MEDICATIONS FOR THE TREATMENT OPIOID USE DISORDER AND ALCOHOL USE DISORDER

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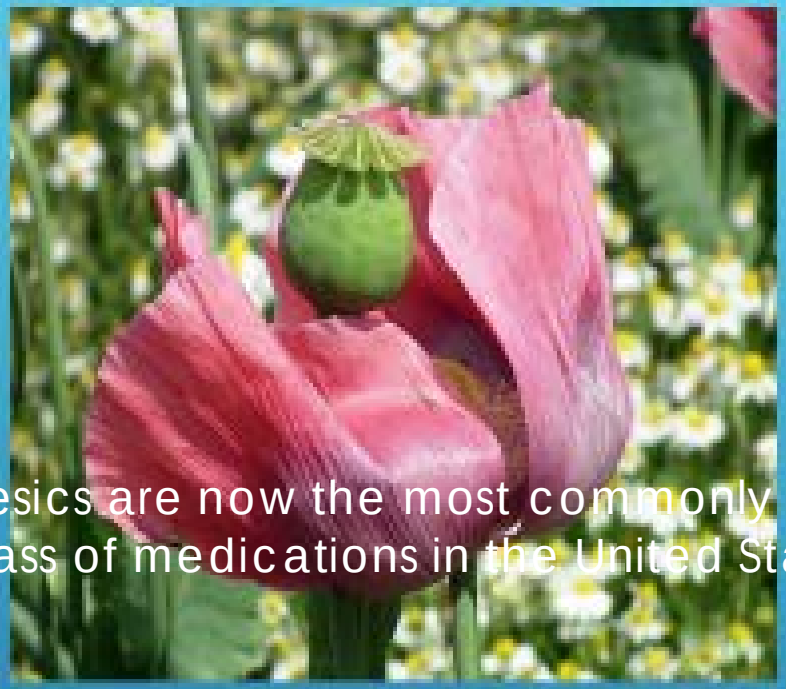
- Richard Rawson, Ph.D., UCLA ISAP and University of Vermont

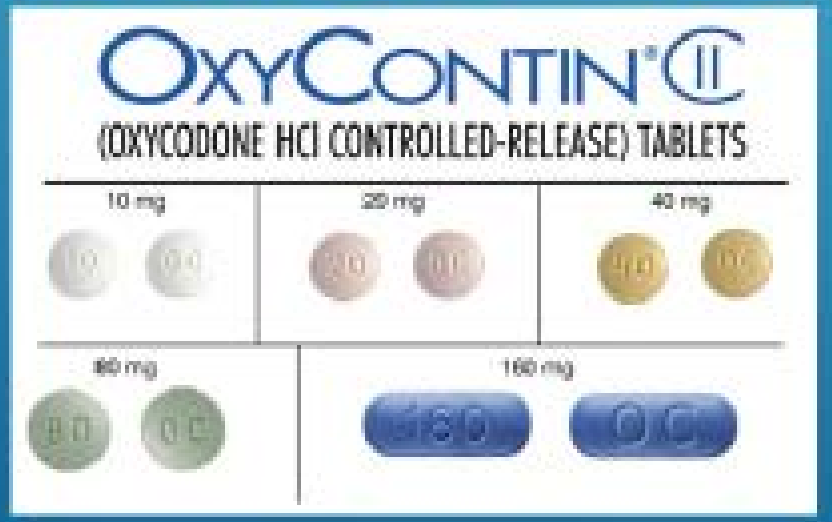
WHAT WE'LL COVER TODAY

- What are opioids?
- Where do they come from?
- Why do we care?
- What is being done about it?
- The pharmacology of alcohol.
- The treatment of alcohol withdrawal symptoms.
- Medications to treat alcohol use disorder.

OPIOIDS



opioid analgesics are now the most commonly prescribed class of medications in the United States.



WHAT ARE OPIOIDS?

- Opiate: derivative of opium poppy
  - Morphine
  - Codeine
  - Opium
- Opioid: any opium-like compound that binds to opiate receptors
  - Semisynthetic (heroin=derived from morphine, buprenorphine from Thebaine,

    oxy + hydrocodone, oxy + hydromorphone)
  - Synthetic (Dextropropoxyphene, Fentanyl, Methadone, Tramadol)
  - Route of Administration: Oral, transdermal, intravenous and implantable formulations
- Narcotic: legal designation

WHAT DO THEY DO?

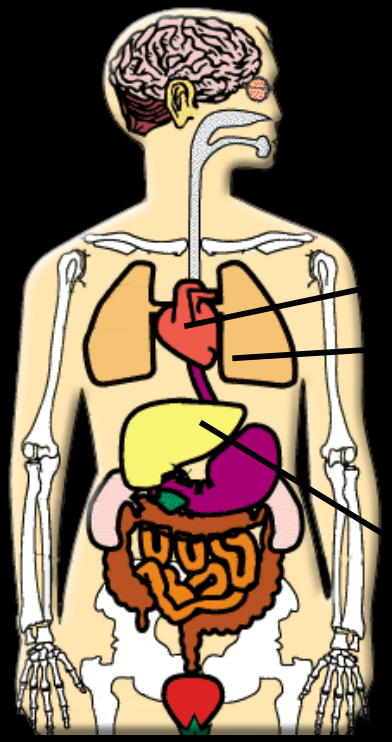
Opioids act on many places in the brain and nervous system, including:

- the **limbic system**, which controls emotions. Here, opioids can create feelings of pleasure, relaxation, and contentment.
- the **brainstem**, which controls things your body does automatically, like breathing. Here, opioids can slow breathing, stop coughing, and reduce feelings of pain.
- the **spinal cord**, which receives sensations from the body before sending them to the brain. Here too, opioids decrease feelings of pain, even after serious injuries.

ACUTE OPIOID EFFECTS

- Pupil constriction
- Slurred speech
- Impaired attention/memory
- Constipation
- Urinary retention
- Nausea
- Confusion, delirium
- Seizures
- Slowed heart rate
- Euphoria
- Sedation
- Pain Relief
- Suppresses Cough
- Warm flushing of the skin
- Drowsiness and lethargy
- Sense of well-being
- Histamine release
- Respiratory depression

Long-Term Effects of Opioids



- Fatal overdose
- Collapsed veins (intravenous use)
- Infectious diseases
- Higher risk of HIV/AIDS and hepatitis
- Infection of the heart lining and valves
- Pulmonary complications & pneumonia
- Respiratory problems
- Abscesses
- Liver disease
- Low birth weight and developmental delay
- Constipation
- Cellulitis

OPIOID WITHDRAWAL

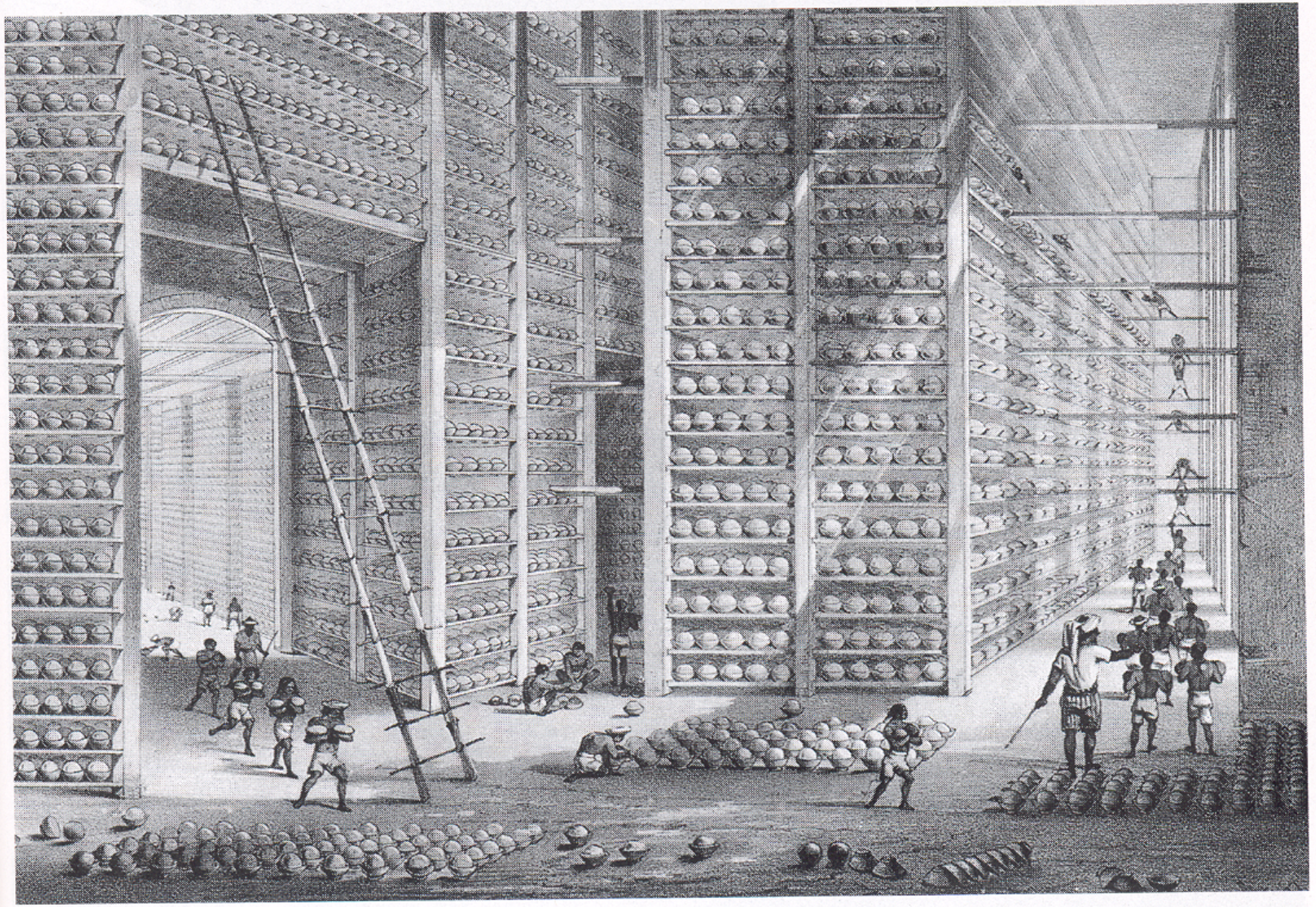
Withdrawal symptoms:

- Intensity of withdrawal varies with level and chronicity of use
- Cessation of opioids causes a rebound in functions depressed by chronic use
- First signs occur shortly before next scheduled dose
- For short-acting opioids (e.g., heroin), peak of withdrawal occurs 36 to 72 hours after last dose
- Acute symptoms subside over 3 to 7 days
- Ongoing symptoms may linger for weeks or months

SYMPTOMS OF OPIOID WITHDRAWAL

- Dysphoric mood
- Nausea or vomiting
- Diarrhea
- Tearing or runny nose
- Dilated pupils
- Muscle aches
- Goosebumps
- Sweating
- Yawning
- Fever
- Insomnia

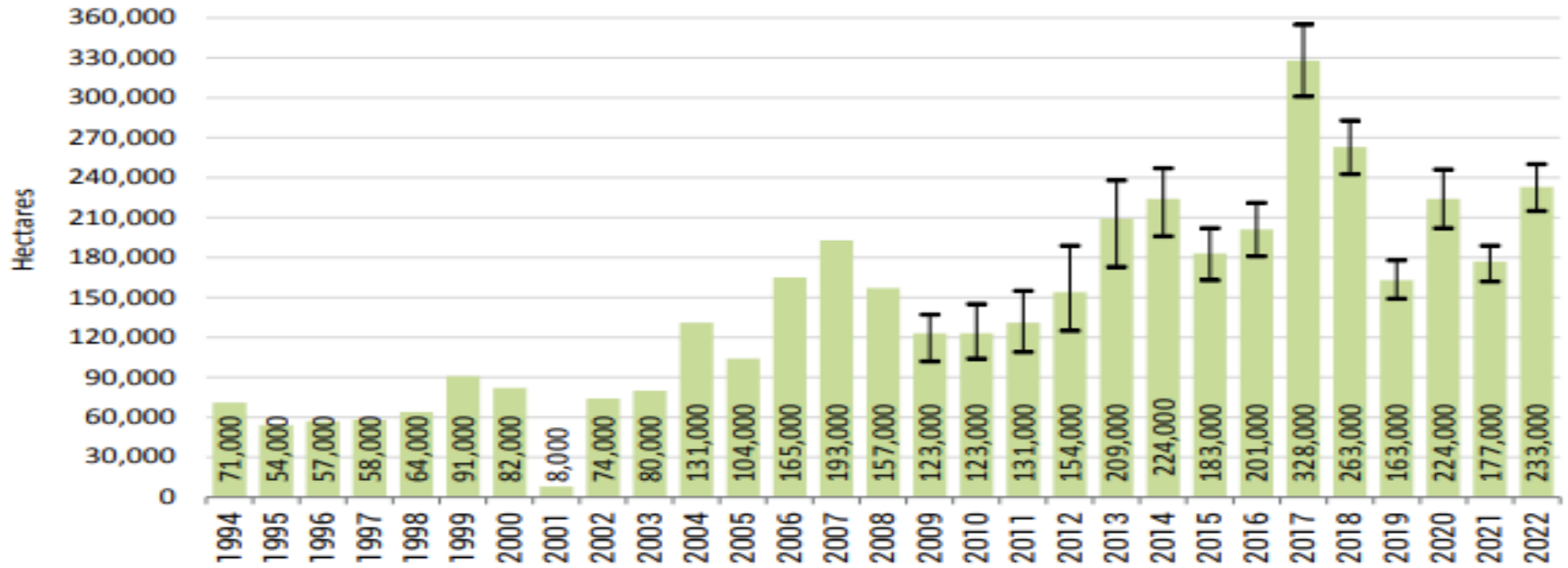
However, it is the fear and anxiety of the onset of withdrawal that drives people to do things they normally would never have done, functionally a panic reaction.



Stacking Room at East India Company's opium factory at Patna (1850). *Wellcome Library, London.*

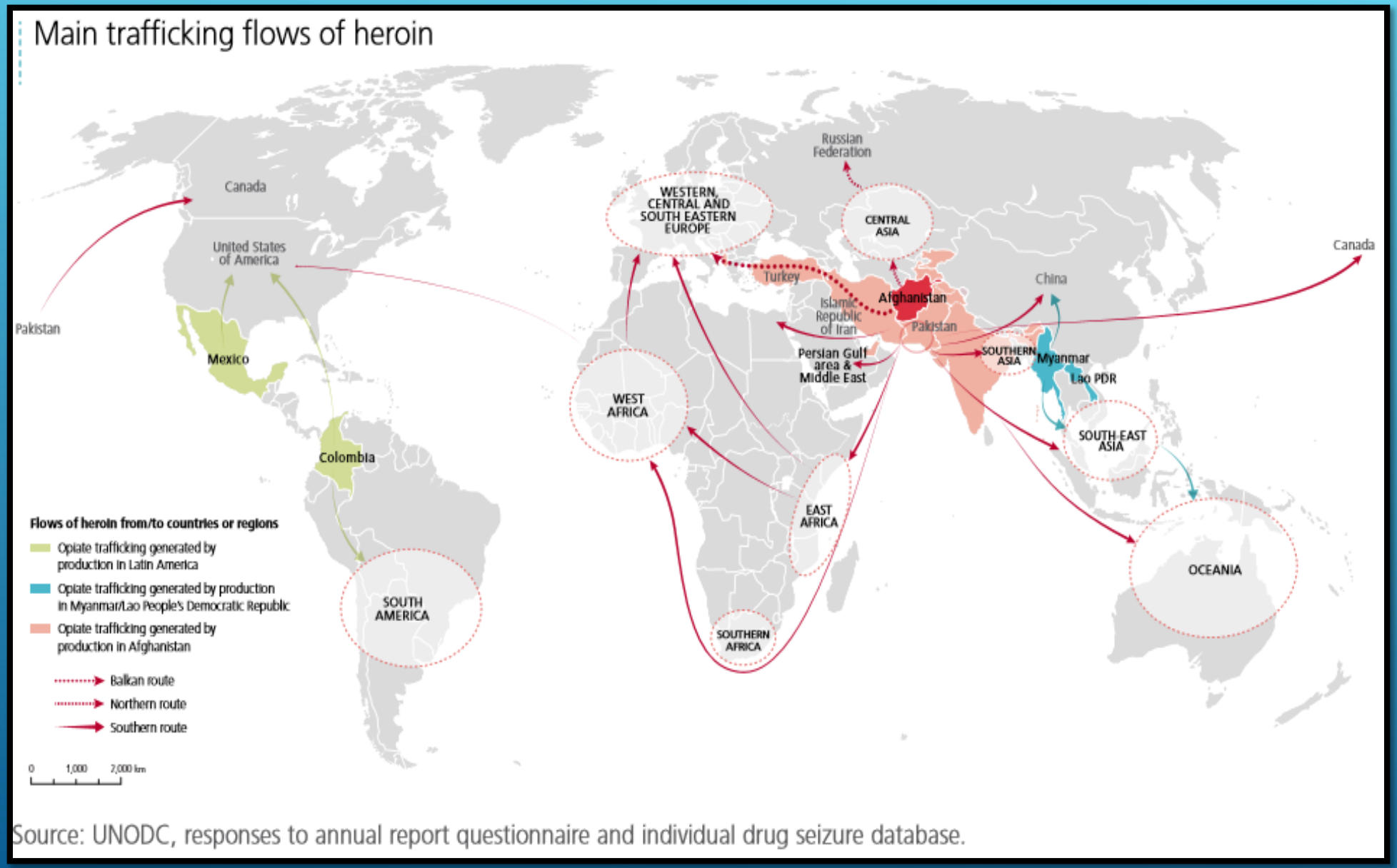
AFGHANISTAN: THE WORLDS LARGEST OPIUM PRODUCING NATION

FIG. 1: Opium cultivation in Afghanistan



1 In some provinces in Afghanistan, opium poppy is harvested two times in the year. This estimate only considers the main season, as the second harvest is marginal in comparison, based on the evidence available.

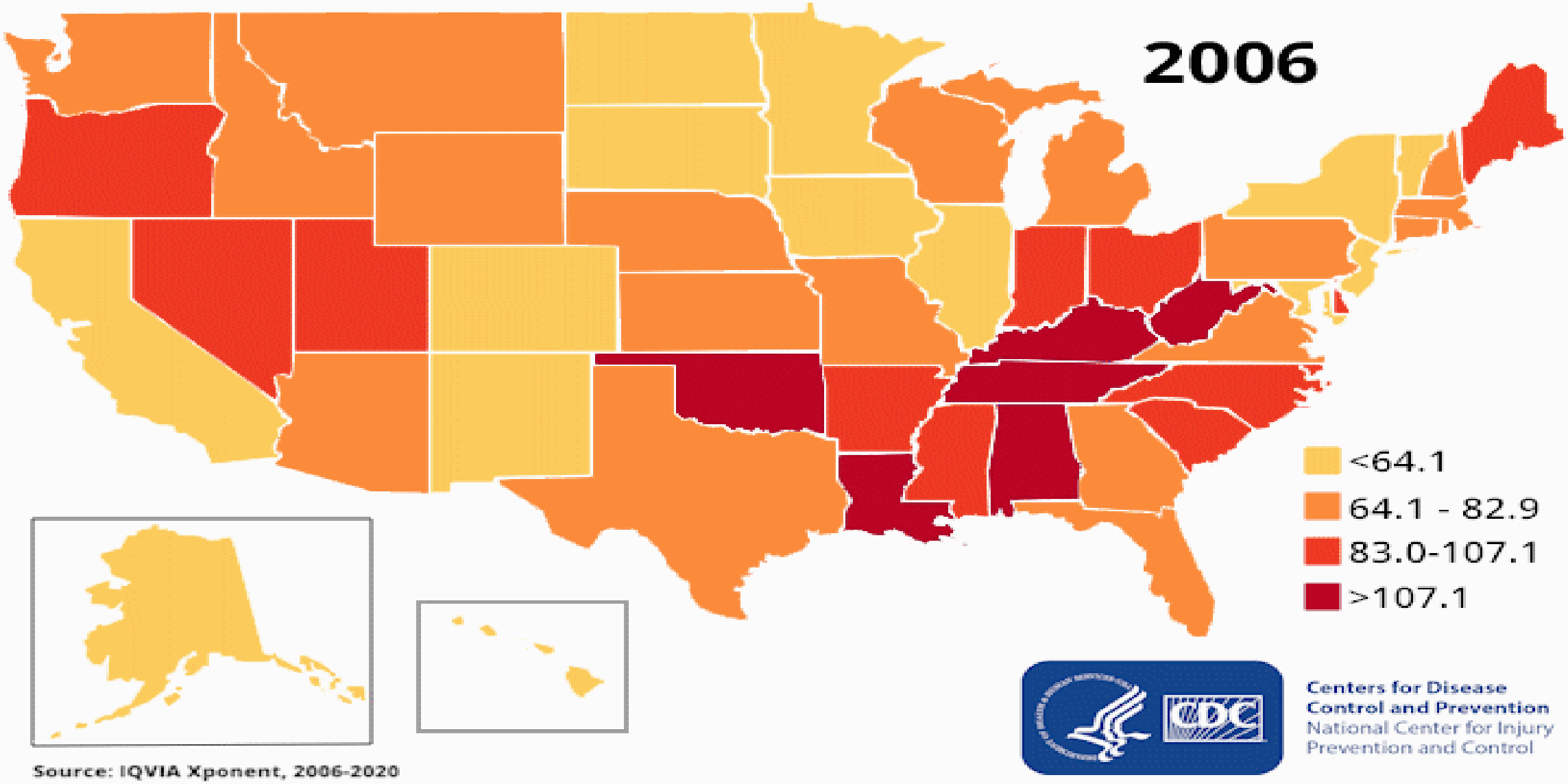
WHERE DOES HEROIN COME FROM?



Source: UNODC, responses to annual report questionnaire and individual drug seizure database.

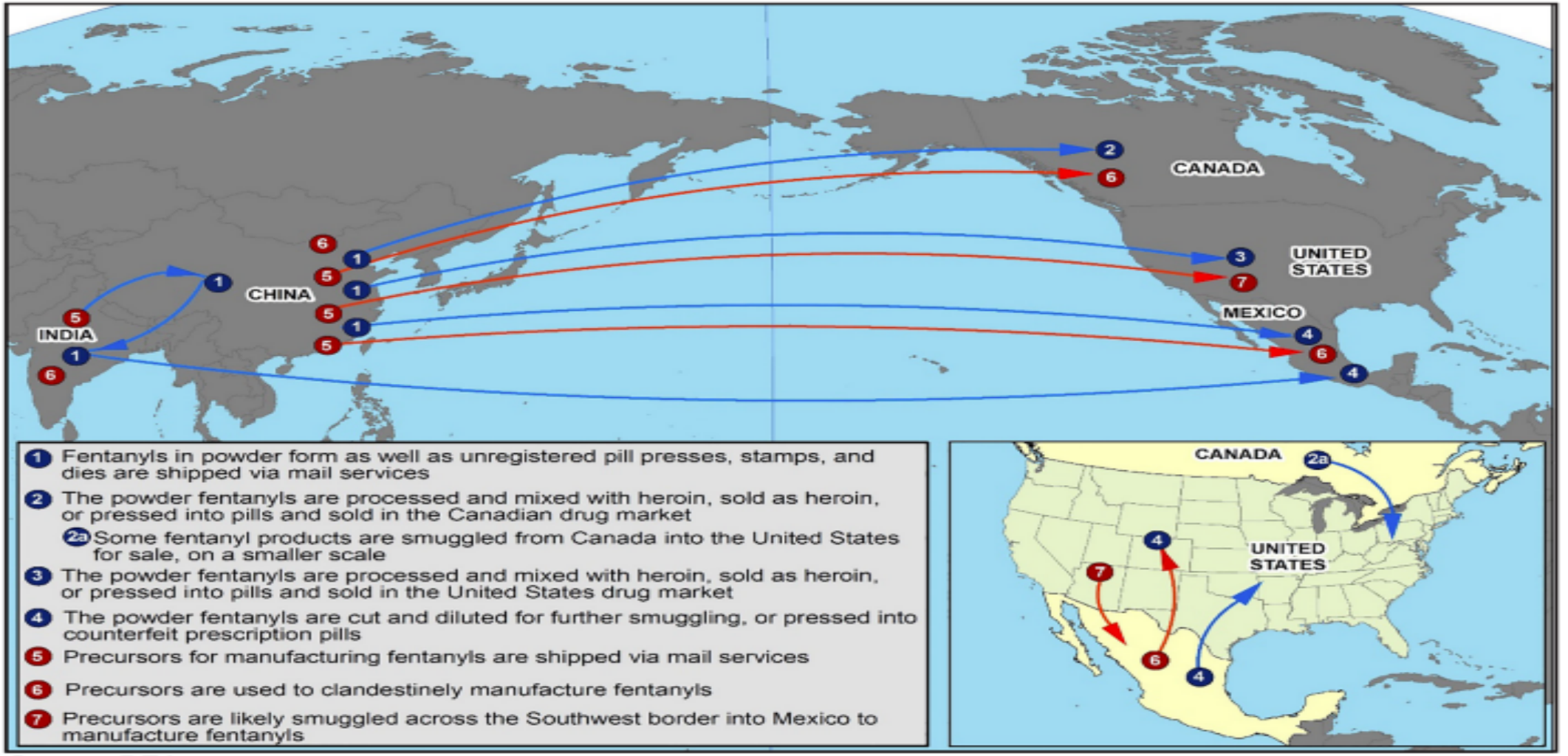
U.S. Opioid Dispensing Rates per 100 people, from 2006 to 2020

How have rates improved over time?



WORLDWIDE FENTANYL DISTRIBUTION

(U) FIGURE 1. FENTANYL FLOW TO THE UNITED STATES 2019



Source: DEA

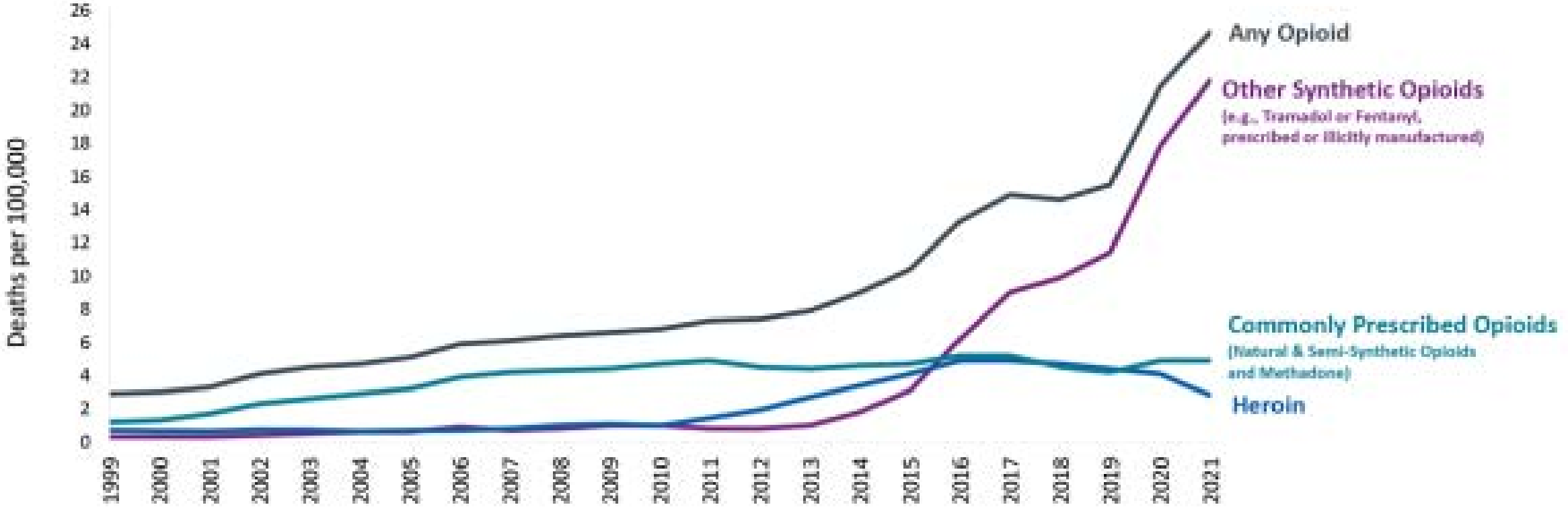
WHY DO WE CARE?

- OPIOID OVERDOSE DEATHS
- HIV
- HCV

OVERDOSE RISK FACTORS

- History of prior overdose
  - Release after emergency care for overdose
- Opioid use disorder
- Prescribed more than 50 mg of oral morphine equivalents daily
- Recent release from incarcerated or residential setting
- Combining opioids with other central nervous system depressants (e.g. alcohol, benzos)
- Medical conditions (e.g. pulmonary diseases)

Three Waves of Opioid Overdose Deaths



Wave 1: Rise in Prescription Opioid Overdose Deaths Started in the 1990s

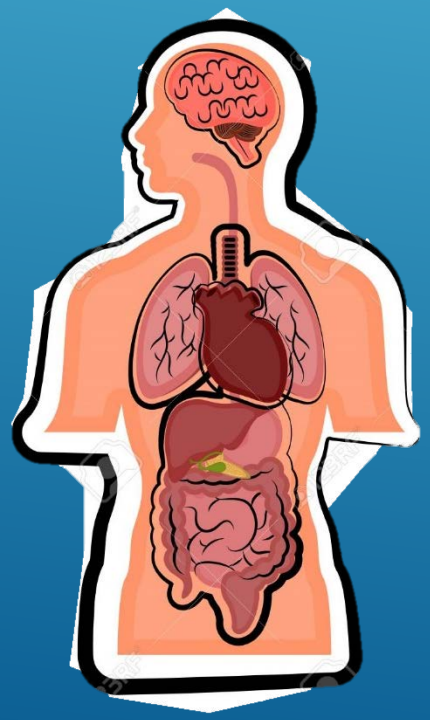
Wave 2: Rise in Heroin Overdose Deaths Started in 2010

Wave 3: Rise in Synthetic Opioid Overdose Deaths Started in 2013

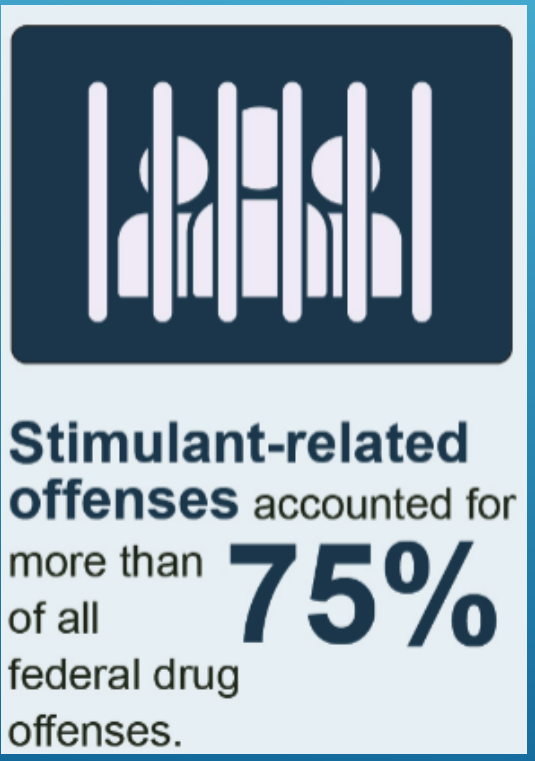
SOURCE: National Vital Statistics System Mortality File.

CO-USE OF OPIOIDS AND STIMULANTS HAVE BEEN REFERRED TO AS THE 4TH WAVE OF THE OPIOID EPIDEMIC

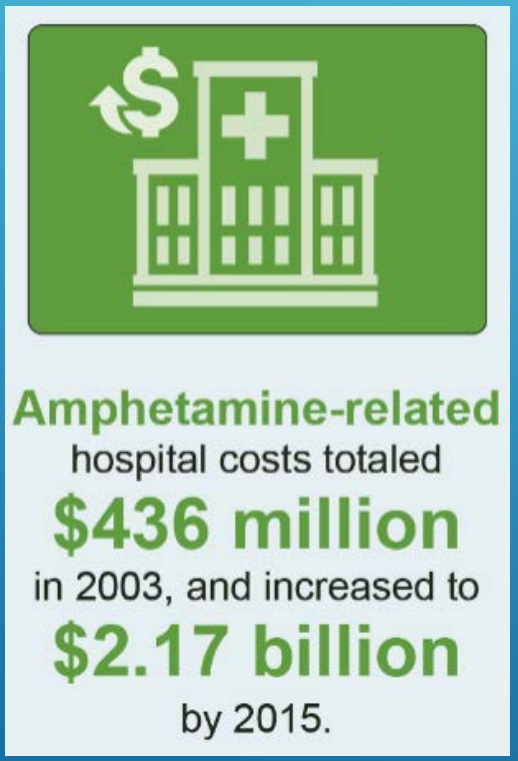
Behavioral & Physical Health



Criminal justice



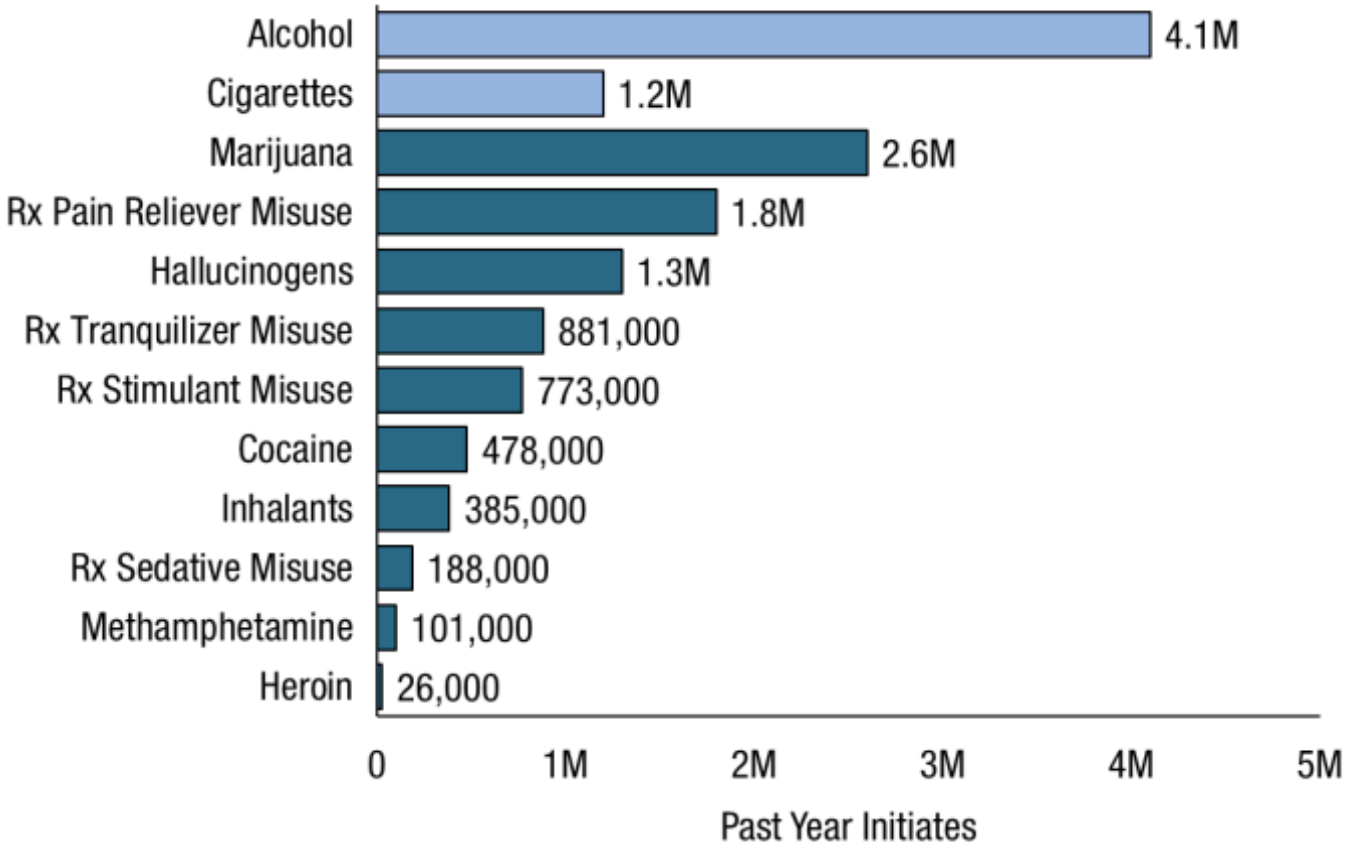
Health care system



Source: Substance Abuse and Mental Health Services Administration (SAMHSA): Treatment of Stimulant Use Disorders. Substance Abuse and Mental Health Services Administration, 2020.

FFR1.26

Past Year Initiates of Substances: Among People Aged 12 or Older; 2021



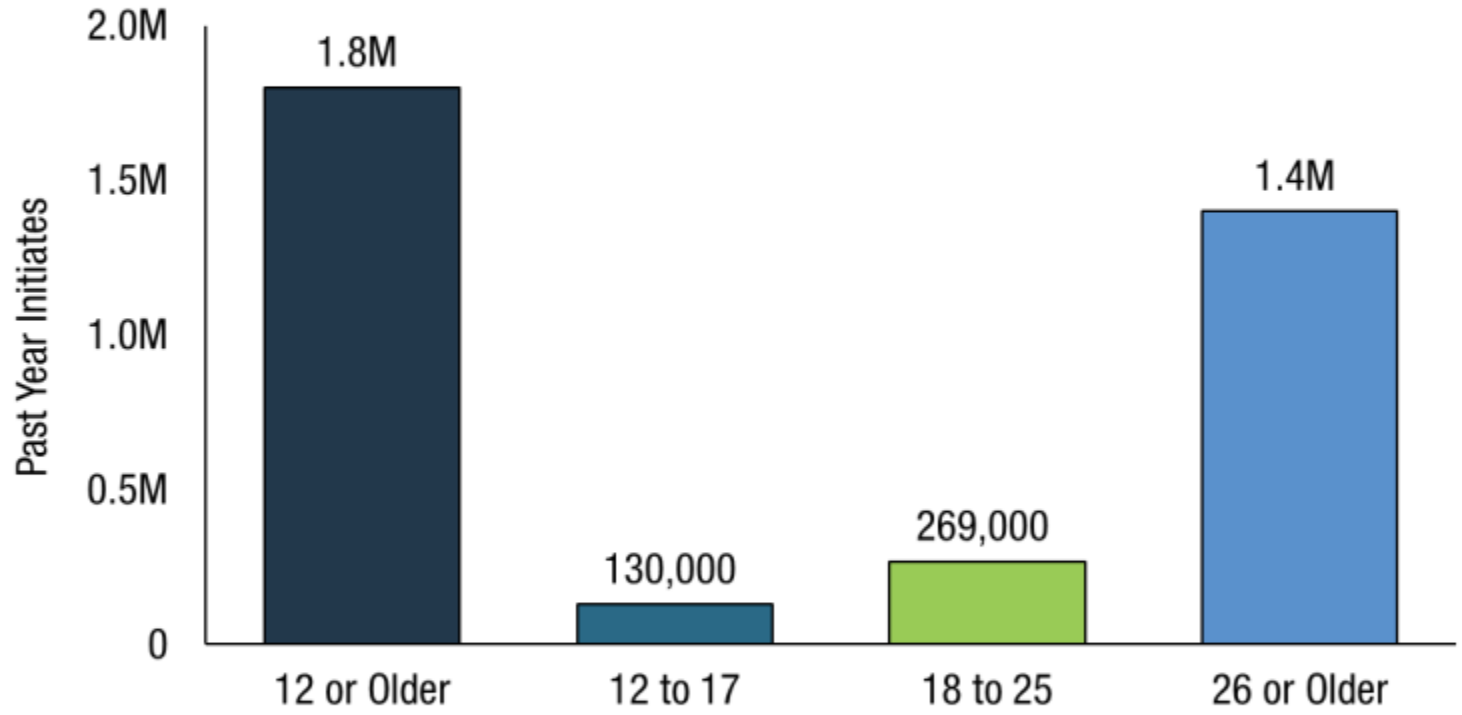
Rx = prescription.

Note: Estimates for prescription pain relievers, prescription tranquilizers, prescription stimulants, and prescription sedatives are for the initiation of misuse.

SAMHSA
Substance Abuse and Mental Health Services Administration

FFR1.29

Past Year Prescription Pain Reliever Misuse Initiates: Among People Aged 12 or Older; 2021



SAMHSA
Substance Abuse and Mental Health Services Administration

OPIOID USE: GEORGIA DEPARTMENT OF PUBLIC HEALTH DATA

- All drug overdose deaths increased by 61.9 % from 2019 – 2021.
- Fentanyl-involved overdose deaths increased by 232.1 % in that same time period.
- In 2021 nearly half of all opioid involved overdose deaths involved a stimulant. (This may define the 4th wave of the opioid epidemic)
- In 2021, there were 2390 drug overdose deaths in Georgia.
  - 71% (1,718) were attributed to opioids
  - 57% (1,379) were attributed specifically to fentanyl

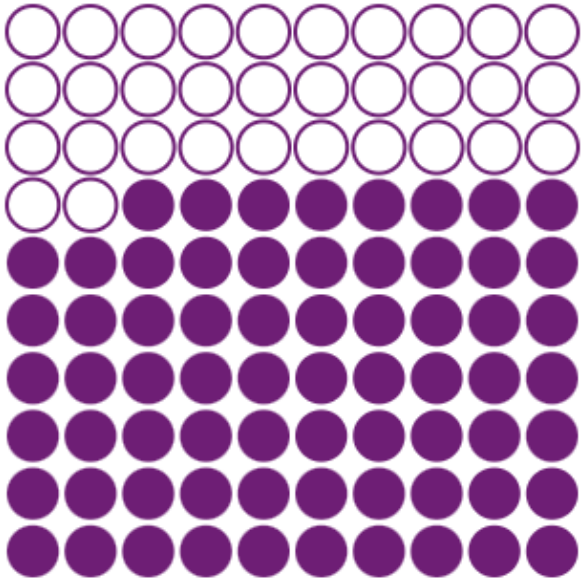
    - https://dph.georgia.gov/stopopioidaddiction#:~:text=In%202021%2C%20there%20were%202%2C390,1%2C379)%20were%20attributed%20to%20fentanyl.

What were the circumstances[i] surrounding overdose deaths in 2021, *Georgia*?

Georgia | 2021

Potential opportunities for intervention[a] in 2021, *Georgia*

Potential opportunities for intervention include linkage to care or life-saving actions at the time of the overdose.



68.2%

of drug overdose deaths had at least one potential opportunity for intervention

- 2.6% — Current treatment for substance use disorder(s)[j]
- 14.9% — Fatal drug use witnessed
- 17.2% — Mental health diagnosis
- 52.7% — Potential bystander present[k]
- 10.9% — Prior overdose
- 7.9% — Recent release from institutional setting[l]

Circumstance percentages are only among decedents with an available medical examiner or coroner report

Additional circumstances surrounding overdose deaths in 2021, *Georgia*

12.6%
Current pain treatment

10.0%
Experiencing homelessness or housing instability[m]

23.2%
Naloxone administered[n]

5.5%
Recent return to use of opioids[o]

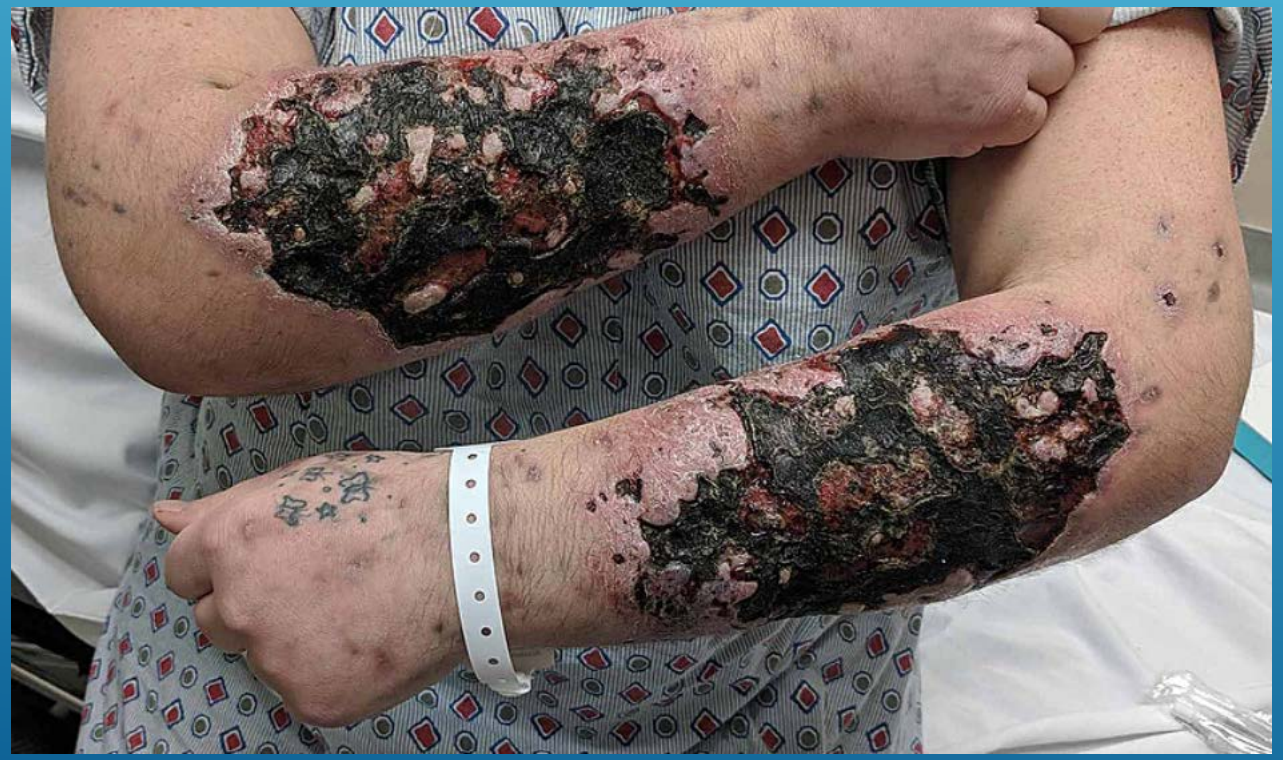
Circumstance percentages are only among decedents with an available medical examiner or coroner report

XYLAZINE

- Xylazine is a non-opioid sedative, analgesic, and muscle relaxant used in veterinary medicine and not approved for human use.
- It has been found among people who use drugs in Puerto Rico since the early 2000s and referred to as “anestesia de caballo” (horse anesthetic).

XYLAZINE EFFECTS IN HUMANS

- In humans xylazine can cause hypotension, central nervous system depression, respiratory depression, and bradycardia.
- It also causes open skin ulcers among injectors who may continually inject affected areas for pain relief.



Spencer MR, Cisewski JA, Warner M, Garnett MF. Drug overdose deaths involving xylazine: United States, 2018–2021. Vital Statistics Rapid Release; no 30. Hyattsville, MD: National Center for Health Statistics. 2023. DOI: https://dx.doi.org/10.15620/ cdc:129519.

INTRODUCTION

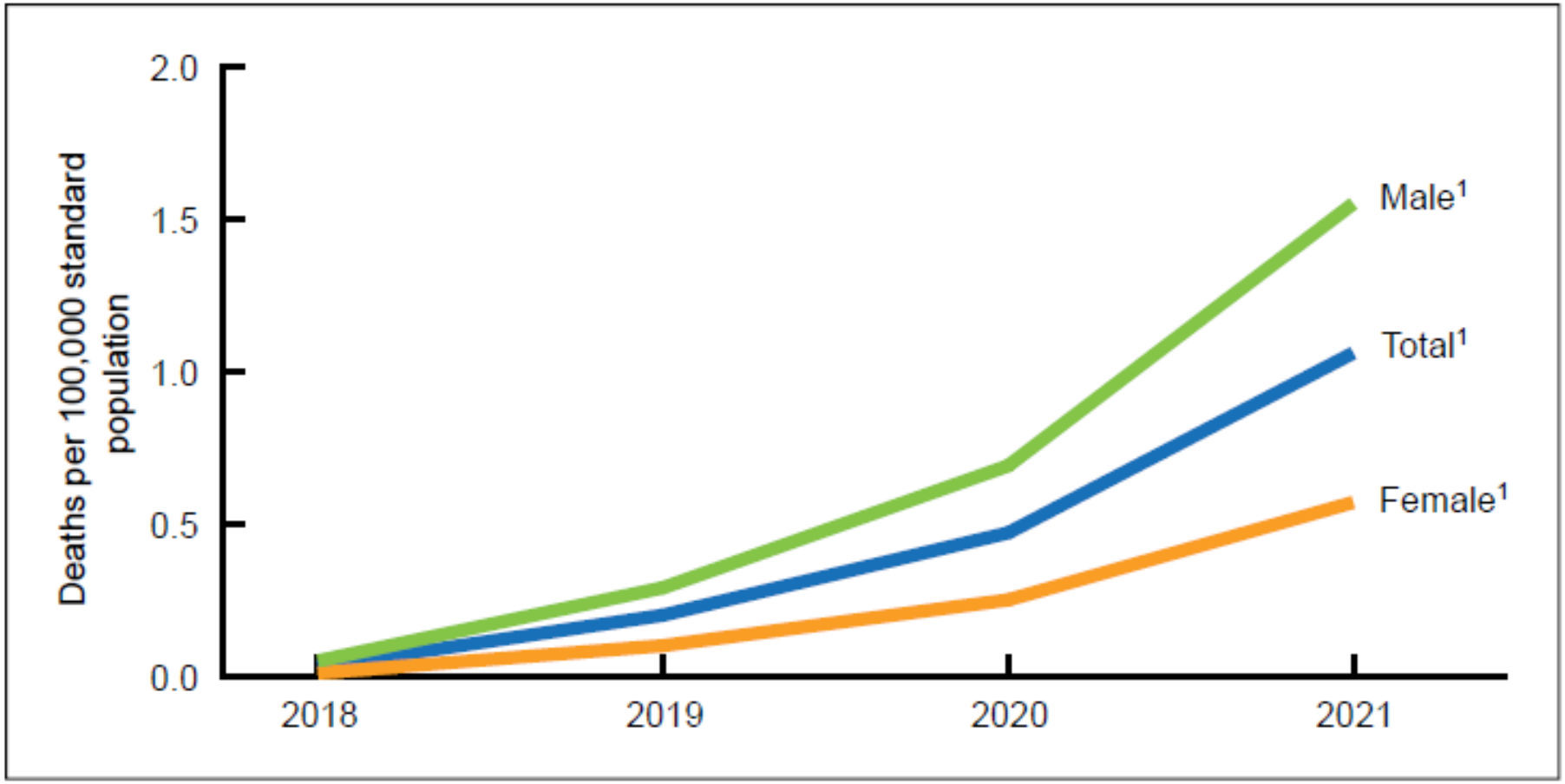
- This study presents trends in drug overdose deaths involving xylazine in the U.S. from 2018 through 2021.
- Drugs involved in death were extracted from the death certificate literal text.
- Rates of these deaths are presented overall and by sex, age group, and race.

RESULTS

- In 2021 the age-adjusted rate of overdose deaths involving xylazine was 35 times higher than the 2018 rate, increasing from 0.03 per 100,000 standard population to 1.06 per 100,000.
- The number of drug overdose deaths involving xylazine was 102 in 2018, 627 in 2019, 1,499 in 2020, and 3,468 in 2021.
- For males the overdose death rate increased from 0.05 in 2018 to 1.55 in 2021.
- For females the rate increased from 0.01 in 2018 to 0.57 in 2021.
- Male rates were at least double rates for females over the 2018-2021 period.

U.S. DRUG OVERDOSE DEATH RATES INVOLVING XYLAZINE

Figure 1. Age-adjusted rate of drug overdose deaths involving xylazine, by sex: United States, 2018–2021

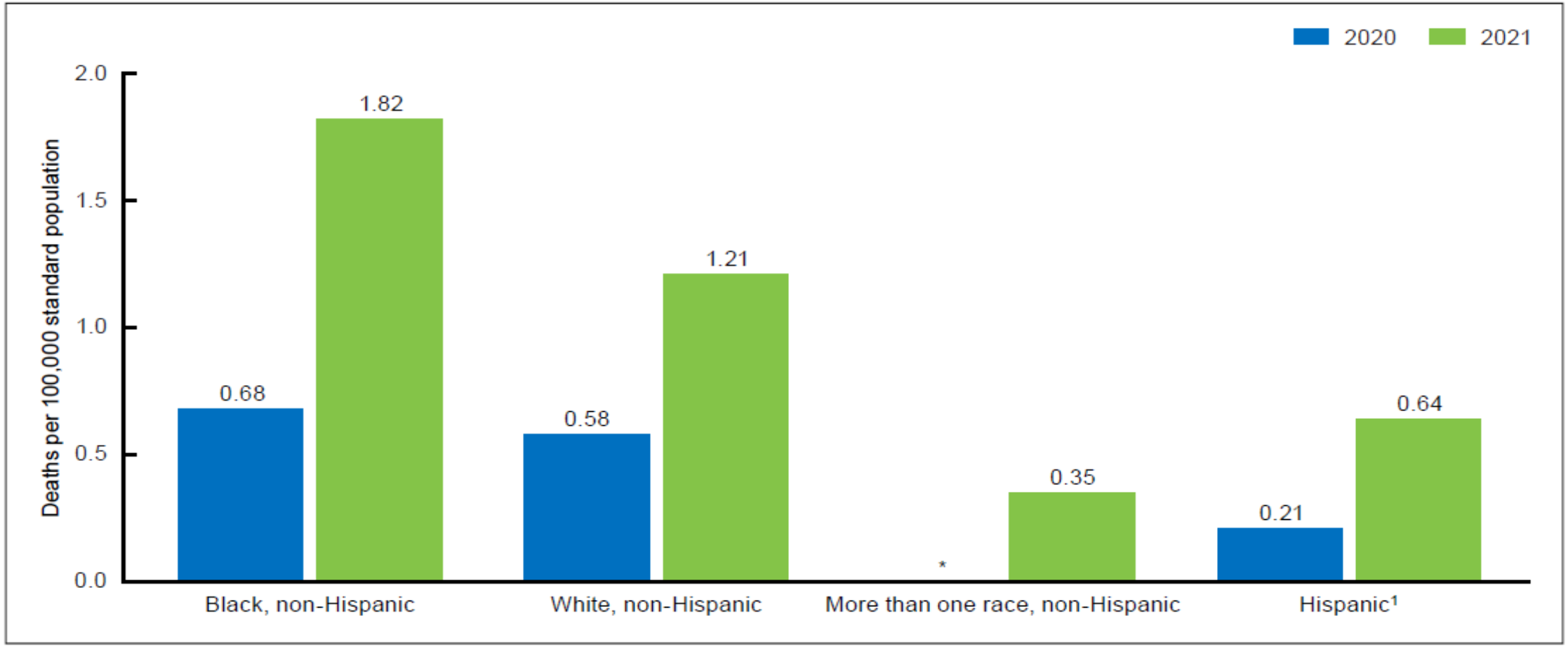


RESULTS

- Rates of overdose deaths from 2020 to 2021 were highest among black people.
- Among blacks the rate of overdose deaths involving xylazine increased from 0.68 per 100,000 in 2020, to 1.82 in 2021.
- Rates among whites was second highest with rates increasing from 0.58 per 100,000 in 2020 to 1.21 in 2021.
- Rates among Hispanic people increased from 0.21 per 100,000 in 2020 to 0.64 in 2021.

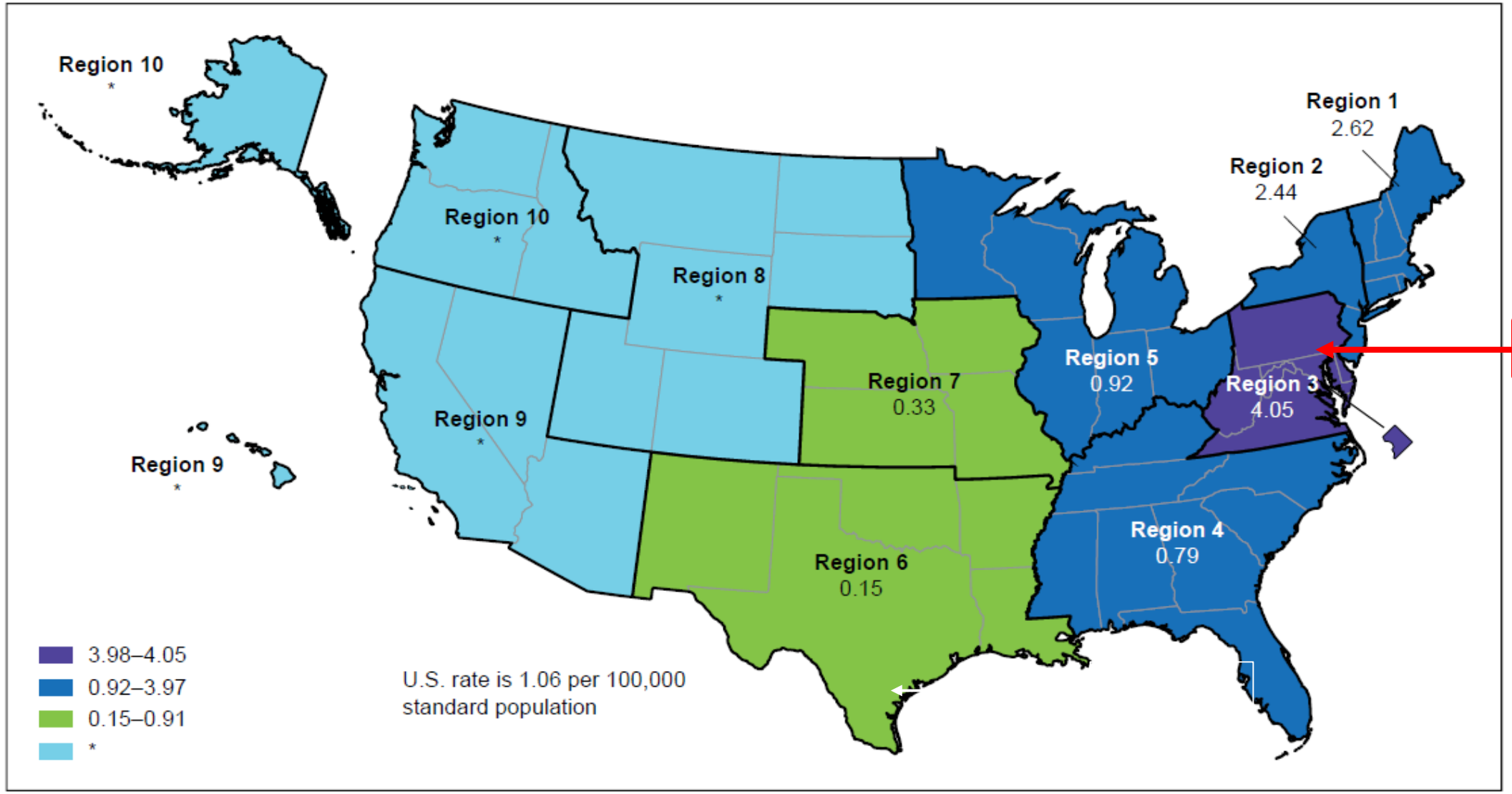
AGE-ADJUSTED OVERDOSE DEATH RATES BY RACE AND HISPANIC ORIGIN, 2020-2021

Figure 3. Age-adjusted rate of drug overdose deaths involving xylazine, by race and Hispanic origin: United States, 2020–2021



AGE-ADJUSTED OVERDOSE DEATH RATES BY REGION, 2021

Figure 4. Age-adjusted rate of drug overdose deaths involving xylazine, by region: United States, 2021



RESULTS

- In 2021 overdose deaths involving xylazine was highest in Region 3 at 4.05 per 100,000.
- Regions 1 (2.62 per 100,000) and 2 (2.44 per 100,000) were the next highest.
- Region 6 was lowest (0.15 per 100,000), followed by Region 7 (0.33), Region 4 (0.79), and Region 5 (0.92).
- Regions 8-10 did not meet the reliability criteria of 20 deaths or more and, as a result, are not reported.

DISCUSSION

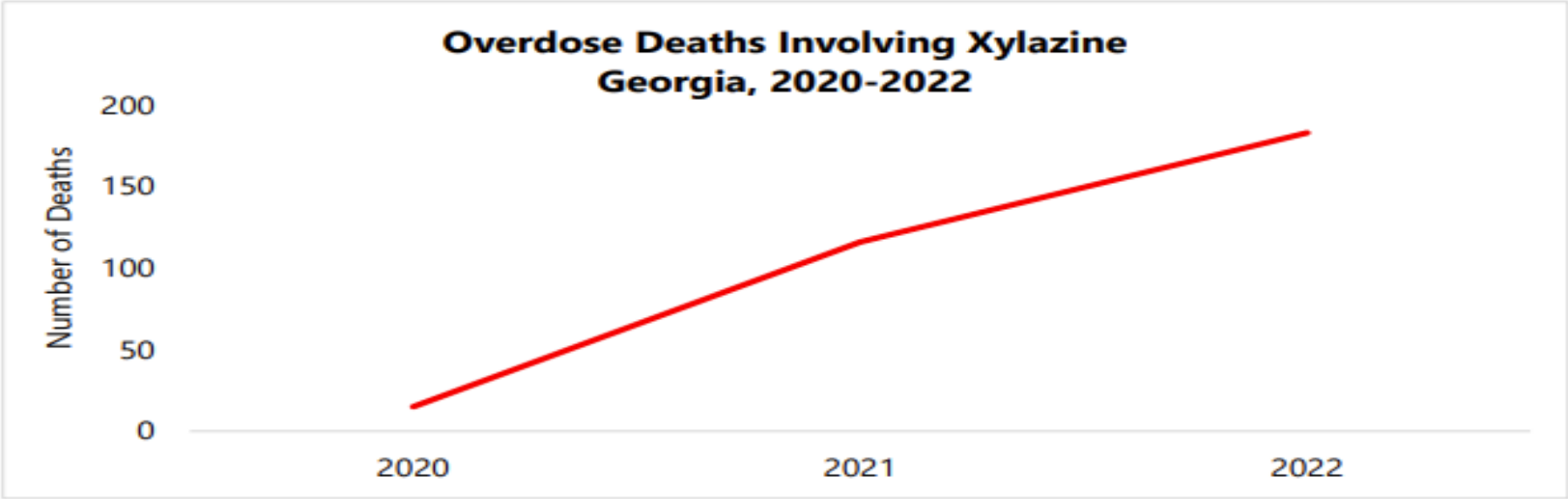
- From 2018 through 2021 more than 97% of drug overdose deaths involving xylazine also mentioned fentanyl.
- Co-involvement of methamphetamine with drug overdose deaths involving xylazine increased over the 3-year period, and methamphetamine surpassed heroin as the third most frequent drug co-involved in overdose deaths for 2020 and 2021.
- Overall, drug overdose deaths have risen over the period, increasing from 20.7 per 100,000 in 2018 to 32.4 in 2021.

XYLAZINE RELATED OVERDOSE DEATHS IN GEORGIA

From 2020 to 2022 in Georgia:

- Deaths involving any drug increased 12%
- Deaths involving xylazine increased **1120%**
- The proportion of overdose deaths involving xylazine increased from 0.8% to **9%**

Drug Overdose Deaths by Drug Type, Georgia, 2020 – 2022							
	2020		2021		2022*		% Change
Drug Type	N	Rate	N	Rate	N	Rate	2020-2022
Any Drug	1888	17.63	2417	22.38	2115	19.58	12%
Xylazine	15	0.14	116	1.07	183	1.69	1120%



Drug Overdose Deaths Involving Xylazine, by Sex, Race, Ethnicity, and Age Group, Georgia, 2020 - 2022							
	2020		2021		2022*		% Change
Characteristic	N	Rate	N	Rate	N	Rate	2020-2022
Sex							
Female	4	--	32	0.58	55	0.99	1275%
Male	11	0.21	84	1.59	128	2.43	1064%
Race							
Black or African American	4	--	21	0.59	35	0.98	775%
White	11	0.17	92	1.43	145	2.26	1218%
Other Race	0	--	3	--	3	--	N/A
Ethnicity							
Hispanic or Latino	1	--	5	0.45	9	0.81	800%
Non-Hispanic or non-Latino	14	0.15	111	1.14	174	1.79	1143%
Age Group							
<15	0	--	0	--	1	--	N/A
15-24	2	--	7	0.47	13	0.88	550%
25-34	4	--	40	2.68	56	3.75	1300%
35-44	3	--	40	2.80	64	4.48	2033%
45-54	2	--	19	1.33	26	1.82	1200%
55-64	2	--	10	0.70	19	1.33	850%
65+	2	--	0	--	4	--	100%

Xylazine-Involved Overdose Deaths & Opioid/Non-Opioid Pairings

All xylazine-involved overdose deaths involved at least one other drug. In 2022 in Georgia:

- **100%** of all suspected xylazine-involved deaths also involved fentanyl
- 19% of all suspected xylazine-involved deaths also involved cocaine
- 34% of all suspected xylazine-involved deaths also involved amphetamines

ADDRESSING THE OPIOID USE EPIDEMIC

WHAT ARE WE DOING ABOUT IT?

- CDC **Prescribing Guidelines**
- **Educational initiatives** delivered in school and community settings (primary prevention)
- Supporting consistent use of **Prescription Drug Monitoring Programs** (PDMPs)
- Implementation of **overdose education and naloxone distribution** programs to issue naloxone directly to opioid users and potential bystanders
- **Aggressive law enforcement** efforts to address doctor shopping and **pill mills**
- Diverting individuals with substance use disorders to **Drug/Treatment/accountability Courts**
- Expansion of access to **Medications for Opioid Use Disorder**
- **Abuse-deterrent formulations** for opioid analgesics

FDA APPROVED MEDICATIONS

- Methadone — **Full Agonist**

- Naloxone
- Naltrexone
- Extended Release Naltrexone

— **Opioid Antagonists**

- Buprenorphine
  - Sublingual
  - Extended-release
  - Implant
- Buprenorphine/Naloxone

— **Partial Agonists**

DIAGNOSIS OF SUBSTANCE USE DISORDER: DSM-5

- Use in larger amounts/longer periods than intended
- Persistent desire or unsuccessful attempts to cut down
- Excess time spent obtaining or recovering from use
- Craving or strong desire to use
- Failure to fulfill major role obligations
- Important social or recreational activities given up
- Recurrent use in physically hazardous situations
- Continued use despite knowledge of medical or psychological consequence(s)
- Continued use despite recurrent social or interpersonal problems
- *Tolerance
- *Withdrawal

*(*if pt taking Rx opioids under medical supervision, tolerance and withdrawal can't be the only criteria to diagnose mild OUD)*

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

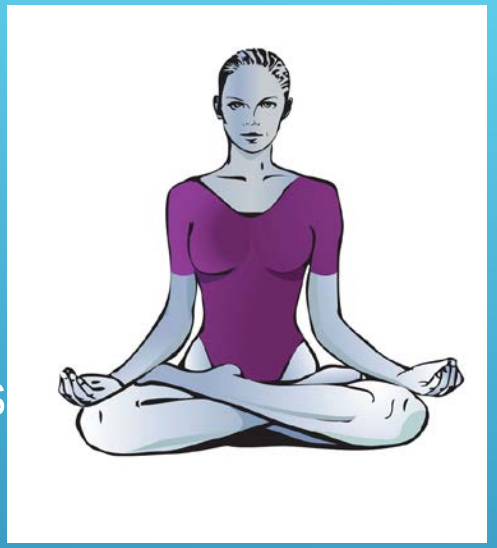
OPIOID TREATMENT

- Methadone was developed in 1930s WWII as an alternative to morphine
- 1964: Methadone is approved.
- 1974: Narcotic Treatment Act limits methadone treatment to specifically licensed Opioid Treatment Programs (OTPs).
- 1984: Naltrexone is approved, but has continued to be rarely used (approved in 1994 for alcohol use disorder).
- 1993: LAAM is approved (for non-pregnant patients only), but is underutilized.

OPIOID TREATMENT - 2

- 2000: Drug Addiction Treatment Act of 2000 (DATA 2000) expands the clinical context of medication-assisted opioid treatment.
- 2002: Tablet formulations of buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®) were approved by the Food and Drug Administration (FDA).
- 2004: Sale and distribution of ORLAAM® is discontinued.
- 2016: Buprenorphine implant (probuphine) is approved by the Food and Drug Administration.
- 2017: Depot buprenorphine (sublocade) is approved by the Food and Drug Administration.

OPIOID USE DISORDER TREATMENT APPROACHES



- Withdrawal management ("detox"):
  - Opioid-based (methadone, buprenorphine)
  - Non-opioid based (clonidine, supportive meds
- Relapse prevention:
  - Agonist maintenance (methadone)
  - Partial agonist maintenance (buprenorphine)
  - Antagonist maintenance (naltrexone)
- Psychosocial treatment
  - To promote lifestyle and behavior change

OPIOID WITHDRAWAL MANAGEMENT ("DETOX")

Medications used to alleviate withdrawal symptoms:

- Opioid agonists (methadone, buprenorphine)
- Clonidine (alpha-2 agonist)
  - ▸ Dose: 0.1 mg PO tid (increase as tolerated)
  - ▸ Caution: hypotension
- Lofexidine (alpha-2 agonist)

  -0.18 mg tabs (up to 0.54mg PO QID)
- Other supportive meds
  - ▸ anti-diarrheals, anti-emetics, ibuprofen, muscle relaxants, BDZs

WHY NOT DETOXIFICATION?

POST-DETOXIFICATION RELAPSE RATES APPROACH 100% WITHIN THE FIRST 90 DAYS FOLLOWING COMPLETION OF DETOXIFICATION.

MOUD Indicated for

- Individuals with opioid use disorder
- Individuals with opioid use disorder and chronic pain
- Individuals with chronic pain with opioid misuse
- Adolescents >16 years of age
- Pregnant persons
- Individuals involved with the criminal legal system

Purpose of MOUD

- Allow reestablishment of balance in the reward pathways in the brain away from substances
- Control symptoms of opioid withdrawal
- Reduce opioid cravings
- Block the reinforcing effects of ongoing opioid use
- Promote and facilitate patient engagement in recovery-oriented activities
- Coupled with behavioral interventions
  - Enhance the salience of natural, healthy rewards
  - Reduce stress reactivity and negative emotional state
  - Improve self-regulation
  - Increase avoidance of triggers that may promote recurrence

Volkow, et al, NEJM. 2016
ASAM National Practice Guideline, June 1, 2015.

PCSS Providers Clinical Support System

Goals of MOUD

- Reduce mortality
  - All cause and substance-related mortality
- Reduce associated morbidity
  - Transmission of blood-borne viruses
  - Infectious complications from injection drug use
- Reduce and/or discontinue opioid use
- Increase retention in addiction treatment
- Improve general health, well-being, and quality of life

Volkow, et al, NEJM. 2016

Misconceptions about opioid agonist MOUD

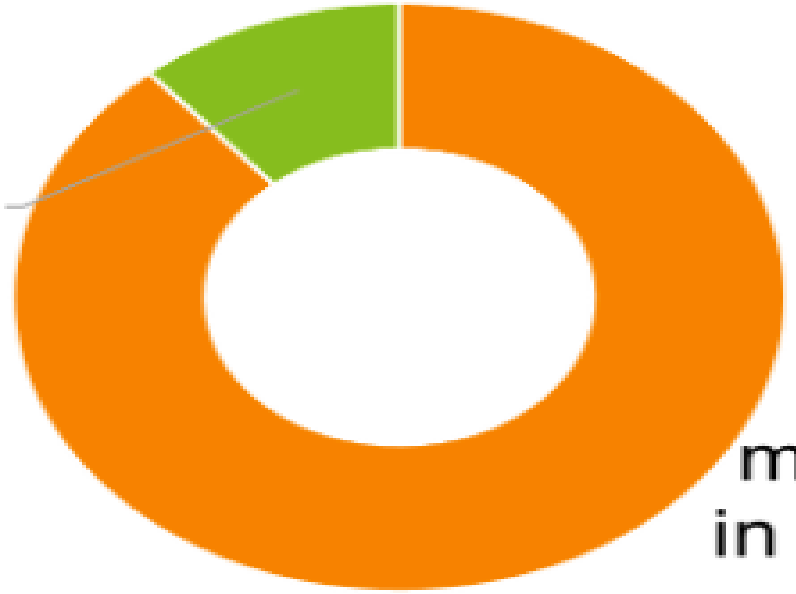
Potential barriers to treatment	Opportunities to facilitate treatment
Opioid agonist medications are substituting one drug addiction for another	Educate patients, families, and colleagues about the effectiveness of methadone and buprenorphine in treating the disease of addiction and reducing mortality
Medications for opioid use disorder require addiction medicine or psychiatry evaluation	Opioid withdrawal management can be started in the ED or hospital without waiting for specialty evaluation – helps reduce risk of discharge "against medical advice"!
Special training is required to prescribe buprenorphine	As of April 2021, licensed physicians or advanced practice providers can obtain a DEA waiver "X-number" to prescribe buprenorphine for up to 30 patients without special training

Slide courtesy: Tiffany Lu, MD

Most Americans with OUD do not receive medication treatment

2.5 million people aged 12+ had an opioid use disorder in 2020

Received medication treatment in the past year, ~11%



Did not receive medication treatment in the past year, ~89%

Source: 2020 National Survey on Drug Use and Health

Slide courtesy: Tiffany Lu, MD

What is Medication Management?

- Treatment of opioid withdrawal
- Medication initiation
- Evaluation for safety and effectiveness
- Confirmation of adherence
  - Urine drug testing, pill counts, patient report
- Evaluating treatment plan based on patient need and adherence
- Referral for or treatment of mental illness, if needed

- Also involves
  - Psychosocial needs assessment
  - Supportive counseling
  - Case management
  - Links to existing family supports
  - Referral to community services

ASAM National Practice Guideline, 2020

PCSS Providers Clinical Support System

Role of Counseling

- Purpose:[1]
  - Modify behaviors that maintain or reinforce drug use
  - Develop coping strategies
  - Encourage medication adherence
  - Treat or identify concomitant mental illness that can complicate SUD or trigger relapse
- Some evidence shows that psychosocial treatment improves adherence and retention in treatment[2-3], but findings are mixed[4-7]

[1] ASAM National Practice Guideline, 2015
[2] Brigham GS, et al, Drug Alcohol Dependence 2014
[3] Ruetsch C, et al, Addict Behav, 2012
[4] Fiellin, DA, et al, Am J Med 2013
[5] Fiellin DA, et al, NEJM 2006
[6] Tetrault JM et al, K Subst Abuse Treat 2012
[7] Weiss RD et al, Arch Gen Psych 2011

METHADONE

Dolophine ®

Methadose ®

HOW DOES METHADONE WORK?

- Methadone binds to the same receptor sites as other opioids.
- Orally effective
- Slow onset of action
- Long duration of action
- Slow offset of action

METHADONE MAINTENANCE

- Suppresses opioid withdrawal and reduces craving
- Oral administration (syrup or tablet forms used)
- Once daily doses enable lifestyle changes
- Counselling promotes long-term lifestyle changes
- Reduced participation in crime
- Reduced transmission of blood borne viruses
- Few long-term side-effects.

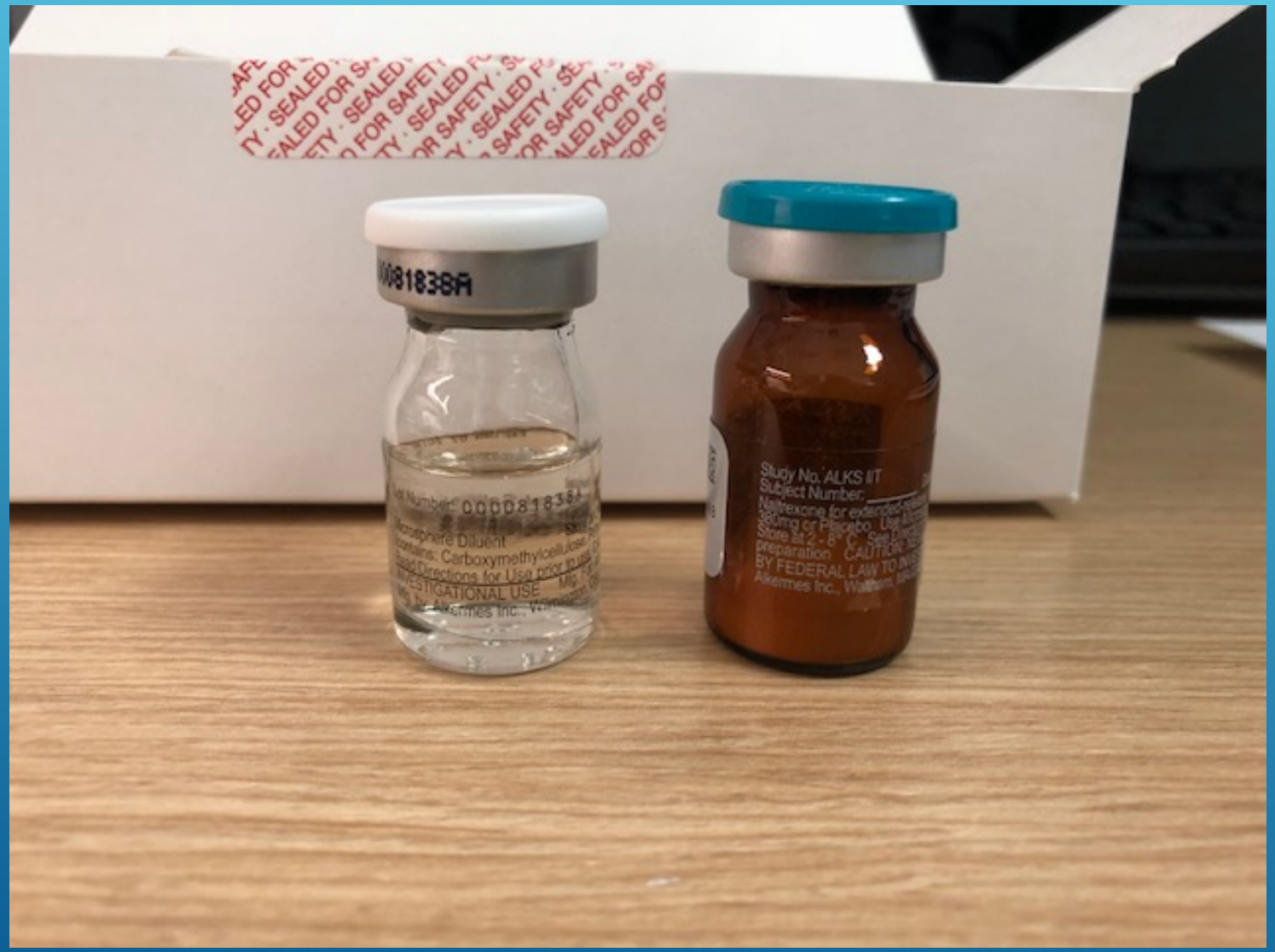
Methadone Safety Overview

- 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 Methadone maintenance
- No evidence of organ damage with chronic dosing

EFFECTIVE METHADONE TREATMENT

- As long as necessary
- Higher doses = > 60mg methadone.
- Make treatment as available as possible.
- Include counseling and ancillary services.
- Promote quality of therapeutic relationship.

EXTENDED-RELEASE NALTREXONE



HOW DOES EXTENDED-RELEASE NALTREXONE WORK?

- Extended-release naltrexone works in the brain exactly like oral naltrexone. Does not produced dependence. Must be opioid free to be inducted.

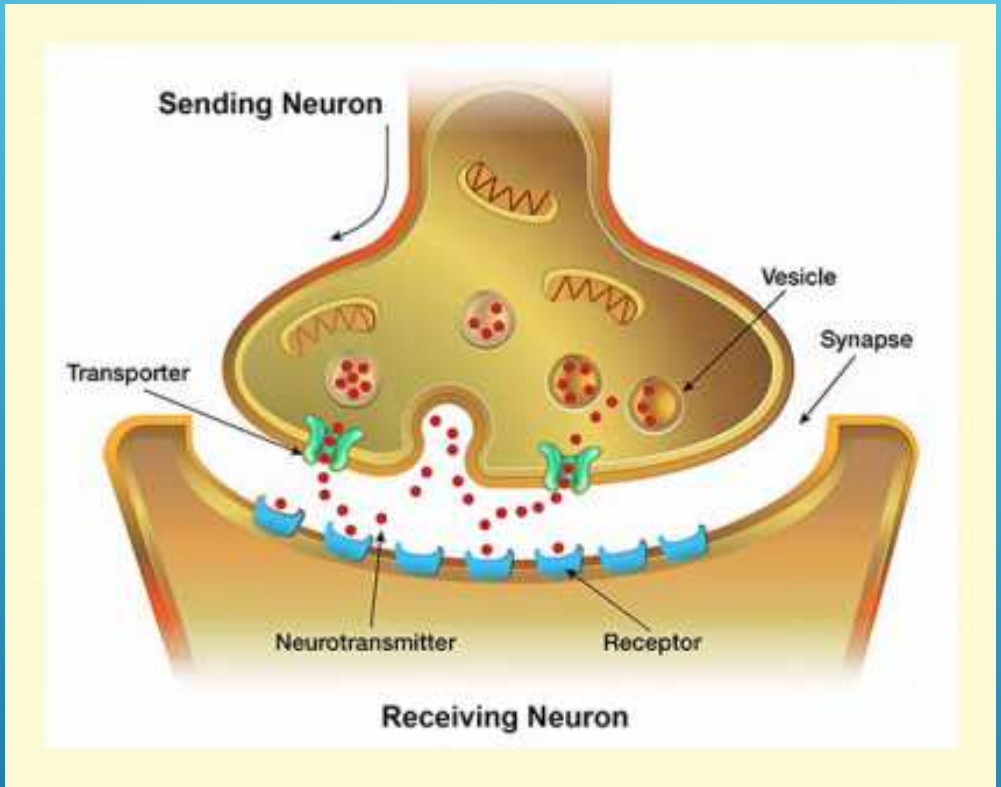
- Blocks opioid receptors for one entire month compared to approximately 28 doses of oral naltrexone to receive the same longevity.

- Since it is an intramuscular injection and not an implanted device, it is not possible to remove it from the body once extended-release naltrexone has been injected.

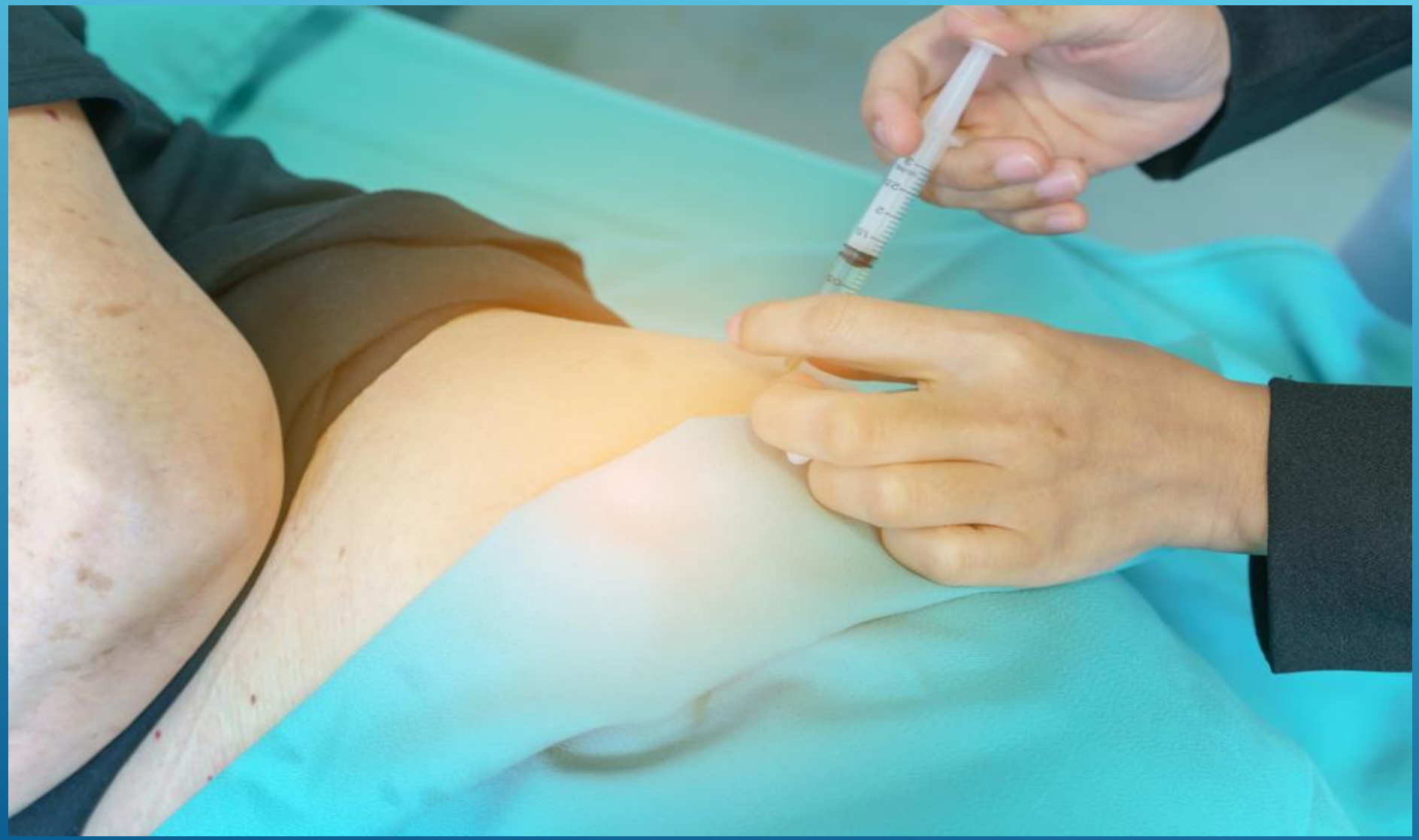
NALTREXONE MECHANISM OF ACTION

- Naltrexone is an opioid receptor antagonist.
- This prevents the effects of exogenously administered opioids.

- Approved for treatment of alcohol use disorder and opioid use disorder.
- Reduces cravings.



EXTENDED-RELEASE INJECTABLE NALTREXONE



EXTENDED-RELEASE NALTREXONE

- Marketed as Vivitrol ®
- **Dosing:** 380mg injection in deep gluteal muscle every 4 weeks; alternate sides each month.
- Blocks opioid receptors for **one entire month** compared to approximately 28 doses of oral naltrexone.
- **Adverse effects:** injection site reactions, nausea/vomiting, precipitated opioid withdrawal, depression, elevated LFTs
- ***Note:*** *Large doses of opioids may be required to override the blockade in a medically monitored setting*.

RESEARCH ABOUT EXTENDED-RELEASE NALTREXONE FOR OUD

When compared to placebo, those receiving extended-release naltrexone for 6 months:

- Had fewer opioid positive urines
- Stayed in treatment longer (improved retention)
- Had fewer cravings
- Showed greater improvement in the mental component of quality of life and overall health status
- Generally tolerated the medication without significant adverse effects

Krupitsky, et al., 2010

RESEARCH ABOUT EXTENDED-RELEASE NALTREXONE CONT'D

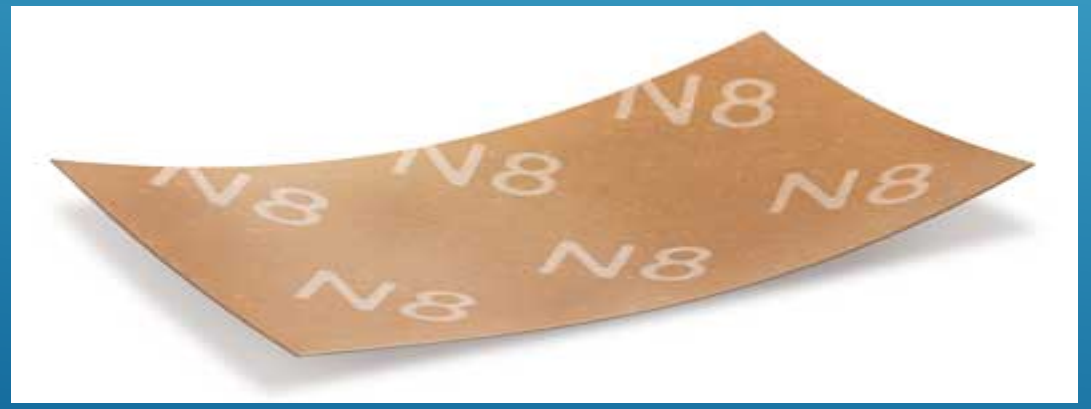
- Importantly, there were no attempts to override the blockade with large doses of opioids
- No accidental or intentional overdoses during or post-treatment
- No increase in rates of non-opioid drug use
  - Consistent with other studies demonstrating reduced use of other drugs when heroin use declines
- No clinically significant elevations in liver function enzymes
- Adverse effects: fatigue, nausea, injection site reactions

Comer et al., 2006

COMPARATIVE MEDICATION EFFECTIVENESS

- Meta-analyses: methadone slightly more effective than buprenorphine in retaining patients in treatment; equally effective in reducing opioid use *(Mattick et al., 2014)*
- X:BOT trial *(Lee et al., 2018)* - XR-naltrexone (NTX) vs. buprenorphine (BUP) for 24 weeks (n=570): induction rates lower for NTX than BUP (72% vs. 94%), but relapse rates equivalent once inducted
- Retrospective comparative effectiveness using claims data (Optum Labs), N=40,855 w/ OUD *(Wakeman et al., 2020):* methadone and buprenorphine associated with reduced OD and OUD-related morbidity at 3 and 12 mos compared w/ NTX, inpatient tx, IOP.

BUPRENORPHINE



BUPRENORPHINE FOR OPIOID USE DISORDER

- FDA approved 2002, age 16+
- Mandatory certification from DEA (up to 275 pt limit approved with qualifications)
- Mechanism: partial mu agonist
- Office-based, expands availability
- Analgesic properties
- Ceiling effect
- Lower abuse potential
- Safer in overdose

Suboxone Tablets 8mg. and 2mg

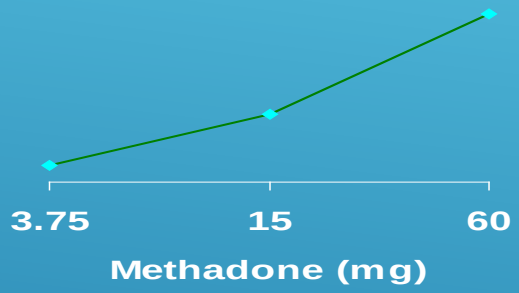
RESEARCH ON BUPRENORPHINE

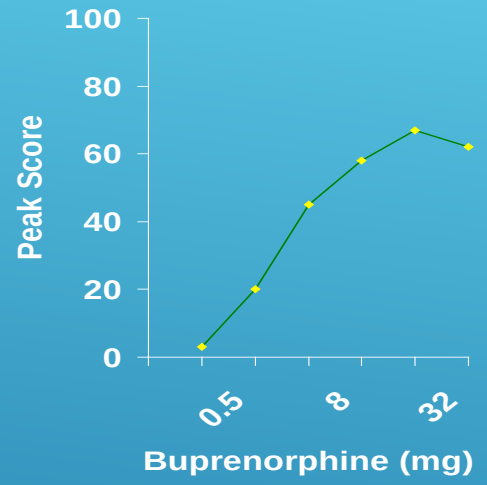
- Buprenorphine is marketed for the treatment of opioid use disorder under the trade names:
  - Subutex®
  - Suboxone® (buprenorphine/naloxone, sublingual film)
  - Probuphine ® (Implant-6 months)
  - Sublocade® (monthly injection)
- Over 5,000 patients exposed during clinical trials
- Over 25 years of research
- Proven safe and effective for the treatment of opioid use disorder

BUPRENORPHINE: PHARMACOLOGICAL CHARACTERISTICS

Partial Agonist (ceiling effect)

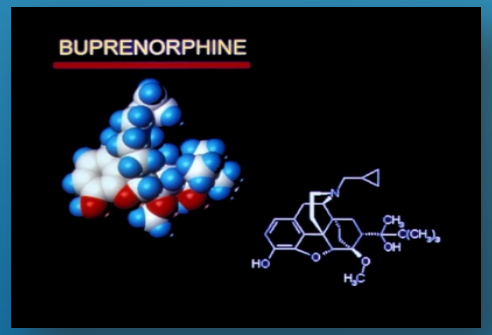
- -less euphoria
- -safer in overdose

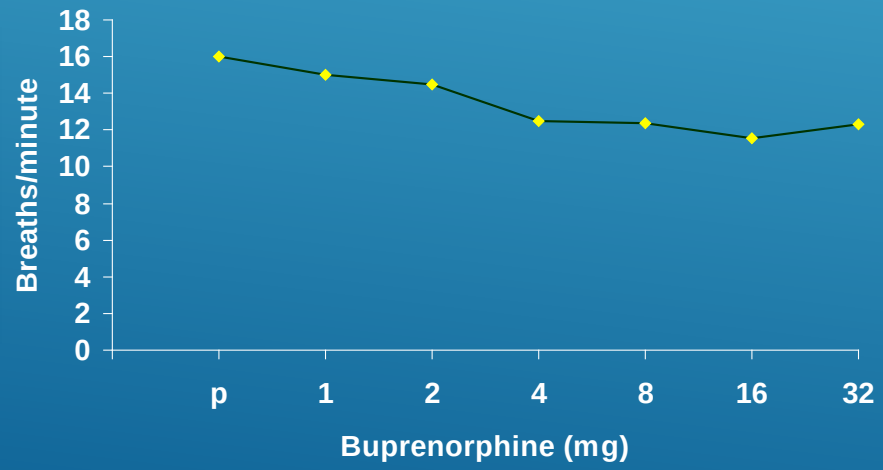


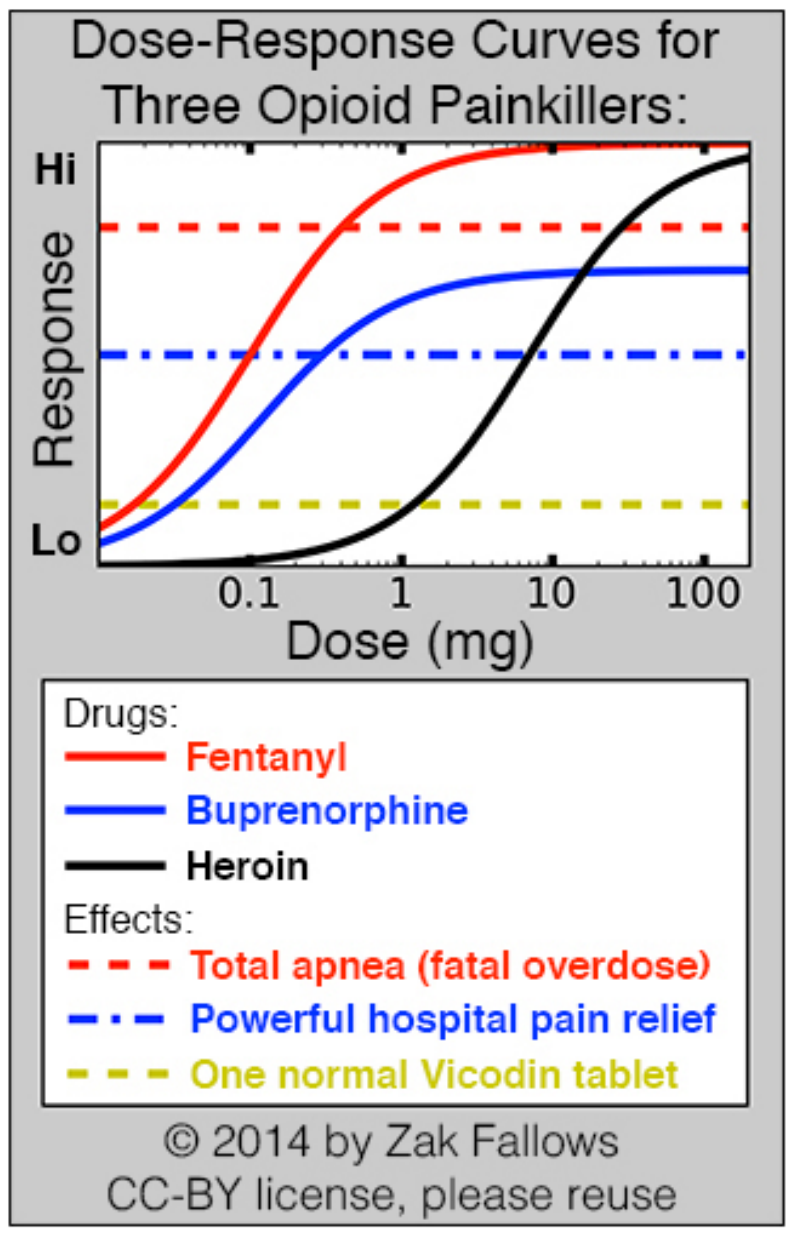


Strong Receptor Binding

- -long duration of action
- -1st dose given during withdrawal







The graph above shows the dose-response curves for three common opioid painkillers. Notice that fentanyl is 70 times more potent than heroin, but addicts and drug abusers generally prefer heroin. Buprenorphine is about 25 times more potent than heroin but it has a lower intrinsic efficacy (IE). As a result, the solid blue buprenorphine line never crosses the dashed red total apnea line. This means that even a massive overdose of buprenorphine will not cause total apnea (total cessation of breathing), so doctors can safely give buprenorphine to recovering addicts. More details on the course home graphic. (Image courtesy of Zak Fallows.) CC-BY.

Rationale for Buprenorphine/Naloxone Combination

- Naloxone present in attempt to decrease misuse or diversion
- Naloxone is mostly inactive unless injected
  - Very low bioavailability of naloxone when medication used sublingually
  - If patient with opioid dependence and not in opioid withdrawal, injection of buprenorphine/naloxone can precipitate withdrawal
  - If patient in opioid withdrawal, injection of buprenorphine/naloxone can have opioid withdrawal relieving effects
  - *Some debate on this topic*
  - *Use of combination product is typically recommended*

SAMHSA TIP 63: https://store.samhsa.gov/system/files/sma18-5063pt3.pdf

PCSS Providers Clinical Support System

TRANSMUCOSAL BUPRENORPHINE FORMULATIONS

- Sublingual dose: 2mg-24mg/day
- Subutex (buprenorphine) (2mg, 8mg)
- Suboxone (4:1 bup:naloxone)
  - -2mg/0.5 mg , 8mg/2mg
  - -(now also in 4mg/12mg)
- Zubsolv (4:1 bup:naloxone)
  - -(1.4/0.36mg- 11.4/2.9mg)
- Bunavail (6:1 buccal film bup:naloxone)
  - -(2.1/0.3mg, 4.2/0.7mg, 6.3/1mg)
- Belbuca (75-900mcg buccal film for pain)

BUPRENORPHINE IMPLANT: PROBUPHINE

- Probuphine™ is an implantable formulation of buprenorphine HCL (80 mg) approved for the treatment of opioid use disorder in patients stabilized on 8 mg/day or less sublingual buprenorphine
- Probuphine is inserted subdermally into the inner side of the upper arm in a brief in-office procedure under local anesthetic, and provides sustained release of buprenorphine for 6 months
  - At the end of each 6-month period, Probuphine is removed in a brief, in-office procedure

BUPRENORPHINE INJECTION: SUBLOCADE

- Sublocade is a monthly injectable formulation of buprenorphine approved in 2017 for the treatment of moderate to severe OUD in individuals who have initiated a transmucosal buprenorphine product and have been stabilized on treatment for at least seven days.
- The approved dosing regimen is 300 mg administered subcutaneously for the first two months, followed by maintenance doses of 100 mg/month.
- It must be prescribed as part of a Risk Evaluation and Mitigation Strategy to ensure that the product is not distributed directly to patients.

OPIOID USE DISORDER MEDICATION: EXTENDED-RELEASE BUPRENORPHINE - BRIXADI®

- FDA Approved May 23rd, 2023
- Subcutaneous administration
- Smaller needle (less injection site pain)
- Does not require refrigerated storage
- Varied dosage formulations (see table)
- Potential for more rapid transition from SL-BUP

Weekly Brixadi®	**Monthly** Brixadi®
8mg	n/a
16mg	64mg
24mg	96mg
32mg	128mg

ED BRIDGE *(D'ONOFRIO ET AL., 2015, JAMA):* PATIENTS WHO OBTAINED BUP RX IN ED WERE TWICE AS LIKELY TO BE ENGAGED IN ADDICTION TX 1 MONTH LATER RELATIVE TO THOSE GIVEN REFERRALS. THIS MODEL IS SIMILAR TO OTHER CHRONIC MEDICAL CONDITIONS SUCH AS HYPERTENSION, DIABETES, AND ASTHMA IN WHICH ED CLINICIANS INITIATE OR RESTART TREATMENT.

NALOXONE FOR OPIOID OVERDOSE

NARCAN/NALOXONE NASAL SPRAY

- Used to counteract life-threatening depression of the central nervous system and respiratory system.
- Non-scheduled.
- Non-addictive.
- Works only if opioids are present.
- No abuse potential.
- Can be injected or used nasally.
- Wears off in 20 – 90 minutes.

NALOXONE: IMPORTANT CONSIDERATIONS

- **Not a replacement for emergency medical treatment**
  - After using the client must **immediately** seek medical care
- Many opioids are long-acting, and naloxone may not last as long as the opioid
  - If overdose symptoms return, a second dose may be needed

Get Naloxone Now

Home | Our Mission | Get Training | Get Naloxone | Institutions | Links | Contact Us

http://www.getnaloxonenow.org/

Save a Life

Learn how to respond to an overdose emergency

Get Naloxone Now is an online resource to train people to respond effectively to an opioid-associated overdose emergency. Get Naloxone Now advocates for widespread access to overdose education and training in how to administer naloxone, the life-saving antidote for opioid-associated overdose. Get Naloxone Now seeks to increase the number of lives saved by bystanders and professional first responders (police officers, firefighters and EMTs). Find out how you can contribute to reducing overdose deaths by accessing our online training modules.

INDIVIDUALS-GET TRAINED! | **INSTITUTIONAL PROGRAM** | **HOW CAN YOU HELP**

OPIOID OVERDOSE PREVENTION: OPVEE® (NALMEFENE)

- FDA Approved May 22nd, 2023
- Over-the-counter nasal spray for emergency treatment of known or suspected opioid overdose
  - For adults and pediatric patients aged 12 years and older
- OPVEE nasal spray is for intranasal use only
- 2.7 mg of nalmefene in 0.1 mL dose
- Higher potency than naloxone (Narcan)

Image retrieved from NPR

OPIOID USE DISORDER & OVERDOSE PREVENTION: OPIOID VACCINE

- Generates anti-opioid antibodies that bind to the consumed opioid, which prevent it from entering the brain
  - Initially studied in animal models and plans for human testing
- Benefits
  - More effective treatment of patients at high risk of misusing other medications
  - Long duration (lasts months to years)
  - Will not interfere with most drug treatment or pain management
  - Protection against accidental exposure

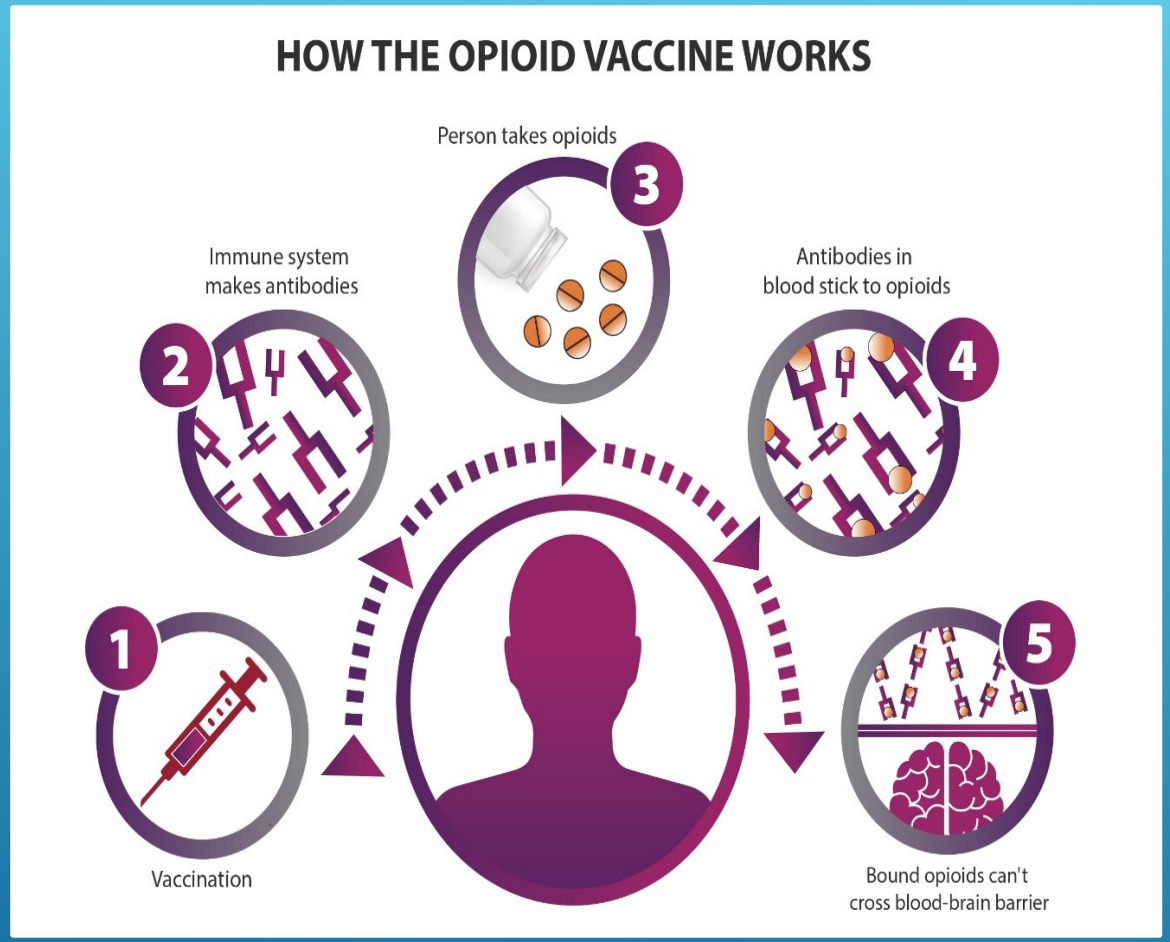


Image retrieved from NIH HEAL Initiative

FINAL NOTE: BEHAVIORAL TREATMENTS

The FDA labeling on these medications is clear:

The medications should be used in combination with behavior treatments for addiction

Good treatment is holistic, integrated and multifaceted, taking into account the physical, behavioral and spiritual wellbeing of the individual.

Medications can help us take care of the physical...

...we need to do the rest

https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document-Including-Executive-Summary-and-Parts-1-5-/SMA18-5063FULLDOC

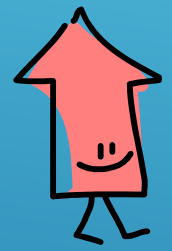
THE PHARMACOLOGY OF ALCOHOL

NEUROTRANSMITTERS

neurotransmitter effects when alcohol is consumed.

dopamine
makes you happy

endogenous opioids
make you euphoric and feel no pain



glutamate
the main excitatory neurotransmitter…it speeds you up

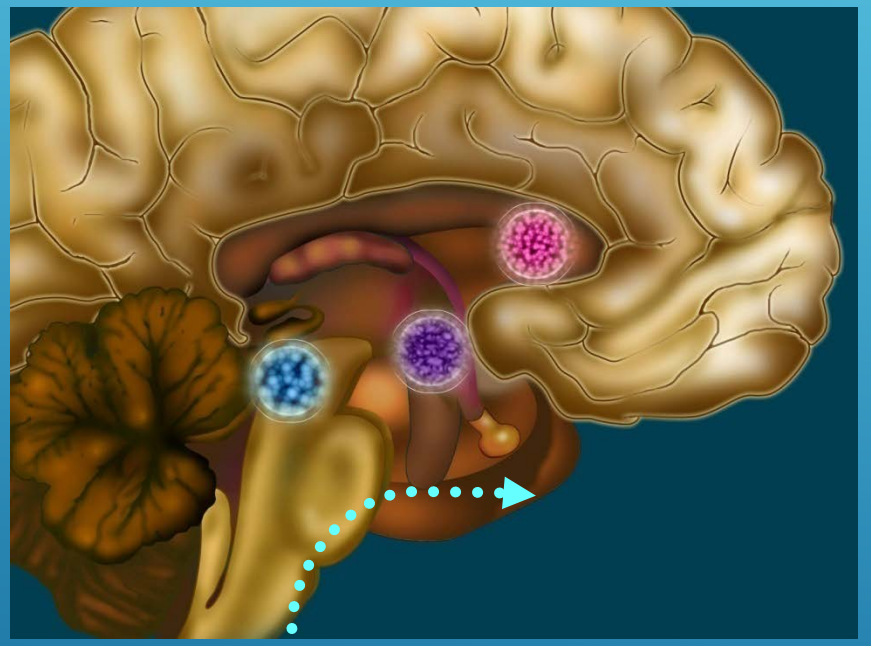
GABA –
the main inhibitory neurotransmitter… it slows you down (Gamma-AminoButyric Acid)

ALCOHOL NEURONAL ACTIVITY

1. Alcohol is ingested

2. The brain's natural endogenous opioids are first released.

3. This activates the areas the pleasure centers of the brain.



ALCOHOL NEURONAL ACTIVITY

3. This causes dopamine to be released.

4. Since dopamine is a main reward neurotransmitter, increases in the nucleus accumbens makes the drinker feel good.

5. The brain remembers those good feelings caused by the dopamine and alcohol.

6. The brain desires to repeat the behavior again to get the same good feelings.

ANOTHER NEURONAL ACTIVITY (AT THE SAME TIME…)

1. Alcohol is ingested.

2. GABA, a major inhibitory neurotransmitter, is increased and creates an imbalance in the brain.

3. The brain is constantly trying to maintain a balance of inhibitory and excitatory signals so homeostasis can be achieved, and this increase in GABA caused by alcohol creates an imbalance.

4. The excitatory signals of glutamate are overridden by the increase in GABA, and the body generally slows down.

ANOTHER NEURONAL ACTIVITY

5. Since the glutamate excitatory signals are overridden by the GABA inhibitory signals, glutamate is not able to activate the NMDA (glutamate) receptors as it usually does.

6. So, the brain increases the amount of NMDA receptors available for glutamate, in hopes that more opportunities for activation will yield more activity.
   This process is called upregulation.

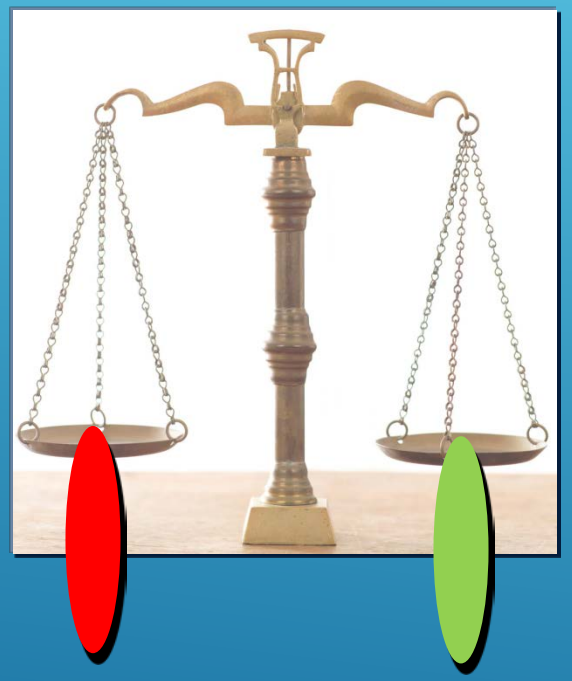
ANOTHER NEURONAL ACTIVITY

7. As the brain desired, this method of upregulation works and the imbalance is corrected.

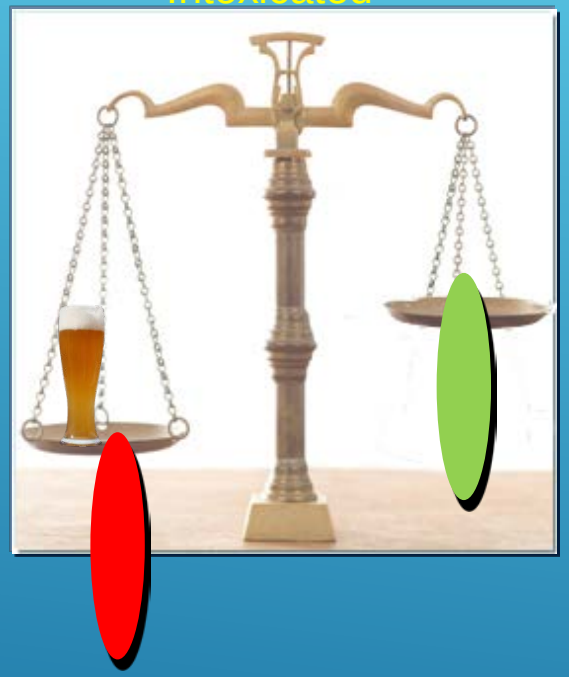
8. However, more alcohol is required to feel the same level of intoxication (tolerance).

ANOTHER NEURONAL ACTIVITY

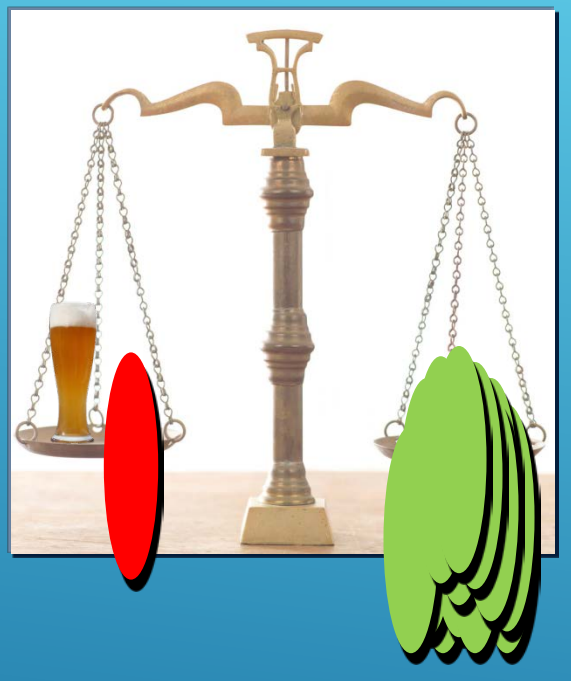
Normal



Intoxicated



Tolerance



So now the brain has fully adapted to constant presence of alcohol. What do you think will happen once alcohol is taken away?

GABA

GLUTAMATE

ANOTHER NEURONAL ACTIVITY

What do you think will happen once alcohol is taken away?

WITHDRAWAL

Gaba

Glutamate

PREDISPOSING FACTORS FOR HIGH-RISK DRINKING

- Family history of alcohol problems
- Childhood problem behaviours related to impulse control
- Poor coping responses in the face of stressful life events
- Depression, divorce, or separation
- Drinking partner
- Working in a male-dominated environment

CONCURRENT MENTAL HEALTH PROBLEMS

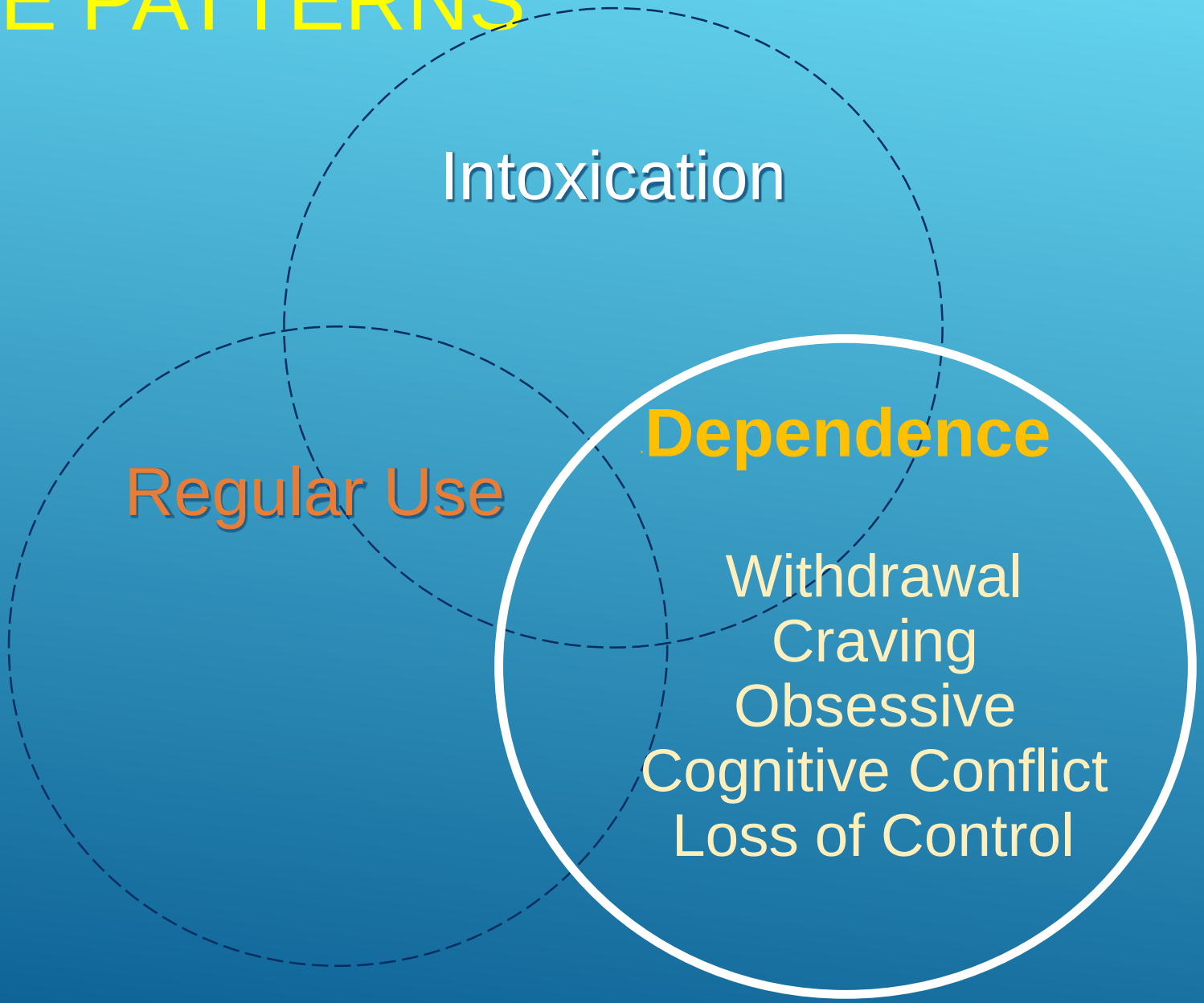
Alcohol may:

- exacerbate existing mental health problems
- interact with prescribed medications
- reduce or exacerbate the effect of certain medications
- reduce patient compliance with treatment regimens

EFFECTS OF ALCOHOL INTOXICATION

.01-.02	Clearing of head
.02-.05	Mild throbbing rear of head, slightly dizzy, talkative, euphoria, confidence, clumsy, flippant remarks
.06-1.0	⇓ inhibitions, ⇑ talkativeness, ⇓ motor co-ord, ⇑ pulse, stagger, loud singing!
0.2-0.3	Poor judgement, nausea, vomiting
0.3-0.4	Blackout, memory loss, emotionally labile
0.4+	Stupor, breathing reflex threatened, deep anaesthesia, death

USE PATTERNS



HARMS ASSOCIATED WITH HIGH-RISK ALCOHOL USE

- Hypertension, CVA (CerebroVascular Accident – Stroke)
- Cardiomyopathy
- Peripheral neuropathy
- Cirrhosis and hepatic or bowel carcinomas
- Cancer of lips, mouth, throat, and esophagus
- Cancer of breast
- Fetal alcohol syndrome

ALCOHOL-RELATED BRAIN INJURY

- Cognitive impairment may result from consumption levels of >70 grams per day
- Thiamine deficiency leads to:
  - Wernicke's encephalopathy
  - Korsakoff's psychosis
- Frontal lobe syndrome
- Cerebellar degeneration
- Trauma

CHOOSING A TREATMENT OPTION - 1

Severity	Goal	Intervention options
No major lifestyle disruptions, not severely dependent	Reducing consumption/ controlled (or even Abstinence)	1. Brief intervention 2. Support 3. Reinforcement of positive behaviors

CHOOSING A TREATMENT OPTION - 2

Severity	Goal	Treatment options
Major lifestyle disruptions, significant dependence	Abstinence	For example: • Motivational interviewing • outpatient counseling • group or individual work (skills training, relapse prevention) • marital and family therapy • loss and grief counseling • self-help / support groups
		**Above options plus**: • withdrawal management • pharmacotherapy • residential rehabilitation

INTERVENTIONS AND TREATMENT FOR ALCOHOL-RELATED PROBLEMS

- Screening and assessment ➔ individualized interventions
- Brief intervention and harm reduction strategies
- Withdrawal management
- Relapse prevention / goal-setting strategies
- Controlled drinking programs
- Residential programs
- Self-help groups
- Medicines

WITHDRAWAL

Usually occurs 6–24 hours after last drink:

- tremor
- anxiety and agitation
- sweating
- nausea and vomiting
- headache
- sensory disturbances – hallucinations

Severity depends on:

- pattern, quantity and duration of use
- previous withdrawal history
- patient expectations
- physical and psychological wellbeing of the patient (illness or injury)
- other drug use/dependence
- the setting in which withdrawal takes place

TREATMENT OF ALCOHOL WITHDRAWAL SYMPTOMS

Medications for Symptomatic Treatment

- Diazepam
- Thiamine & multivitamins
- Antiemetic
- Analgesia (e.g., paracetamol)
- Antidiarrhoeal

POST-ACUTE WITHDRAWAL MANAGEMENT

- Treatment options:
  - retain in treatment, ongoing management
  - seek referral
- Considerations:
  - patient’s wants (abstinence or reduced consumption, remaining your patient)
  - severity of problems

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MEDICATIONS FOR ALCOHOL USE DISORDERS

- **Acamprosate**
- **Naltrexone**
- **Disulfram**
- **Extended-Release Naltrexone**


ACAMPROSATE
Campral ®

ACAMPROSATE GENERAL FACTS

- Generic Name:
  - acamprosate calcium
- Marketed As:
  - Campral®
- Purpose:
  - Encourages sobriety by reducing post-acute withdrawal symptoms from alcohol dependence
- Indication:
  - For the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation.
- Year of Food and Drug Administration(FDA)-Approval: 2004

ADDITIONAL INFORMATION

Addictive Properties:

- Has not been found to be addictive and no reports of misuse

Cost:

- $135.90 per month, which is around $4.53 a day.[46]

Third-Party Payer Acceptance:

- Patient Assistance Program through Forest Laboratories, Inc.
- Covered by most major insurance carriers,
- Covered by Medicare, Medicaid, and the US Department of Veterans Affairs (VA) (if naltrexone is contraindicated).

HOW DOES ACAMPROSATE WORK?

Mechanism of Action:

glutamate receptor modulator

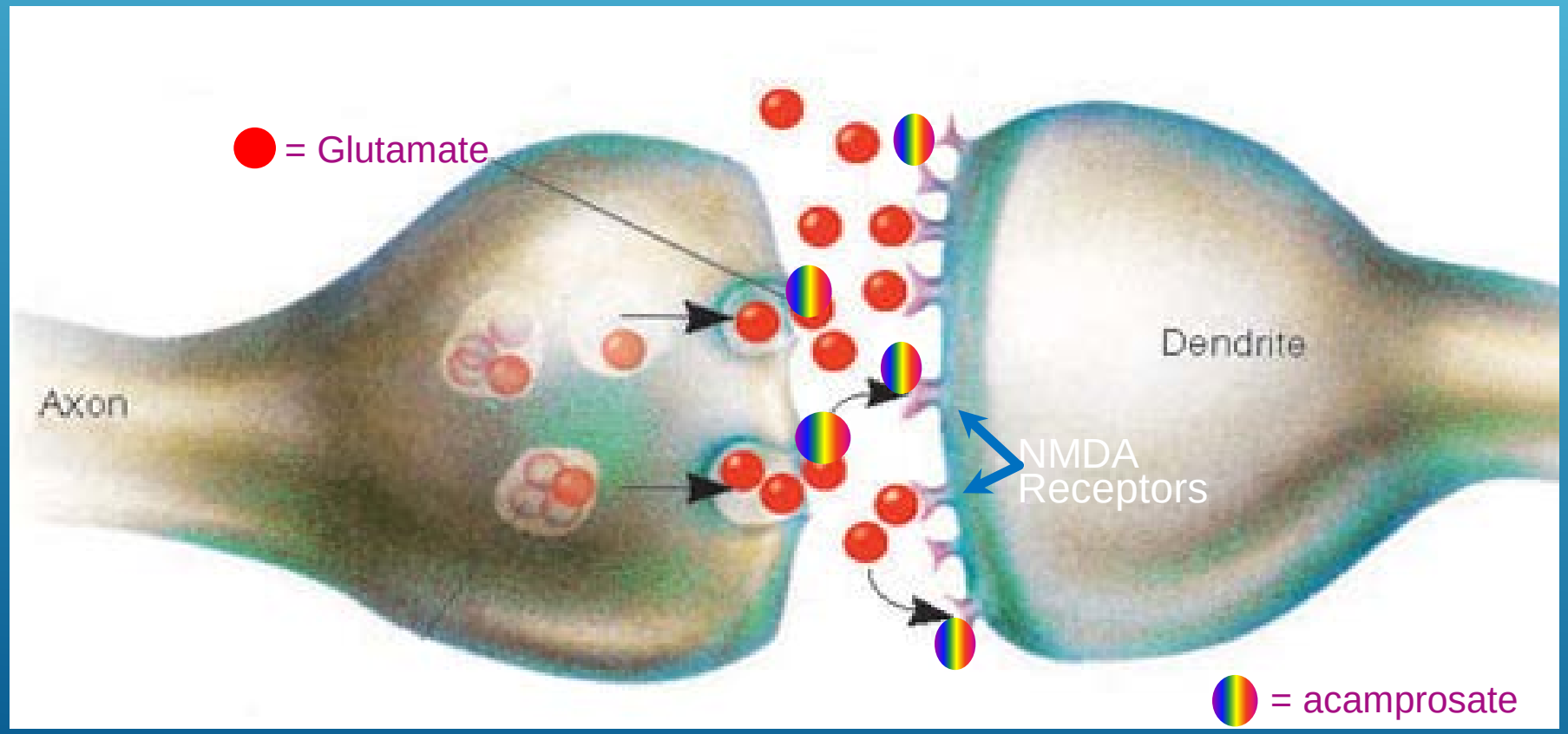
Remember that repetitive consumption of alcohol causes:

the brain to suppress glutamate activity,
which causes an increase in NMDA receptors,
counteracting alcohol's depressive effects.

NOTE: The mechanism of action of acamprosate is not completely understood.

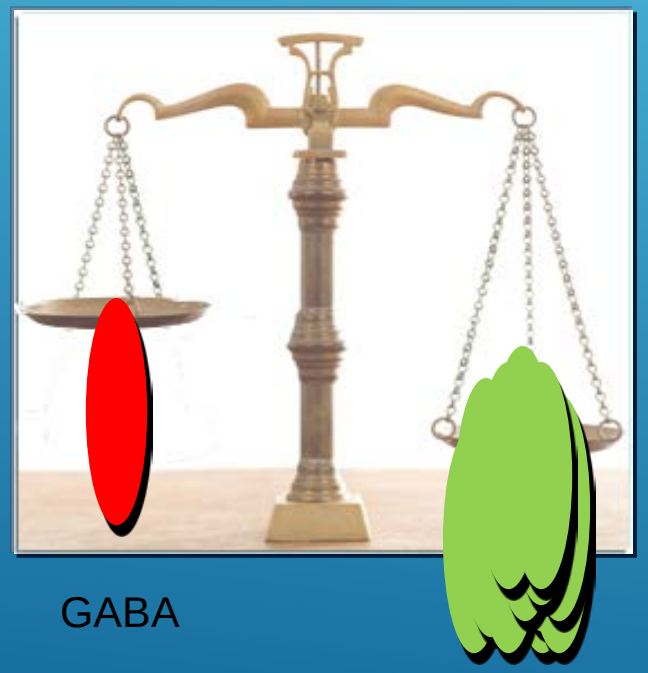
HOW DOES ACAMPROSATE WORK?

- reduces glutamate activity by “monitoring” the amount of glutamate that can react at the NMDA receptors
- limits the amount of glutamate released by the neuron



HOW DOES ACAMPROSATE WORK?

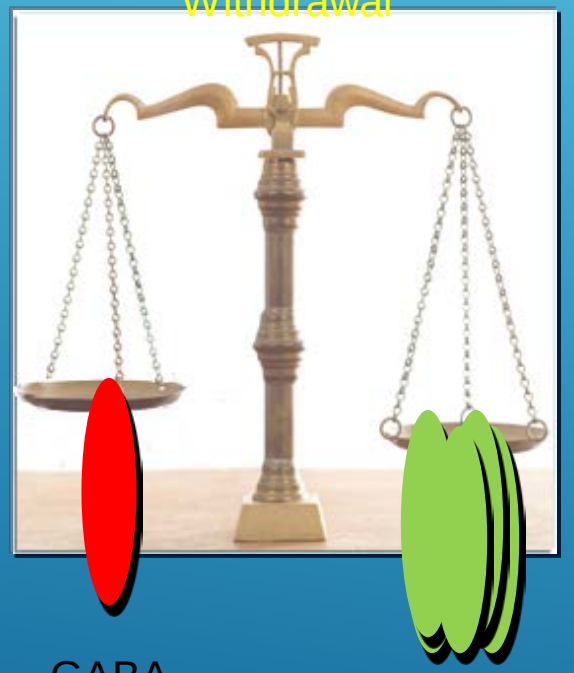
Withdrawal



GABA

Glutamate

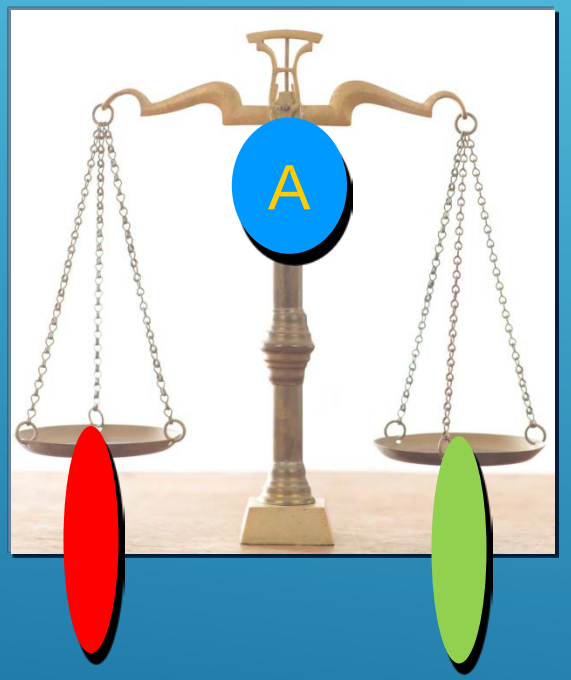
Post Acute Withdrawal



GABA

Glutamate

Normal



GABA

Glutamate

RESEARCH ABOUT ACAMPROSATE

When compared to placebo, participants treated with acamprosate:

- **Were able to maintain complete abstinence more frequently**
- **Had a greater reduction in the number of drinking days**
- **Were able to regain complete abstinence after one relapse more frequently than those treated with placebo.**

(Paille, et al., 1994; Pelc, et. al, 1997; Sass, et al., 1996)


NALTREXONE
Revia ® or Depade ®

NALTREXONE GENERAL FACTS

- Generic Name:
  naltrexone hydrochloride
- Marketed As:
  ReVia® and Depade®
- Purpose:
  To discourage drinking by decreasing the pleasurable effects experienced by consuming alcohol.
- Indication:
  In the treatment of alcohol dependence and for the blockade of the effects of exogenous administered opioids.
- Year of FDA-Approval: 1994

ADDITIONAL INFORMATION

- Addictive Properties:
  Has not been found to be addictive or produce withdrawal symptoms when the medication is ceased.

- Administering naltrexone will invoke opioid withdrawal symptoms in patients who are physically dependent on opioids.

- Cost:
  ~ $30.00 to $100.00 per month, which is around $1.00 to 3.33 a day.

- Third-Party Payer Acceptance:
  Covered by most major insurance carriers, Medicare, Medicaid, and the VA.[68]

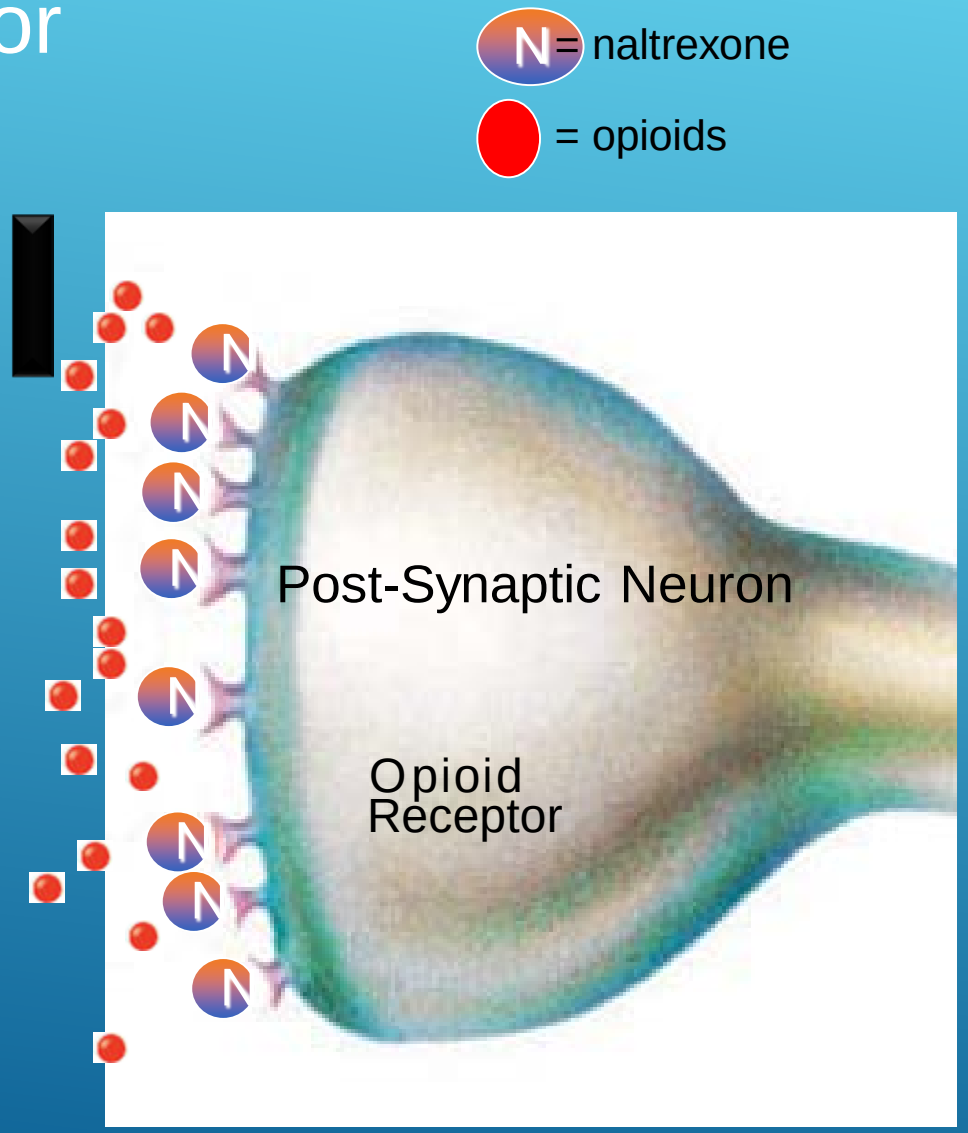
HOW DOES NALTREXONE WORK?

Remember:

1. Endogenous opioids are first released from the arcuate nucleus, which activates the areas of the brain known as the ventral tegmental area and the nucleus accumbens.
2. In response to this increased endogenous opioid activity, dopamine is released.
3. Since dopamine is a main reward neurotransmitter, increases in the nucleus accumbens makes the drinker feel good.
4. The brain remembers those good feelings caused by the dopamine and alcohol.
5. The brain desires to repeat the behavior again to get the same good feelings.

HOW DOES NALTREXONE WORK?

- Naltrexone is an opioid receptor antagonist, so it blocks opioid receptors.



By blocking opioid receptors, the “reward” and acute reinforcing effects from dopamine are diminished, and alcohol consumption is reduced.

RESEARCH FOR NALTREXONE

When compared to placebo, those receiving naltrexone

- **Were NOT able to maintain complete abstinence more frequently**
- **Had a greater reduction in relapse during the entire study**

(Paille, et al., 1994; Pelc, et. al, 1997; Sass, et al., 1996)

NALTREXONE FOR EXTENDED-RELEASE INJECTABLE SUSPENSION

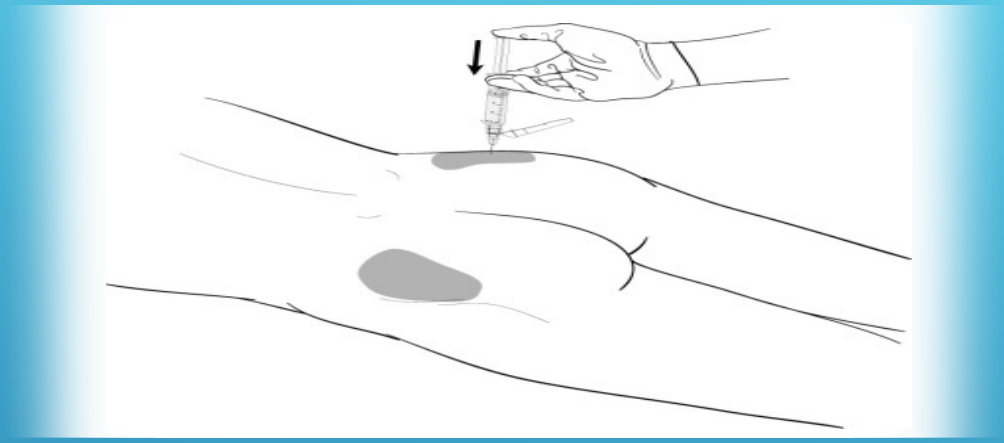
Vivitrol®

EXTENDED-RELEASE NALTREXONE ADMINISTRATION

Amount: one 380mg injection

Method: deep muscle in the buttock

Frequency: every 4 weeks



Must be administered by a healthcare professional and should alternate buttocks each month.

HOW DOES EXTENDED-RELEASE NALTREXONE WORK?

- Extended-release naltrexone works in the brain exactly like oral naltrexone.
- Blocks opioid receptors for one entire month compared to approximately 28 doses of oral naltrexone to receive the same longevity.
- Since it is an intramuscular injection and not an implanted device, it is not possible to remove it from the body once extended-release naltrexone has been injected.

ADDITIONAL INFORMATION FOR EXTENDED-RELEASE NALTREXONE

- Addictive Properties: Not addictive, no high abuse liability, does not build tolerance, nor produce withdrawal symptoms when the medication is ceased. There were no reports of misuse, such as injection, smoking or prescription deviation during the clinical trials. However, administering naltrexone will invoke opioid withdrawal symptoms in patients who are physically dependent on opioids.

- Cost: Average cost of ERN is $859.66 (VA) - $1,309.00

- Third-Party Payer Acceptance: Approximately 90% of patients thus far have received insurance coverage with no restrictions. In addition, extended-release naltrexone now has a J code for payors.

SCIENTIFIC RESEARCH ABOUT EXTENDED-RELEASE NALTREXONE (CONT.)

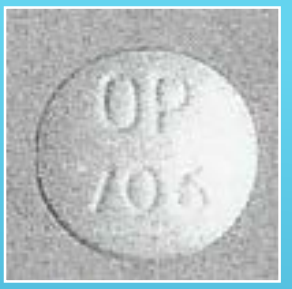
When compared to placebo, those treated with extended-release naltrexone

- **Did NOT maintain complete abstinence more frequently**
- **Had a greater reduction in the number of heavy drinking days during the entire study**
- **Those who had a seven-day abstinence period prior to treatment initiation had a greater reduction in the number of heavy drinking days during the entire study**

DISULFIRAM

Antabuse ®

DISULFIRAM GENERAL FACTS



- Generic Name: disulfiram
- Marketed As: Antabuse®
- Purpose: Discourages drinking by making the patient physically sick when alcohol is consumed.
- Indication: An aid in the management of selected chronic alcohol patients who want to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage.
- Year of FDA-Approval: 1951

ADDITIONAL DISULFIRAM INFORMATION

- Addictive Properties: Has not been found to be addictive, have a high abuse liability, or produce withdrawal symptoms when the medication is ceased. There were no reports of misuse, such as injection, smoking or prescription deviation during the clinical trials.[61]

- Cost: $57.59 per month, which is around $1.92 a day.[62]

- Third-Party Payer Acceptance: Covered by most major insurance carriers, Medicare, Medicaid, and the VA.[61]

HOW DOES DISULFIRAM WORK?

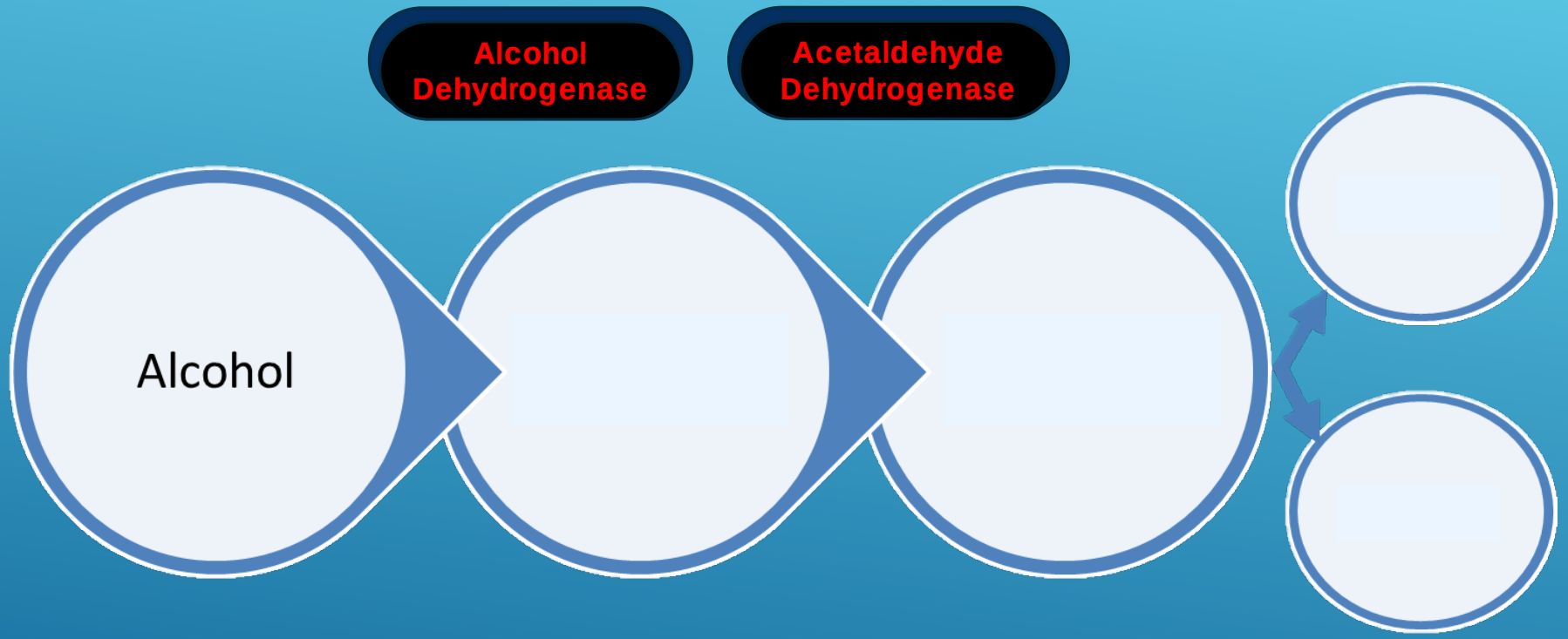
Disulfiram works by blocking the oxidation of alcohol during the acetaldehyde stage. When alcohol is ingested:

1. alcohol is broken down in the liver by the enzyme alcohol dehydrogenase to acetaldehyde;

2. then, acetaldehyde is converted by the enzyme **acetaldehyde dehydrogenase** to acetic acid.

Disulfiram works by blocking the enzyme acetaldehyde dehydrogenase. This causes acetaldehyde to accumulate in the blood at 5 to 10 times higher than what would normally occur with alcohol alone.

How Does Disulfiram Work?



HOW DOES DISULFIRAM WORK?

Since **acetaldehyde is poisonous**, a buildup of it produces a highly unpleasant series of symptoms, which is commonly referred to as the "disulfiram-alcohol reaction."

- throbbing in head/neck
- brief loss of consciousness
- throbbing headache
- lowered blood pressure
- difficulty breathing
- marked uneasiness
- copious vomiting
- nausea
- flushing
- sweating
- thirst
- weakness
- chest pain
- dizziness
- palpitation
- hyperventilation
- rapid heartbeat
- blurred vision
- confusion
- respiratory depression
- cardiovascular collapse
- myocardial infarction
- congestive heart failure
- unconsciousness
- convulsions
- death

SIDE EFFECTS OF DISULFIRAM

- Common side-effects:
  - skin rash
  - acneform eruption
  - headache
  - mild drowsiness
  - mild fatigue
  - impotence
  - metallic or garlic-like aftertaste

- Consult a physician:
  - extreme fatigue
  - weakness
  - loss of appetite
  - nausea
  - vomiting
  - general sense of uneasiness
  - yellowness of the skin or eyes (liver disease)
  - dark urine (liver disease)

Serious side effects = eye pain, peripheral neuritis, polyneuritis, peripheral neuropathy, hepatitis, hepatic failure

SCIENTIFIC RESEARCH ABOUT DISULFIRAM (CONT.)

When compared with placebo, those receiving disulfiram:

- Did NOT maintain complete abstinence more frequently
- Had a greater reduction in the number of drinking days during the entire study

(Fuller, et al., 1986)

Thank you for your attention

What additional questions

do you have?

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What is the difference between “tolerance,” “dependence,” and “addiction”?

Opioid tolerance occurs when a person using opioids begins to experience a reduced response to medication, requiring more opioids to experience the same effect.

Opioid dependence occurs when the body adjusts its normal functioning around regular opioid use. Unpleasant physical symptoms occur when medication is stopped.

Opioid addiction (Opioid use disorder (OUD)) occurs when attempts to cut down or control use are unsuccessful or when use results in social problems and a failure to fulfill obligations at work, school, and home. Opioid addiction often comes after the person has developed opioid tolerance and dependence, making it physically challenging to stop opioid use and increasing the risk of withdrawal.