbidity of lost productivity, disability, medical complications, etc...

Current standard of care – not good!

- Most affected patients are missed
 - 50% on internal medicine inpatient
 - >80% on surgery inpatient
 - ~90% missed in outpatient primary care
- Less than half of diagnosed have a treatment plan
- Frequent prescribing of controlled drugs (EPD)
- Little disease monitoring
- Much patient blaming or enabling



Chemical Dependence

- The intermittent inconsistent repetitive ***loss of control*** over the use of euphoria producing drug (EPD), resulting in repetitive adverse consequences.
- EPD's:
 - Opioids
 - Stimulants
 - Sedative-hypnotics
 - Cannabinoids
 - Other – PCP, ketamine, etoh

Public Policy Statement: Definition of Addiction

ASAM 2011

Short Definition 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.

Public Policy Statement: Definition of Addiction

ASAM 2011

Short Definition of Addiction

- This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other **chronic illnesses**, addiction often involves cycles of *relapse and remission*. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

Substance Use Disorder DSM-V

TABLE 1:

DSM-5 CRITERIA FOR SUBSTANCE USE DISORDER AND SEVERITY SCALE

1. Hazardous use;
2. Social/interpersonal problems related to use;
3. Neglected major roles to use;
4. Withdrawal;
5. Tolerance;
6. Used larger amounts/longer;
7. Repeated attempts to quit/control use;
8. Much time spent using;
9. Physical/psychological problems related to use;
10. Activities given up to use;
11. Craving.

Substance use disorder severity:

Mild: 2–3 criteria

Moderate: 4–5 criteria

Severe: 6 or more criteria

Euphoria Producing Drugs- EPD's

- EPD's include: opioids, stimulants, sedative-hypnotics, cannabinoids, EtOH, and phencyclidine (PCP)
- Very different substances
- Totally different primary brain effects
- ALL produce an acute surge of dopamine from the midbrain to the fore-brain
- Dopamine surges mediate addictive disease

The Pleasure Centers Affected by Drugs

- **Alcohol and sedatives-hypnotics**: benzo, barbituates, soma, butalbital, pregabalin, zolpidem, etc.
- Affect not only the basic structures of the reward circuit, but also several other structures that use GABA as a neurotransmitter. GABA is a widespread neurotransmitter in the cortex, cerebellum, hippocampus, amygdala, and the superior and inferior colliculi

The Pleasure Centers Affected by Drugs

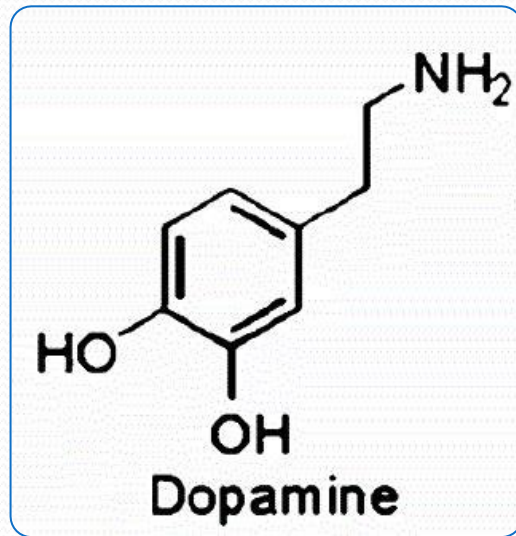
- **Opiates / Opioids**
- Act on the central structures of the reward circuit (VTA and nucleus accumbens), but also on other structures that are modulated by endorphins – including the amygdala, the locus coeruleus, the arcuate nucleus, and the periaqueductal grey matter – which influences dopamine levels indirectly. Opioids also effect the thalamus, which would explain their analgesic effects.

The Pleasure Centers Affected by Drugs

- **Cocaine and stimulants** – methamphetamine, ecstasy, bath salts, prescribed stimulants.
- Concentrate in the central link of the reward circuit (the VTA and the NA). These areas contain especially high concentrations of dopaminergic synapses , which are the preferred target of these drugs.

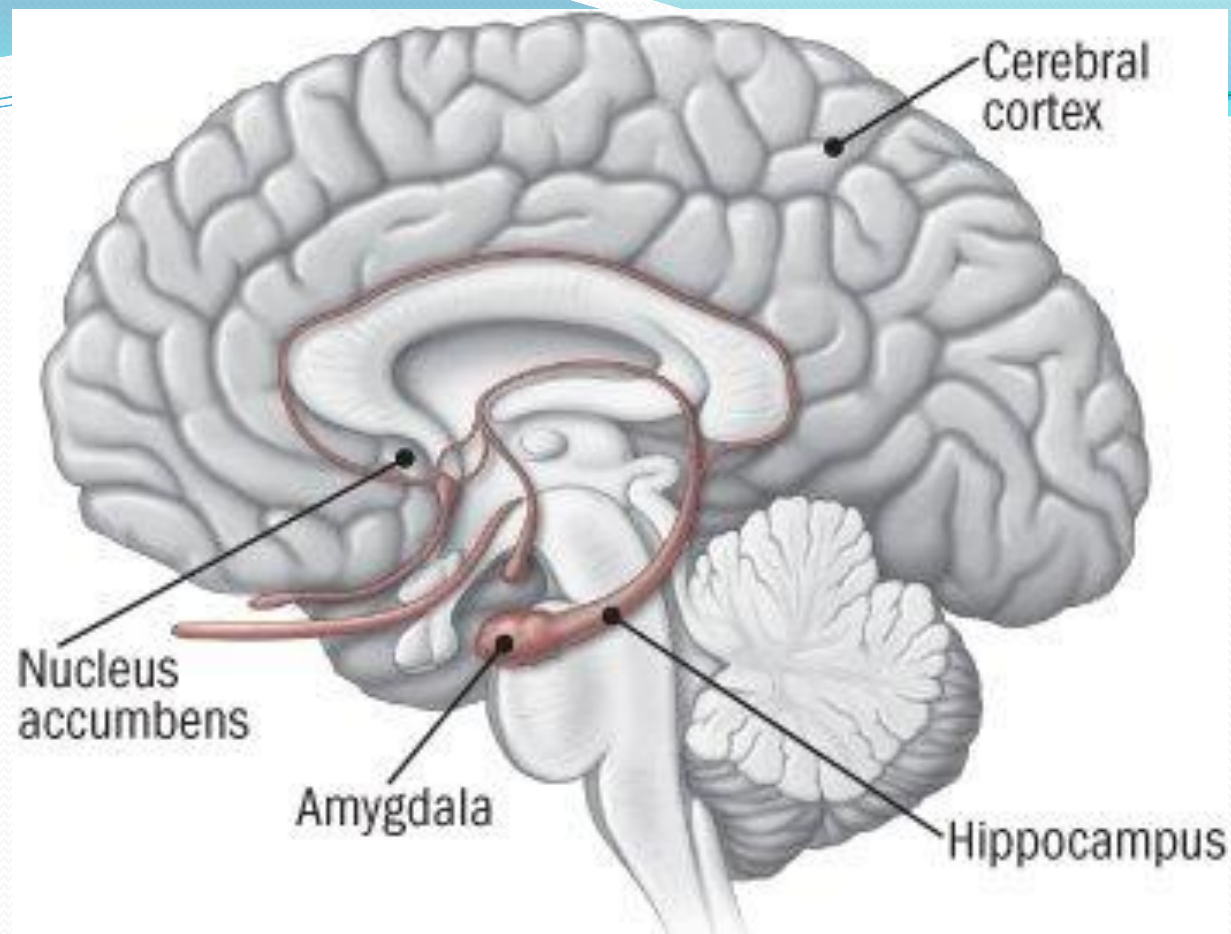
The Pleasure Centers Affected by Drugs

- Cannabinoids, marijuana, THC, marinol, synthetic cannabinoids – “spice”, “K2”, etc
- Cannabinoids concentrate chiefly in the Ventral tegmental area (VTA) and the Nucleus Accumbens (NA), but also in the hippocampus, caudate nucleus and the cerebellum
- Hippocampus effects may explain memory problems that can develop, and cerebellum effects might explain loss of coordination and balance in those who abuse cannabinoids



- All drugs of abuse and potential compulsive behaviors release Dopamine
- Dopamine is first chemical of a pleasurable experience - at the heart of all reinforcing experiences
- DA is the neurochemical of salience (it signals survival importance)
- Tells the brain this is “better than expected”

Addiction Neurotransmitter #1: Dopamine

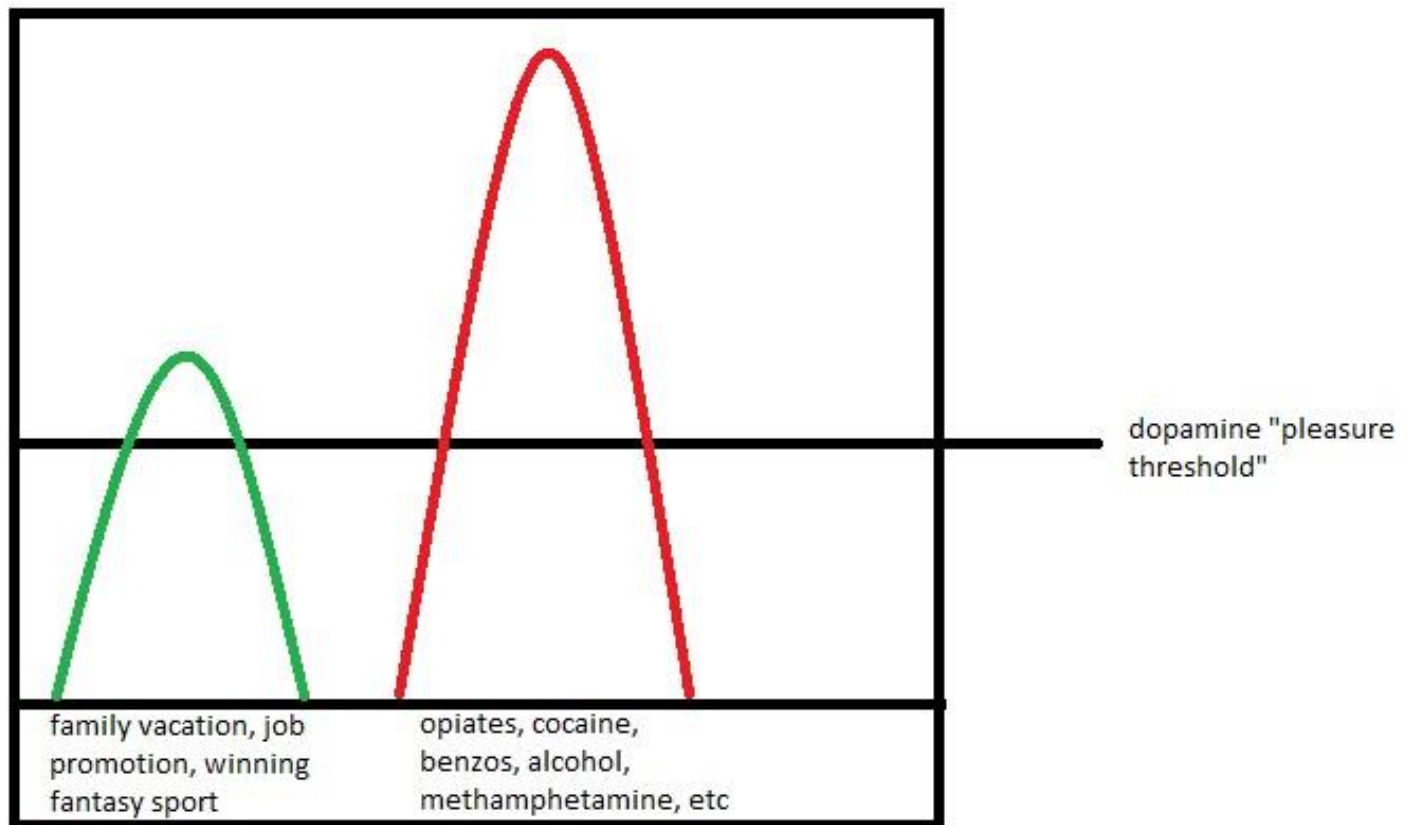


EPD's provide a shortcut to the brain's reward system by flooding the nucleus accumbens with dopamine. The hippocampus lays down memories of this rapid sense of satisfaction, and the amygdala and VTA creates a conditioned response to certain stimuli associated with drug use

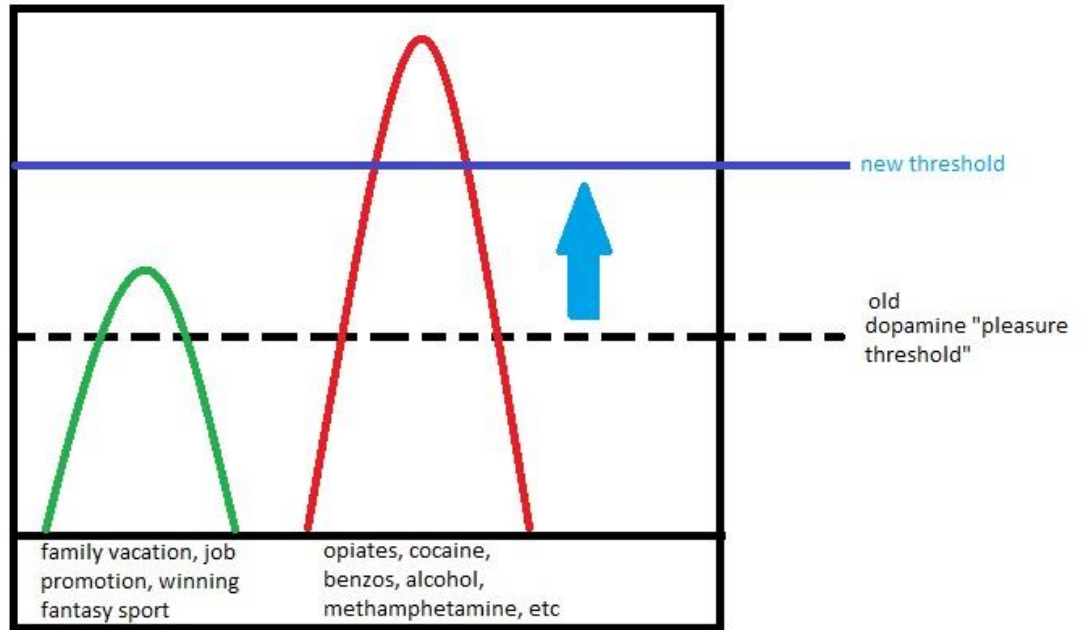
Neurobiology of Addiction

- **Dopamine** not only contributes to the experience of pleasure, but also plays a role in learning and memory—two key elements in the transition from liking something to becoming addicted to it.
- Dopamine interacts with another neurotransmitter, **glutamate**, to take over the brain's system of reward-related learning. This system links activities needed for human survival (such as eating and sex) with pleasure and reward.
- The reward circuit in the brain includes areas involved with motivation and memory as well as with pleasure. EPDs stimulate the same circuit—and then overload it.
- Repeated exposure to an EPDs causes nerve cells in the nucleus accumbens and the prefrontal cortex to communicate in a way that couples liking something with wanting/needing for survival, in turn driving us to go after it. This process motivates us to take action to seek out the source of pleasure.

The Brain has a pleasure “Set Point”



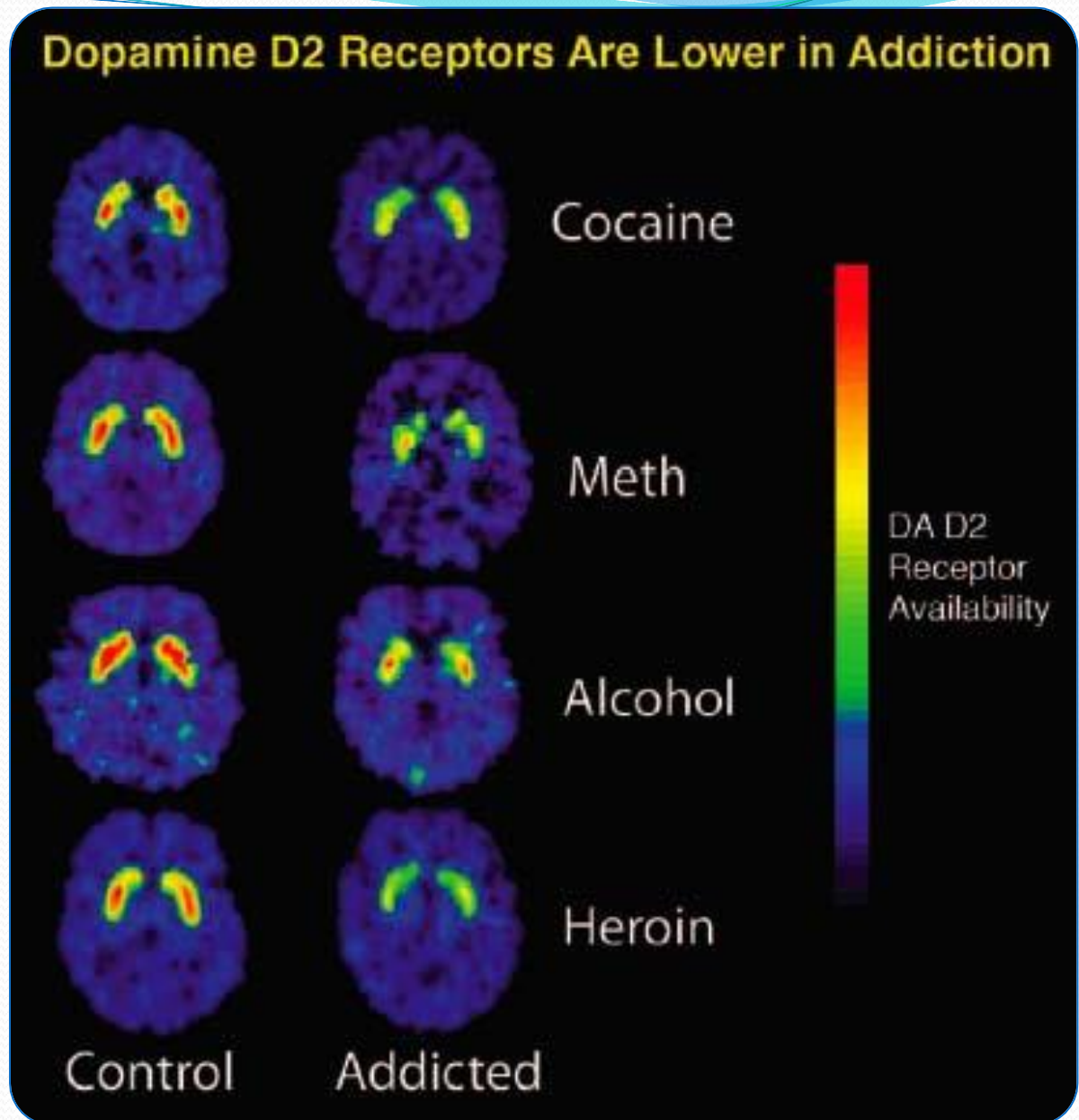
Increased
drug use
reset
the brain's
pleasure "set
point"



Neurobiology of Addiction

- Compulsion and drive for the EPD takes over. The memory of the desired pleasure and the need to recreate it persists. The normal machinery of motivation in the mid-brain no longer functionings.
- The hippocampus and the amygdala store information about environmental cues associated with the EPD. These memories help create a conditioned response—intense craving—whenever the person encounters those environmental cues.

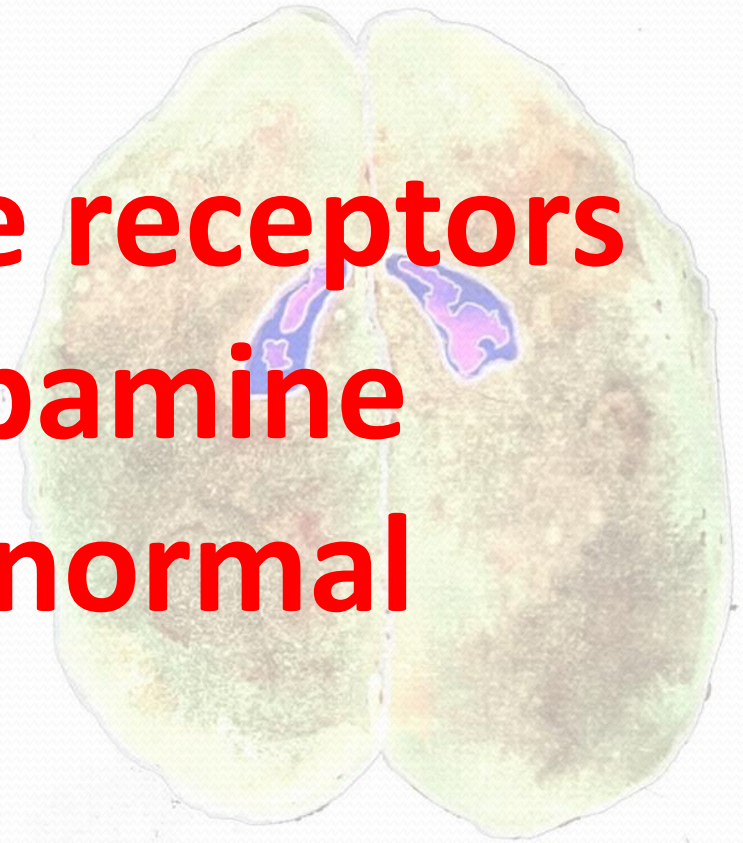
Midbrain changes in D2 receptors



**Fewer dopamine receptors
means more dopamine
needed to feel “normal
pleasure”**



control

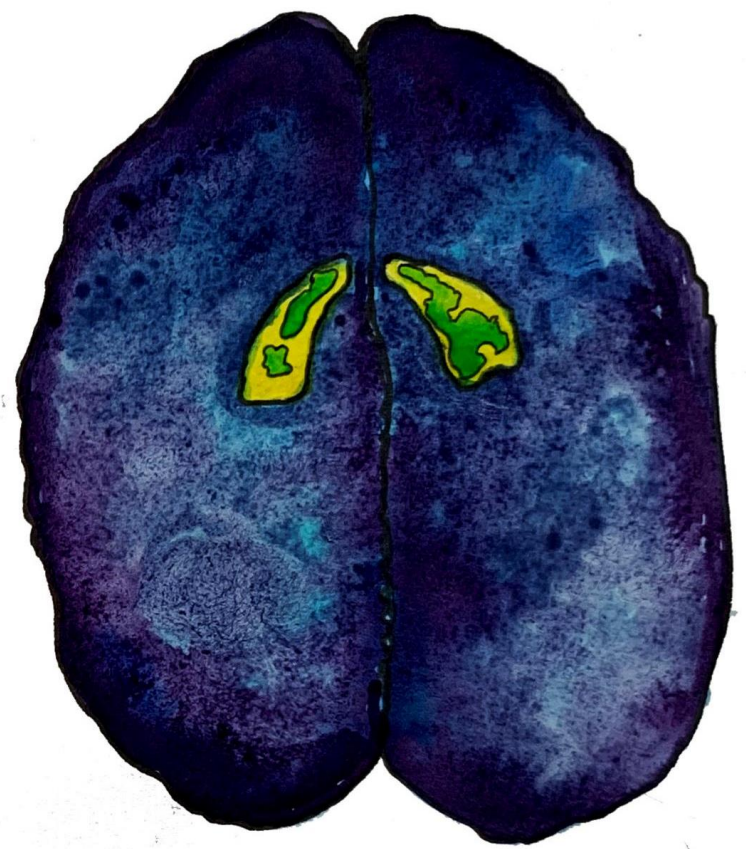


addicted



SHOW THE INDIVIDUAL THEIR DRUG OF CHOICE WHILE IN FUNCTIONAL MRI...

- The non-addict will show activity in the frontal cortex
 - THINKING about how the drug is “good” or “bad”
- The addict will show activity in the midbrain and very little activity in the frontal cortex
 - CRAVING/SURVIVAL



Cortex changes

SO WHAT'S GOING ON IN THE CORTEX?

- SKILL SETS ARE BUILT OVER TIME, WITH PRACTICE
 - THINK OF A PATH THROUGH THE WOODS
- DRUGS – cause MALADAPTIVE COPING MECHANISMS to REPLACE EXISTING PATHWAYS AS THEY ARE DEEMED ‘MORE APPEALING’
 - THINK: INSTANT, HIGHLY REWARDING
- EXISTING PATHWAYS (IF THEY WERE PRESENT AT ALL) DETERIORATE IN FAVOR OF THE HIGH DOPAMINE COPING
 - CAN'T ACCESS THEM EASILY



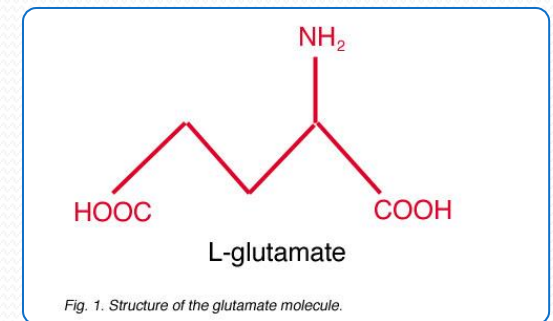
People dying of thirst in the desert will risk losing everything they value for a drink of water → this is the midbrain in action shutting down the frontal cortex in an effort to SURVIVE

SUPER REWARDS BECOME EQUIVELANT WITH SURVIVAL

Addiction Neurotransmitter #2: Glutamate

THE EXECUTIVE ASSISTANT TO DOPAMINE

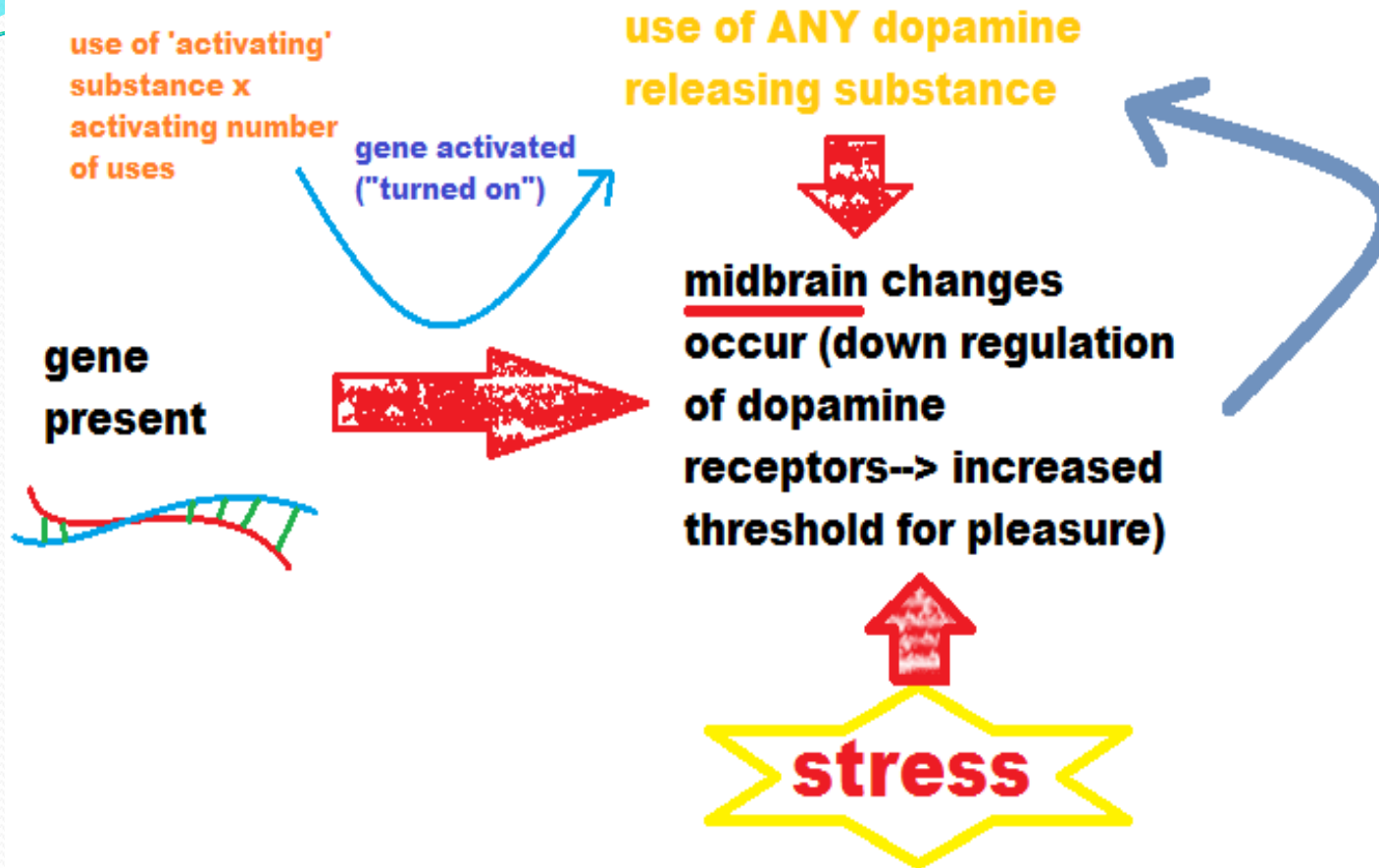
- The most abundant neurochemical in the brain
- Critical in memory formation & consolidation
- EPD's effect Glutamate, which preserves drug memories and creates drug cues (triggers, people, places and things)
- And ... glutamate is the neurochemical of "motivation" (it initiates drug seeking)



PEOPLE and PLACES and THINGS

Addiction as a familial disorder

- Aristotle – “drunken women bring forth children like themselves”
- Plutarch- “one drunk begets another”
- Every study since the late 1800’s shows higher rates of addiction in relatives of alcoholics.
- 3-4 times higher rate in 1st degree relatives
- Genetics vs environmental and family influences?



How genetics may play a role in addiction

What causes Relapse?

1. Brief exposure to **ANY abusable drug OR compulsive behavior** (DA release and DA receptor down regulation)
2. Stress (CRF release and DA receptor down regulation)
3. Exposure to drug cues (people, places and things)

THREE THINGS ARE
KNOWN TO CAUSE
RELAPSE IN
HUMANS

Craving

- Increased stress = increased pleasure threshold = increased need for dopamine = midbrain thinks it is dying = CRAVING
- CRAVING is a physiological response to a neurochemical deficiency resulting in symptoms including sweating, stomach cramps, obsession, increased respirations, etc.
- CRAVING – addict loses control. Willpower is useless.
 - No person can choose to crave or not.
 - You don't actually have to have drug use for the defective physiology of addiction to be active



A vertical traffic light with three circular lenses. The top lens is red, the middle lens is yellow and is currently illuminated, and the bottom lens is green. The traffic light is set against a background of light blue and white wavy lines.

And the 'reason' becomes the
'green light'

And willpower is rendered useless

Once there is a “reason”, suddenly behaviors become “justified”



LYING/STEALING



MANIPULATING



REASONING/MAKING
EXCUSES



RATIONALIZATION



JUSTIFICATION



This is what “WE” see

ONCE THE MALADAPTIVE BEHAVIORS BECOME HABITUAL COPING SKILLS, THOSE SKILLS BECOME PART OF THE DISEASE



**The need for instant
gratification**

And subsequent inability to wait or
practice



**Needing a pill or chemical
for EVERYTHING- while
OTC sleep medications have
few addictive properties,
the BEHAVIOR of needing
something to make the
body do what it should
naturally learn to do, IS
addictive**



**Looking for reasons to avoid
recovery related behaviors
and activities**

Seeking reasons to use

Addiction Treatment



How do we best treat addiction?



Treat most acute medical issues first



Detox



(quiet the midbrain with medication or abstinence)



Restore cortex



IT ALL BEGINS WITH DETOX

- ALCOHOL/BENZOS
 - Withdrawal can cause death- DT's
- OPIATES
 - Withdrawal is not life threatening but may feel like it!
 - Indirect death
- EVERYTHING ELSE
 - No death, but still stinks



Tasks to treat addiction

QUIET THE MIDBRAIN

Abstinence. Medication.

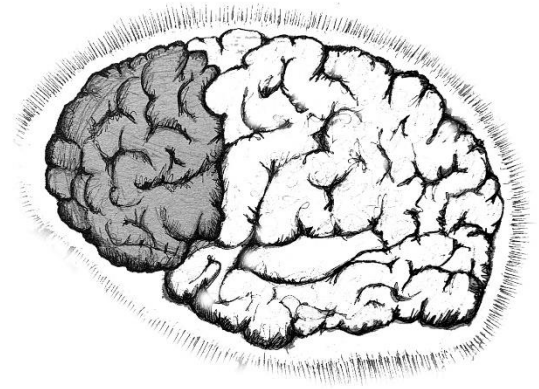


BUILDING THE CORTEX

Traditional treatment. 12 step groups.
Spiritual growth



The Goal of
treatment-
regardless of the
drug or length of
use is to RESTORE
THE CORTEX



THE CORTEX GOES TO THE GYM

COGNITIVE SKILL SETS

- We must build/rebuild pathways for appropriate *coping skills*
- We must provide tools to combat maladaptive coping skills
- We must provide a framework for continued treatment that supports a chronic disease model

SPIRITUAL SKILL SETS

- We must help them find personal meaning in other things
- We must help them develop emotional relationships with healthy PEOPLE
- We must help them develop a sense of self INDEPENDENT OF THE DRUG
- WE MUST HELP THEM FIND PURPOSE

Cognitive Behavior Therapy (CBT)

- Individual
- Group Based
- Recognize and stop negative patterns of behavior
- Become aware of how stressors, feelings, situations lead to substance use
- Learn to avoid situations
- Reframe thoughts
- Cope with cravings
- Inpatient or outpatient
- Requires some degree of cognitive abilities

The Tasks of Addiction Treatment:

To give the addict workable, credible tools to proactively manage stress and decrease craving

1. COPING SKILLS
2. STRESS RELIEF
3. SAFE ENVIRONMENT
4. SOCIAL SUPPORTS

The Tasks of Addiction Treatment:

For each individual addict,
find the thing which is more
emotionally or spiritually
meaningful than the drug-
and displace the drug with it

1. SPIRITUAL GROWTH
2. PERSONAL DEVELOPMENT

A TOOLBOX FOR CHANGE

CORTEX

- COUNSELING
 - Important, but also need group therapy
- 12 STEP
 - 'SPIRITUAL GROWTH'
- THRIVE
 - WELLNESS. SELF-CARE.

MIDBRAIN

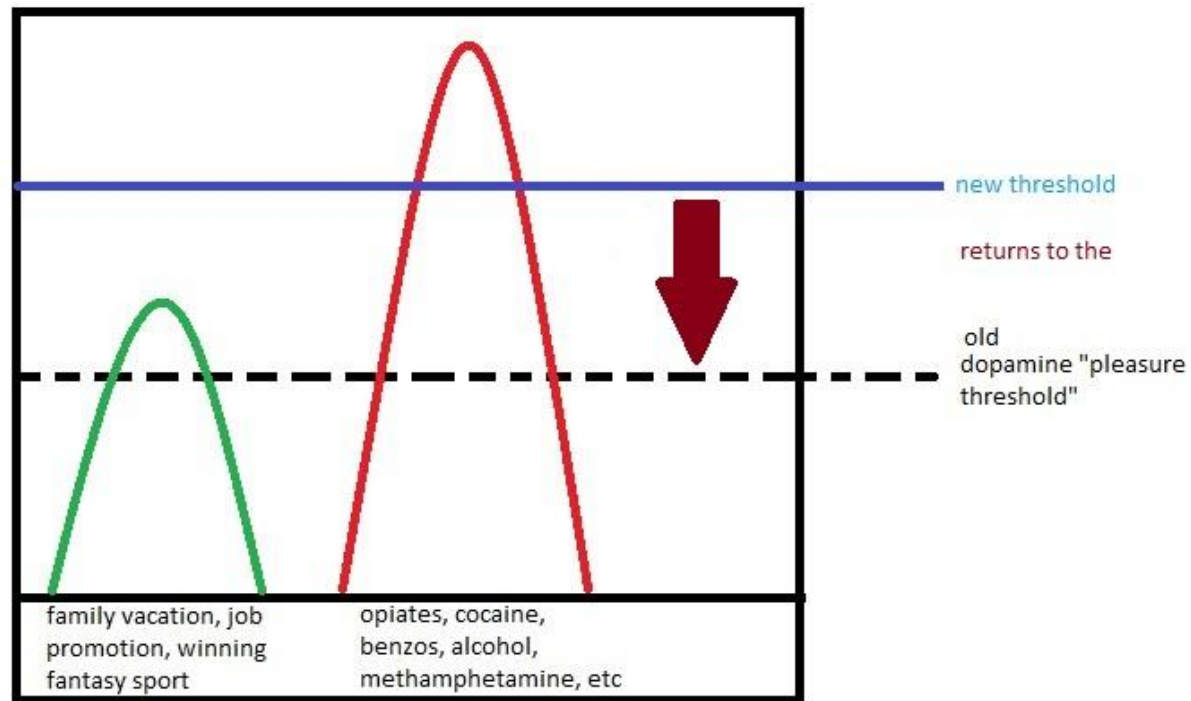
- ABSTINENCE
- MEDICATION ASSISTED TREATMENT
 - As in, TREATMENT ASSISTED BY MEDICATION
 - A lot of high quality evidence supporting use of MAT in OUD. MAT is the standard of care in OUD.

12 step model

- Most widely used treatment model
- Provides long term support

The Twelve Steps

1. We admitted we were powerless over alcohol—that our lives had become unmanageable.
2. Came to believe that a Power greater than ourselves could restore us to sanity.
3. Made a decision to turn our will and our lives over to the care of God as we understood Him.
4. Made a searching and fearless moral inventory of ourselves.
5. Admitted to God, to ourselves, and to another human being the exact nature of our wrongs.
6. Were entirely ready to have God remove all these defects of character.
7. Humbly asked Him to remove our shortcomings.
8. Made a list of all persons we had harmed, and became willing to make amends to them all.
9. Made direct amends to such people wherever possible, except when to do so would injure them or others.
10. Continued to take personal inventory, and when we were wrong, promptly admitted it.
11. Sought through prayer and meditation to improve our conscious contact with God as we understood Him, praying only for knowledge of His will for us and the power to carry that out.
12. Having had a spiritual awakening as the result of these steps, we tried to carry this message to alcoholics, and to practice these principles in all our affairs.



- WITH ABSTINENCE OVER TIME, OR WITH MEDICATION, THE THRESHOLD RETURNS TO NORMAL (OR ALMOST NORMAL)
- IT IS FRIABLE
- IT WILL NOT STAY THERE WITHOUT DEVELOPMENT OF THE CORTEX

A chemical will not cure chemical dependency

- Medication should be used to stabilize the midbrain so that the work can be done in the cortex
- Without the constant spike of dopamine throughout the day, the threshold will come back to a level closer to normal
- Relying on a medication alone will likely result in relapse (on other substances first, then drug of choice)

medications

alcohol

- Disulfiram (Antabuse)
- Acamprosate (Campral)
- Oral naltrexone (ReVia)
- Injectable naltrexone (Vivitrol)

opiates

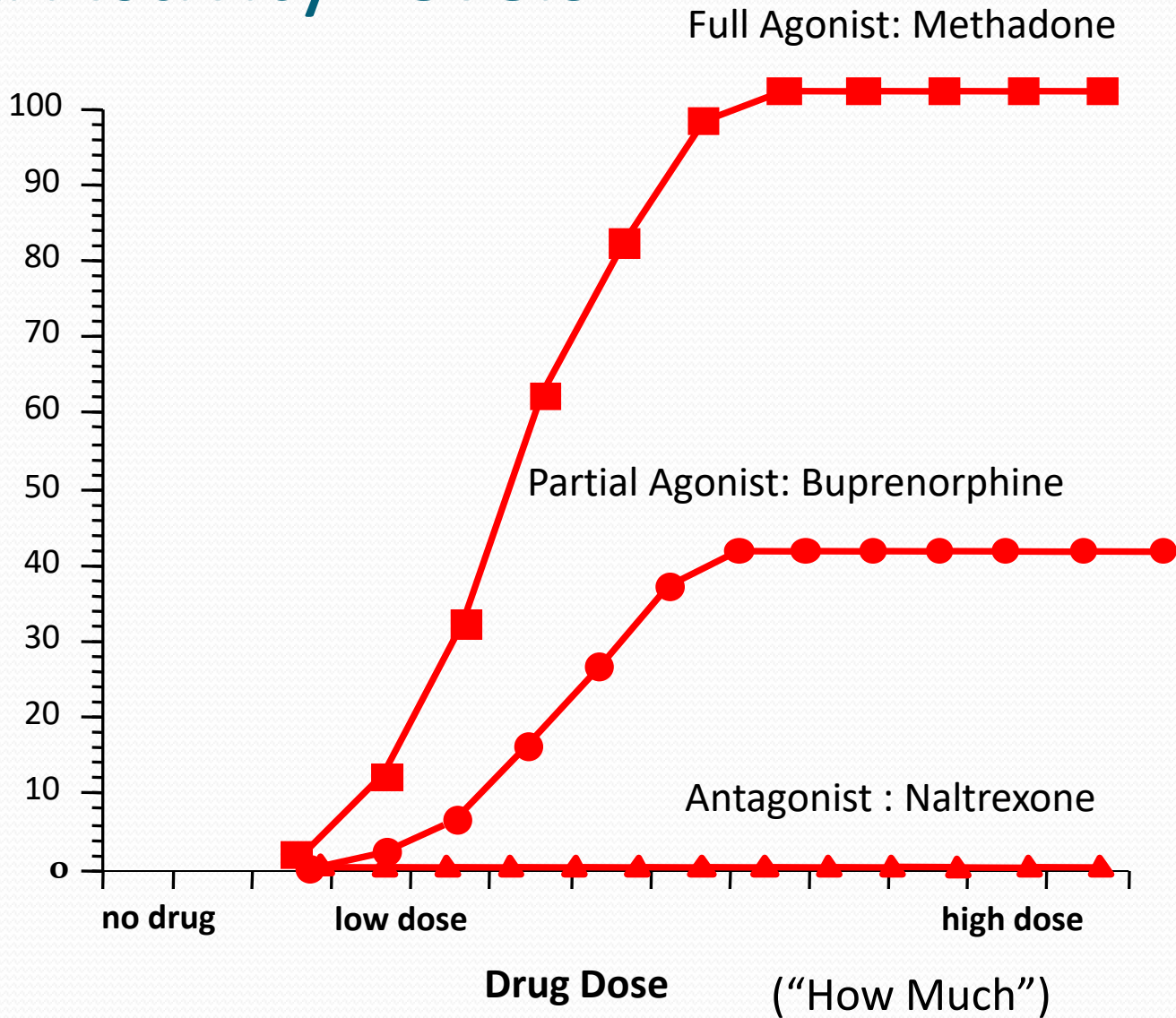
- Oral naltrexone (ReVia)
- Injectable naltrexone (Vivitrol)
- Sublingual buprenorphine/naloxone (Suboxone, Zubsolv, Bunavail, Subutex*)
- Injectable buprenorphine (Sublocade)
- methadone

*Subutex does not contain naloxone

Opioid Activity Levels

%
Mu Receptor
Intrinsic
Activity

("How High")



Buprenorphine (Subutex™) /naloxone (Suboxone™) (4:1 combination)



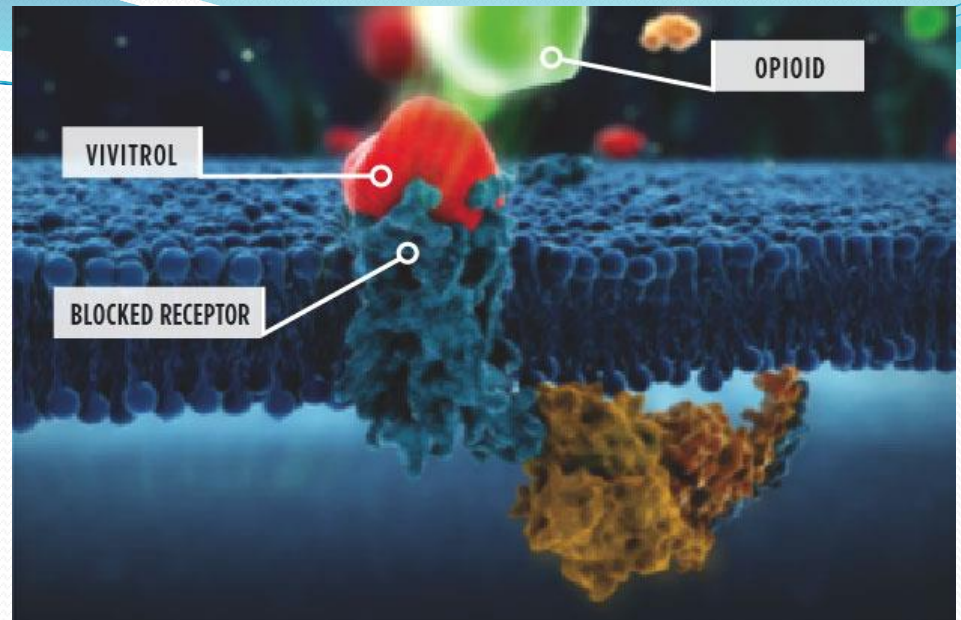
- Partial opioid agonist (plateau effect)
- Long half-life. High affinity for opioid receptor
- Typically once daily, but BID is safe
- 16mg usually the highest effective dose, but *8mg sufficient for most addicts*
- Less euphoric effect and respiratory depression than other opioids
- Paired with antagonist (naloxone) to prevent abuse through injection
- Office based prescribing with DEA waiver or “X license”
 - One day or online training
 - Treat up to 30 patients first year, then up to 100 patients

Methadone Vs. Buprenorphine

- Low dose Buprenorphine (2-6mg) was less effective than methadone in retaining people in treatment.
- Buprenorphine (>7 mg/day) was not different from methadone (≥ 40 mg/day) in retaining people in treatment or in suppression of illicit opioid use.

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.

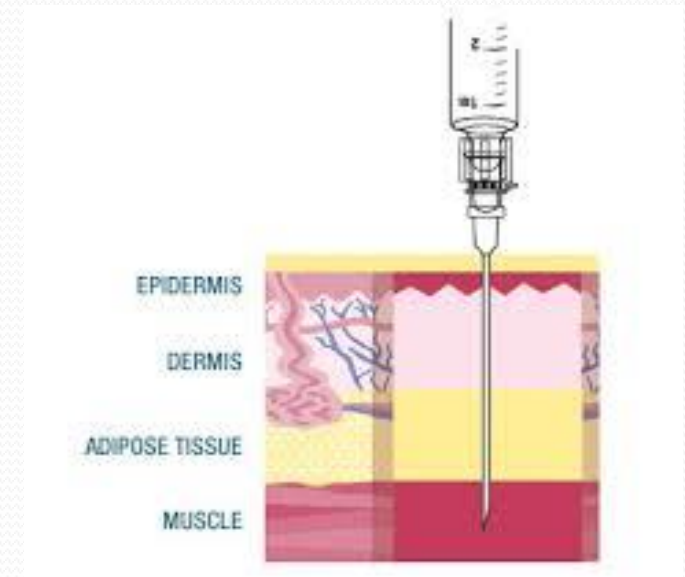
Naltrexone: opioid antagonist



Two formulations approved in US
Oral Naltrexone (1984), 50mg once daily
Extended Release Naltrexone, (2010) Q 28 days

Blocks all Opioid receptors
Not controlled
Blocks euphoric effects of opioids
Also treats alcohol dependence
ER Naltrexone has important use in criminal justice

Extended release naltrexone



Who is a Candidate for Naltrexone?

- The patient is opioid free for 7-10 days (DIFFICULT IN OUTPATIENT SETTINGS)
- The patient does not have severe or active liver or kidney problems
- (Typical guidelines suggest liver function tests no greater than 3 times the upper limits of normal, and bilirubin normal)

COMBINATION THERAPY (THE ULTIMATE TOOLBOX)

**-ALLOWING THE MIDBRAIN
TO 'REST' BUT
SIMULTANEOUSLY
STRENGTHENING THE
FRONTAL CORTEX**

**-ALLOWING THE
BEHAVIORAL AND
EMOTICO-MENTAL TOOLS
TO DEVELOP AND BE
PRACTICED IN A "LESS
STRESSFUL" ENVIRONMENT
(THE BRAIN)**

Reconstructed... THRIVE

Recover

- A Chronic disease with a chronic timeline
- Relapse/remission/recovery can be like sliding back and forth
- Where do we go after 'recovery'

Reconstruction

- Improving all areas of wellness
- Nutrition
- Movement
- Mindfulness
- Savings (finances and memories/experiences)

Recovery Supports

- Augment treatment both during, but particularly after a treatment episode
- Transportation
- Employment support
- Specialized living
- Peer-to-peer supports (12 step or other)
- Support groups
- Drop in centers
- Respite
- Wellness coaching

A word about marijuana

- THC releases dopamine... just like alcohol, opiates, cocaine, benzodiazepines, etc
 - It will awaken the midbrain 'tiger' and trigger the inability to cope without chemicals and put the addict in a position of needing stronger chemicals to deal with larger stressors, ultimately leading back to the drug of choice
 - The “marijuana maintenance plan” used as a ‘recovery tool’ is a nonsensical approach created BY addicts FOR addicts
 - Some evidence supporting its use in some medical conditions... in NON-addicts

References:

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? Questions ?

