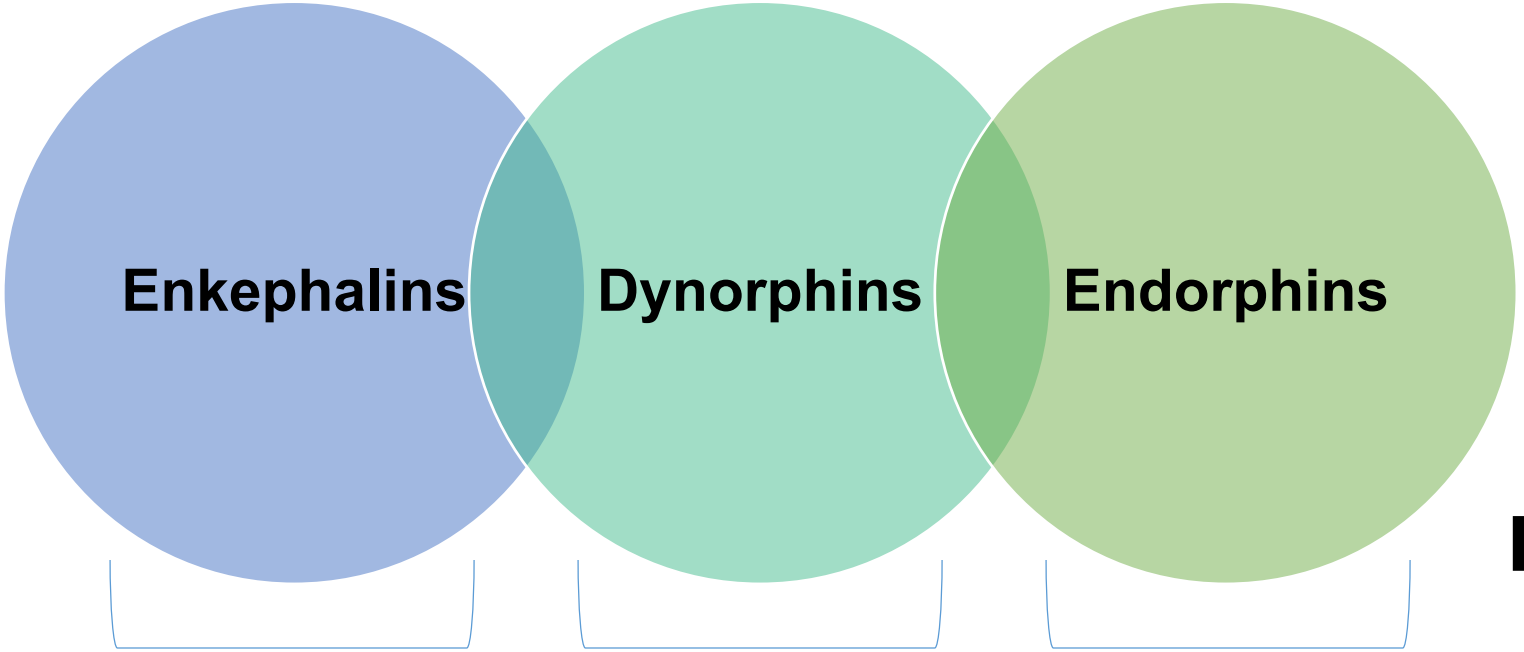
Opioid Use Disorder: Pharmacology, the Addiction Model of Disease, MOUD, and more

Aditi Ringwala, MD


What are Opioids?

Endogenous Opioids



Mu, Kappa, Delta Receptors

- Decreased pain
- Decreased anxiety
- Respiratory depression

“Natural” Opioids (Opiates)

- Opium
- Morphine
- Codeine
- Heroin

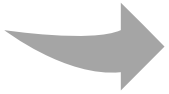
Pharmacology 101

- Natural = derived directly from poppy
  - Opium
  - Morphine
  - Codeine
  - Heroin
- Semi-synthetic = chemical modifications to natural opioids
  - Oxycodone
  - Hydrocodone
  - Hydromorphone
  - Oxymorphone
  - Buprenorphine
- Synthetic= chemically manufactured
  - Methadone
  - Fentanyl
  - Fentanyl Analogues: Carfentanyl (30-100x potency to fentanyl), furanylfentanyl (7x), Sufentanil (10x)

Pharmacology 102

Affinity

How tightly does it bind to the opioid receptor



Agonism

How large is the effect after binding to the opioid receptor

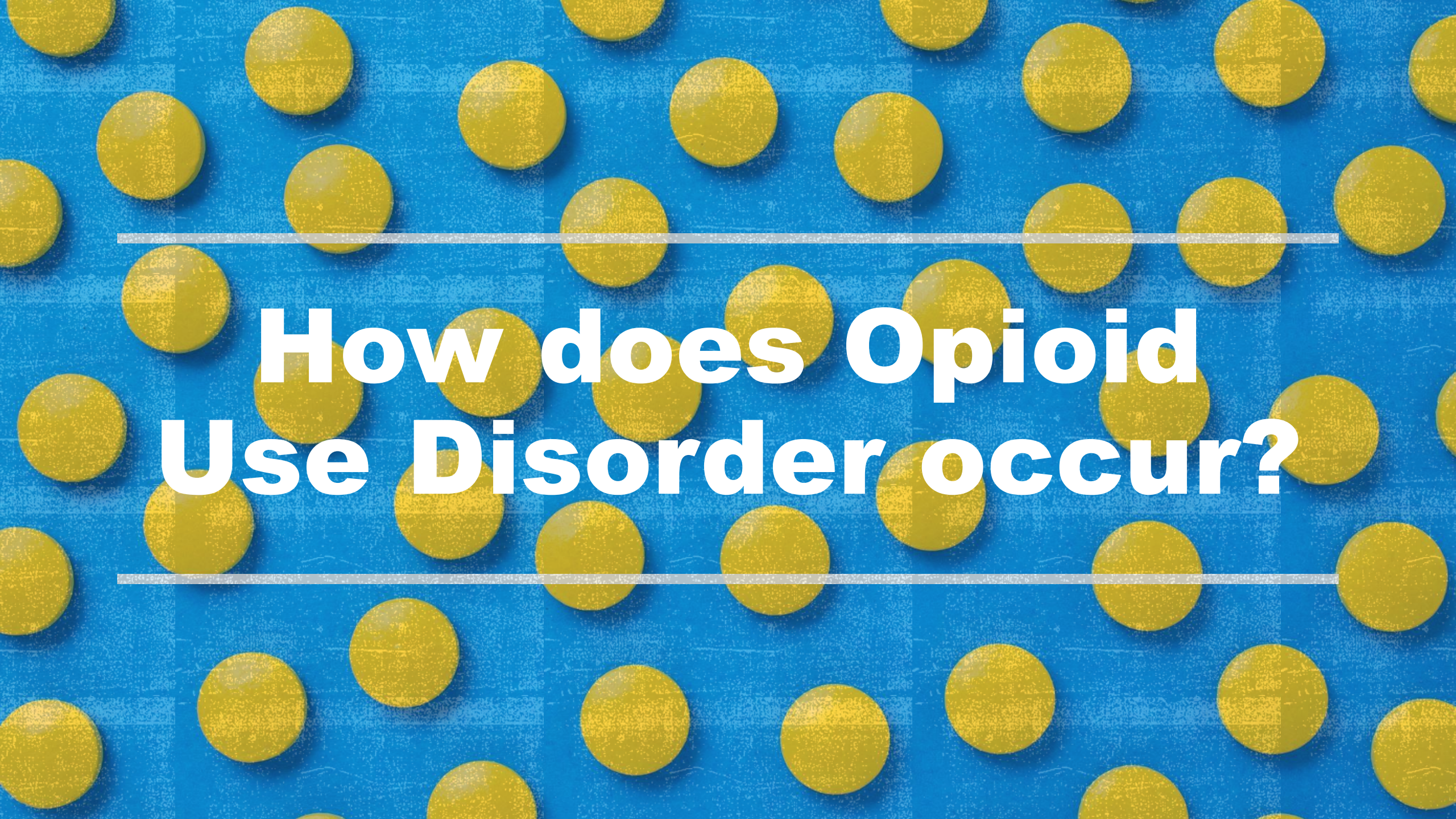
Dissociation

How long does it stay bound to the opioid receptor

Half-Life

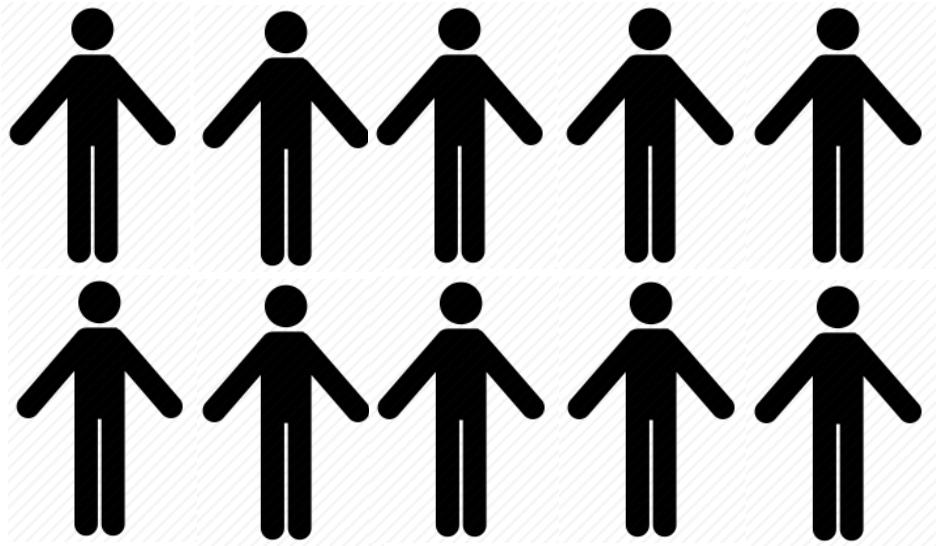
How long does it take for the drug to be metabolized

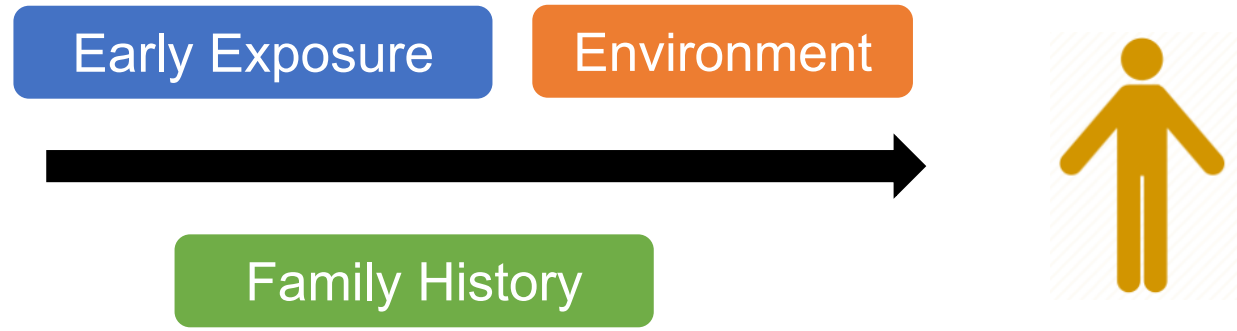
Pharmacology Matters


How does Opioid Use Disorder occur?

Disease Model of Addiction

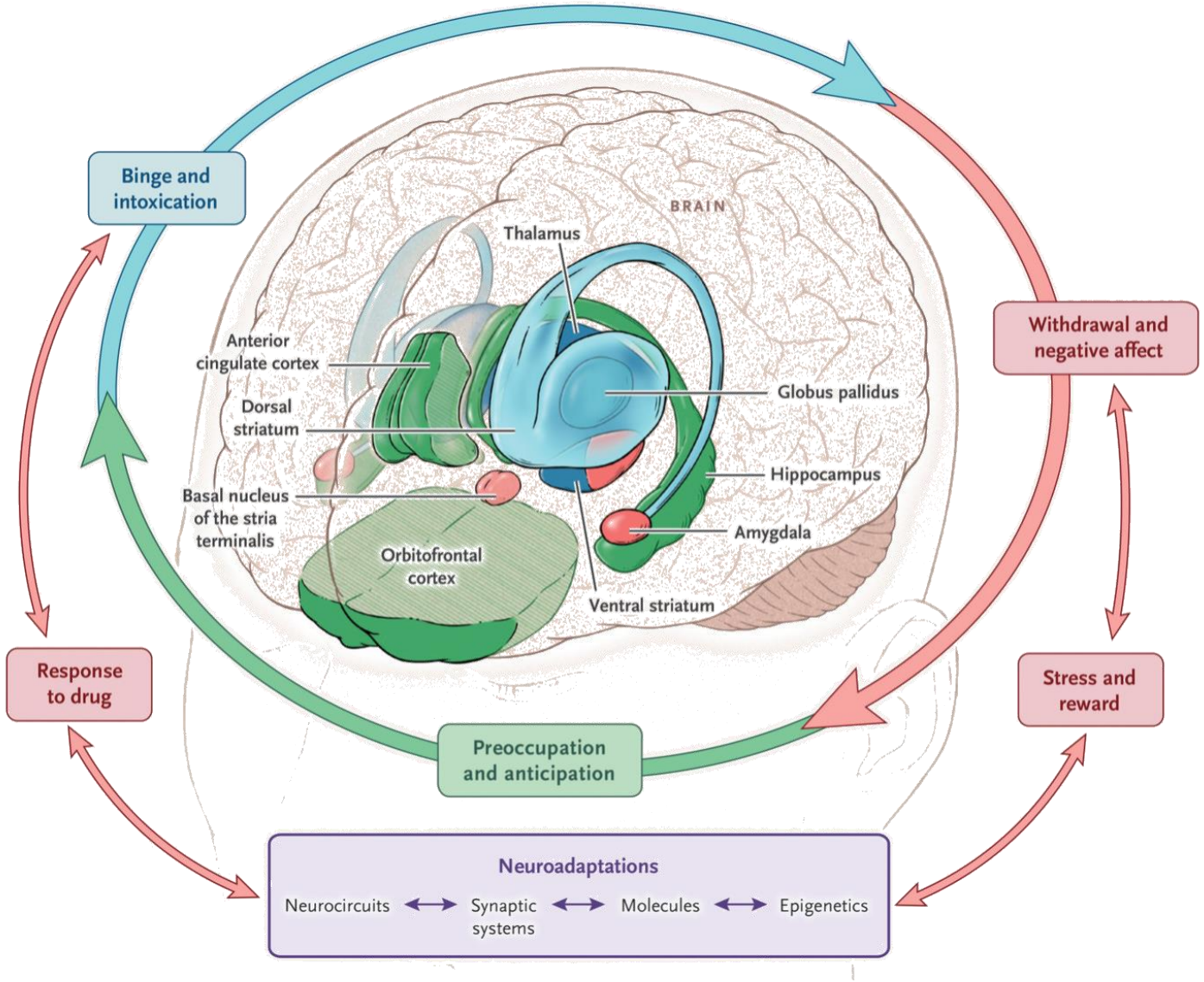
- Addiction is an acquired disease of the brain
- Stages of addiction are consistent across substances
- Social and biologic factors contribute





Volkow, NEJM 2014

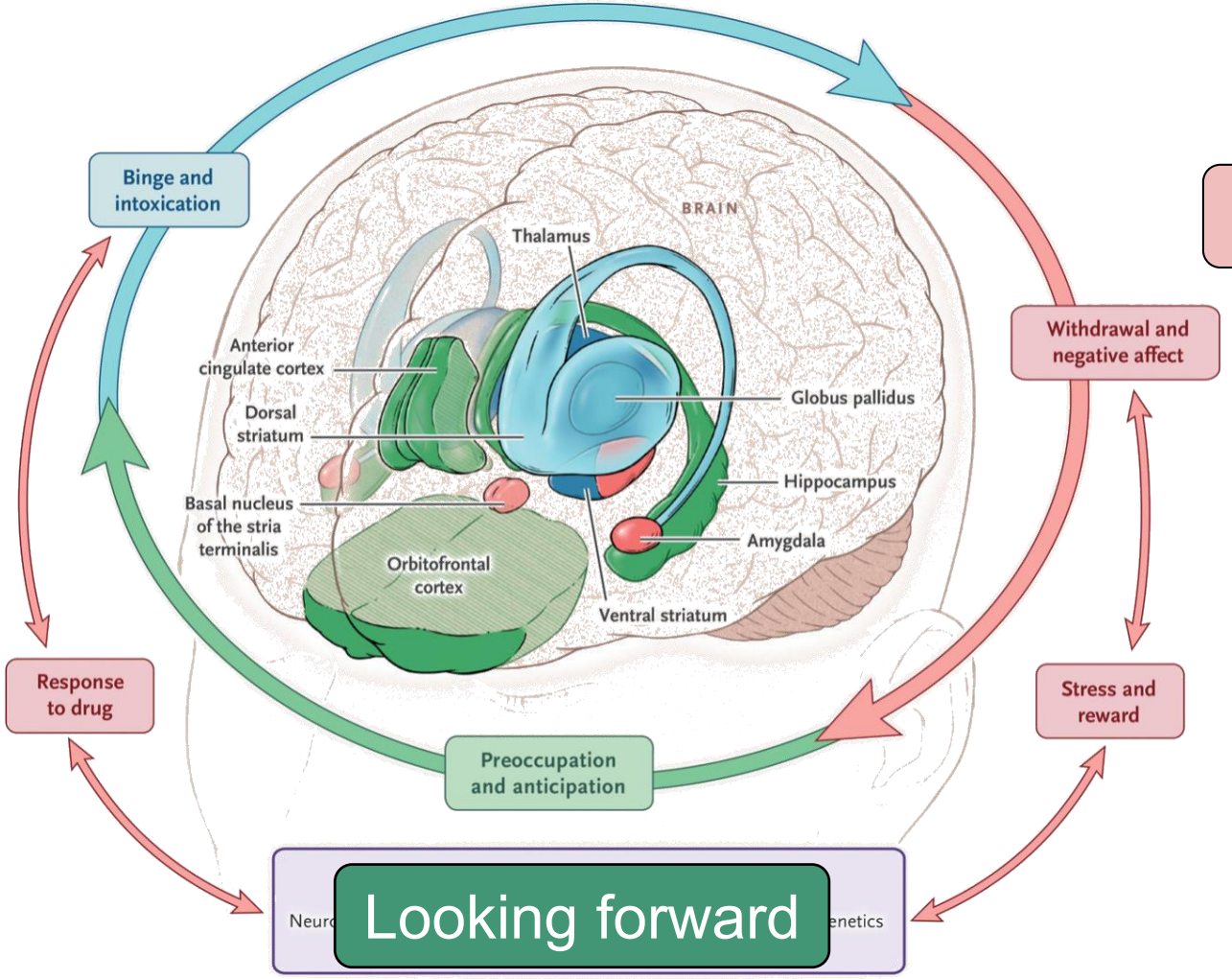
Disease Model of Addiction



Volkow ND et al. N Engl J Med 2016

Disease Model of Addiction

Feeling euphoric

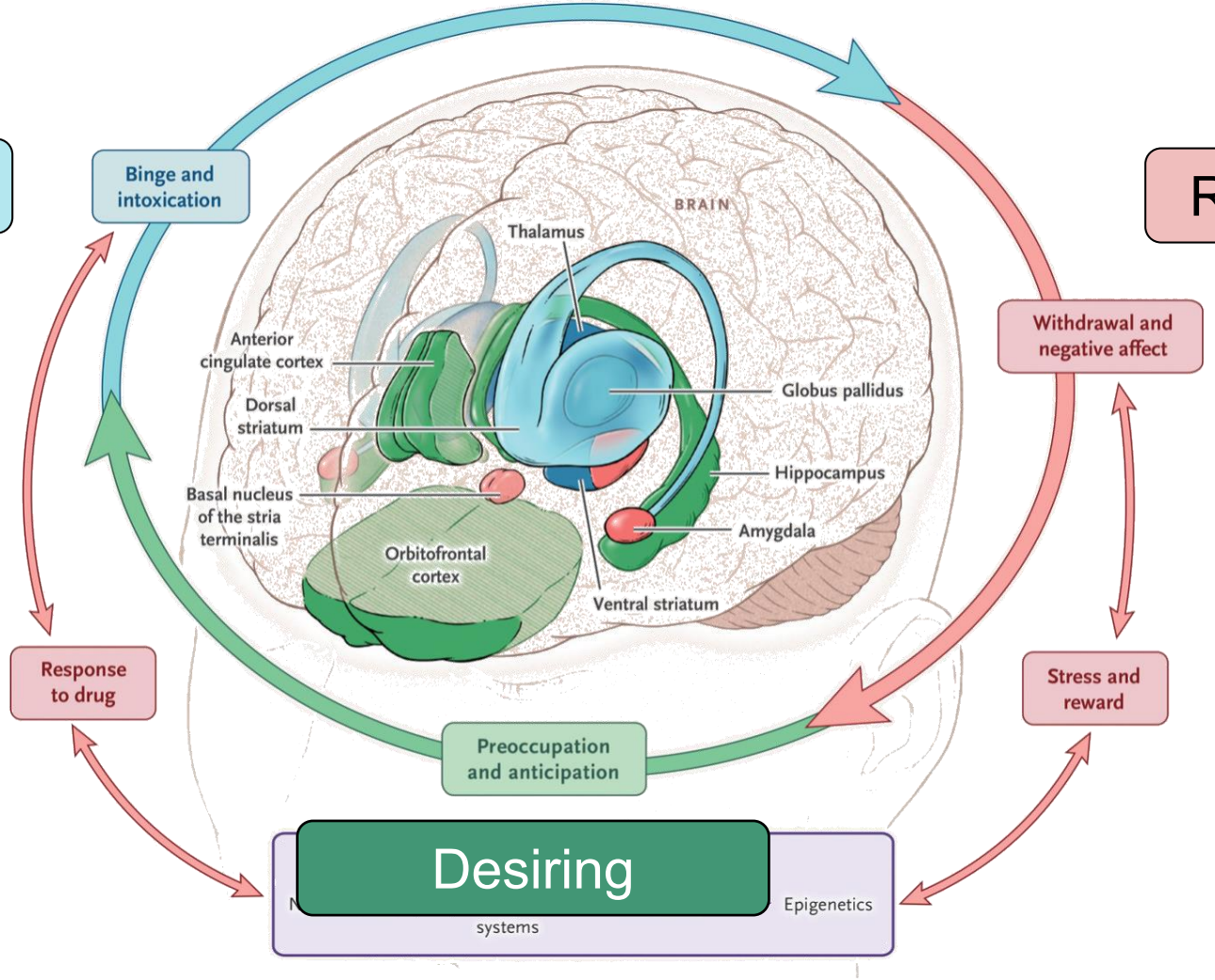


Reduced energy

Volkow ND et al. N Engl J Med 2016

Disease Model of Addiction

Feeling good

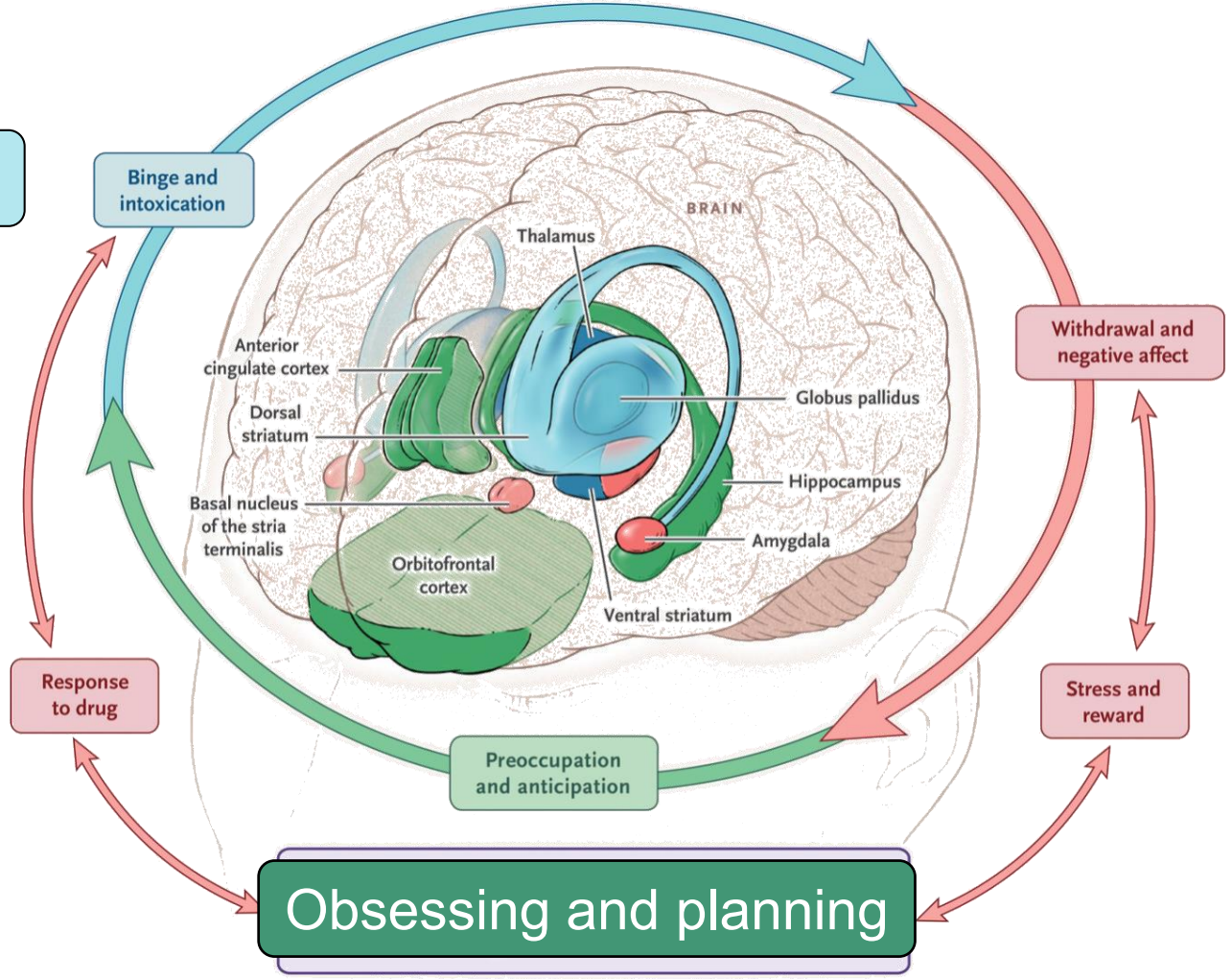


Reduced excitement

Volkow ND et al. N Engl J Med 2016

Disease Model of Addiction

Escaping dysphoria



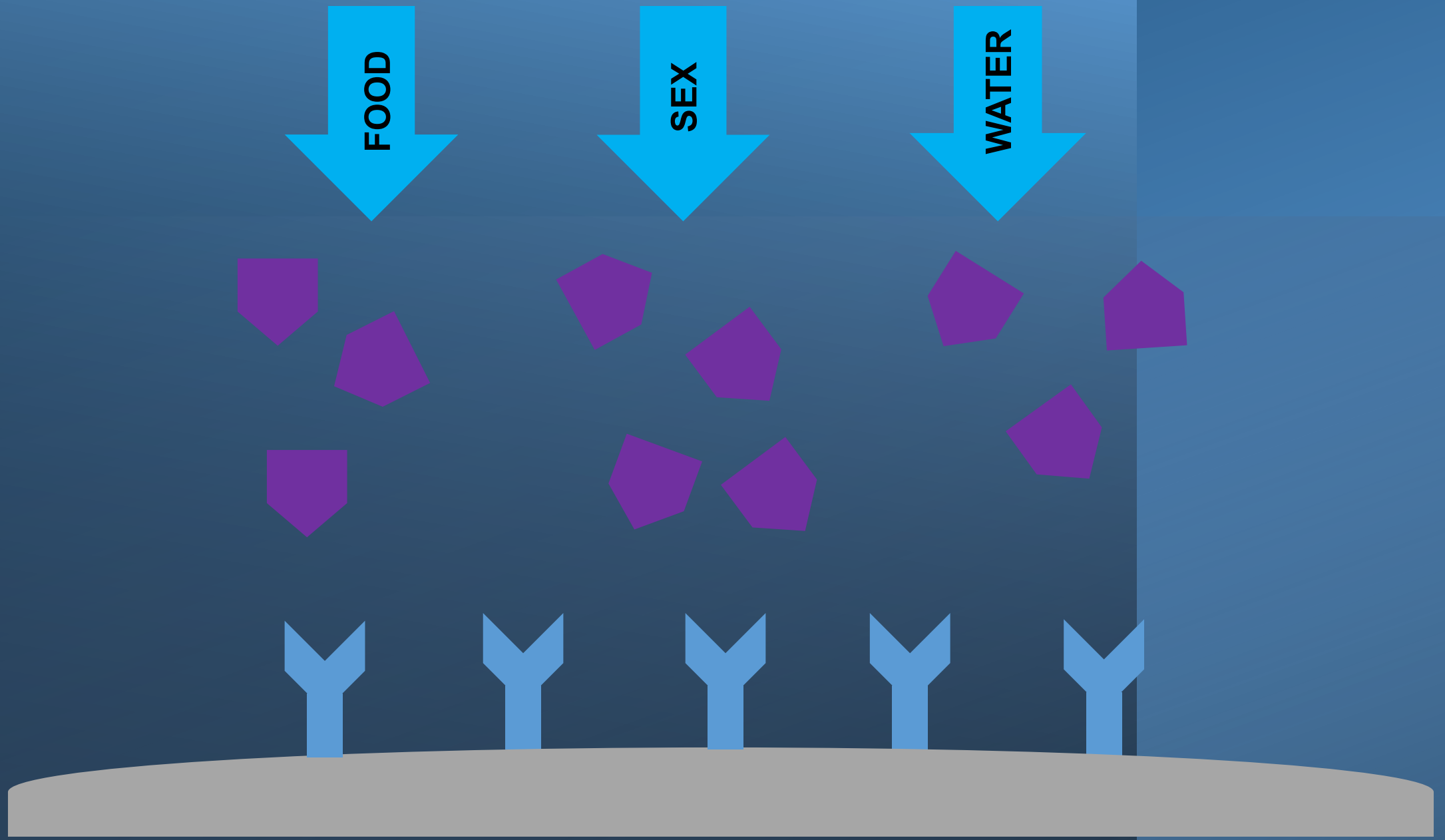
Depression, anxiety, restlessness

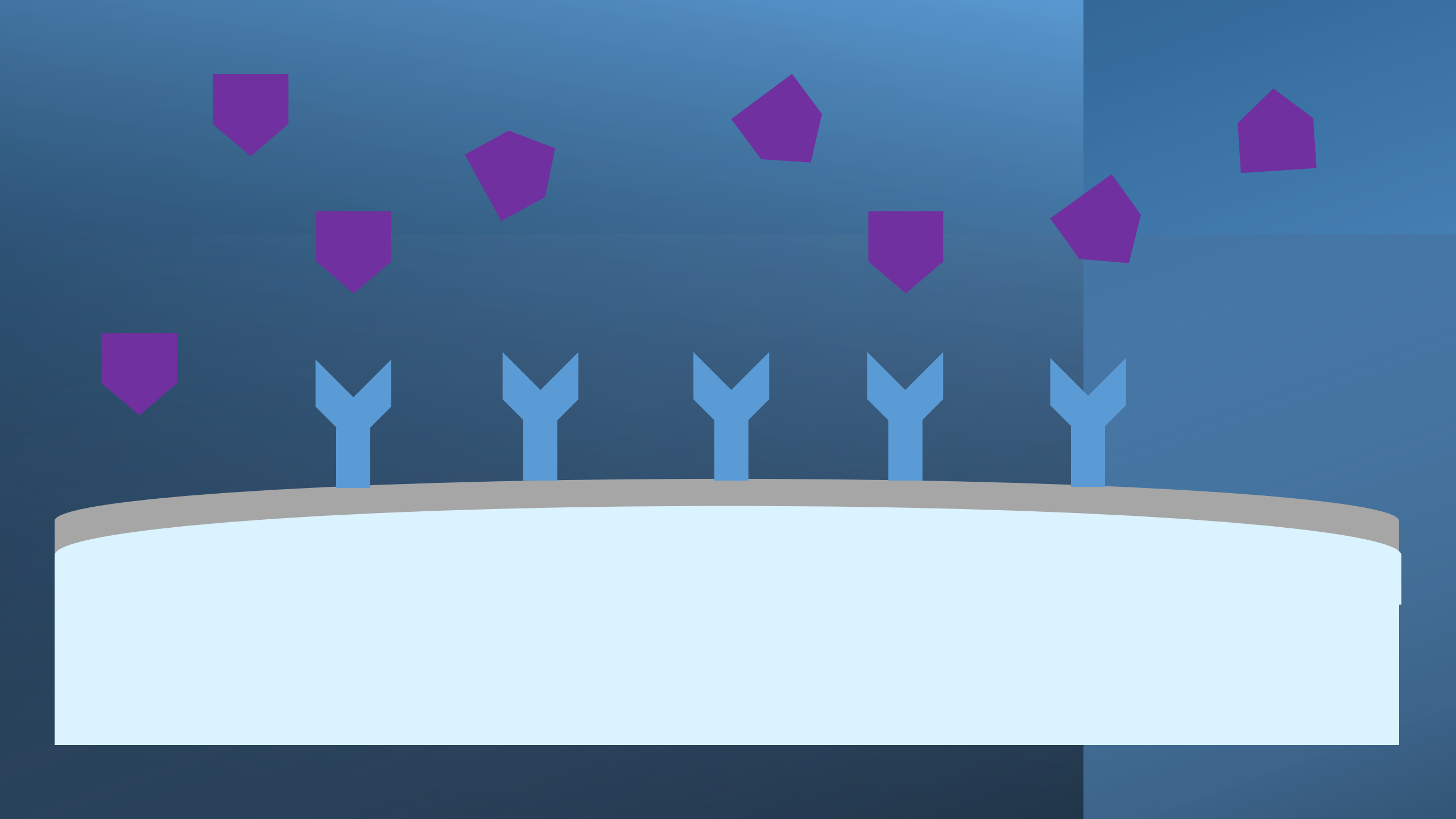
Obsessing and planning

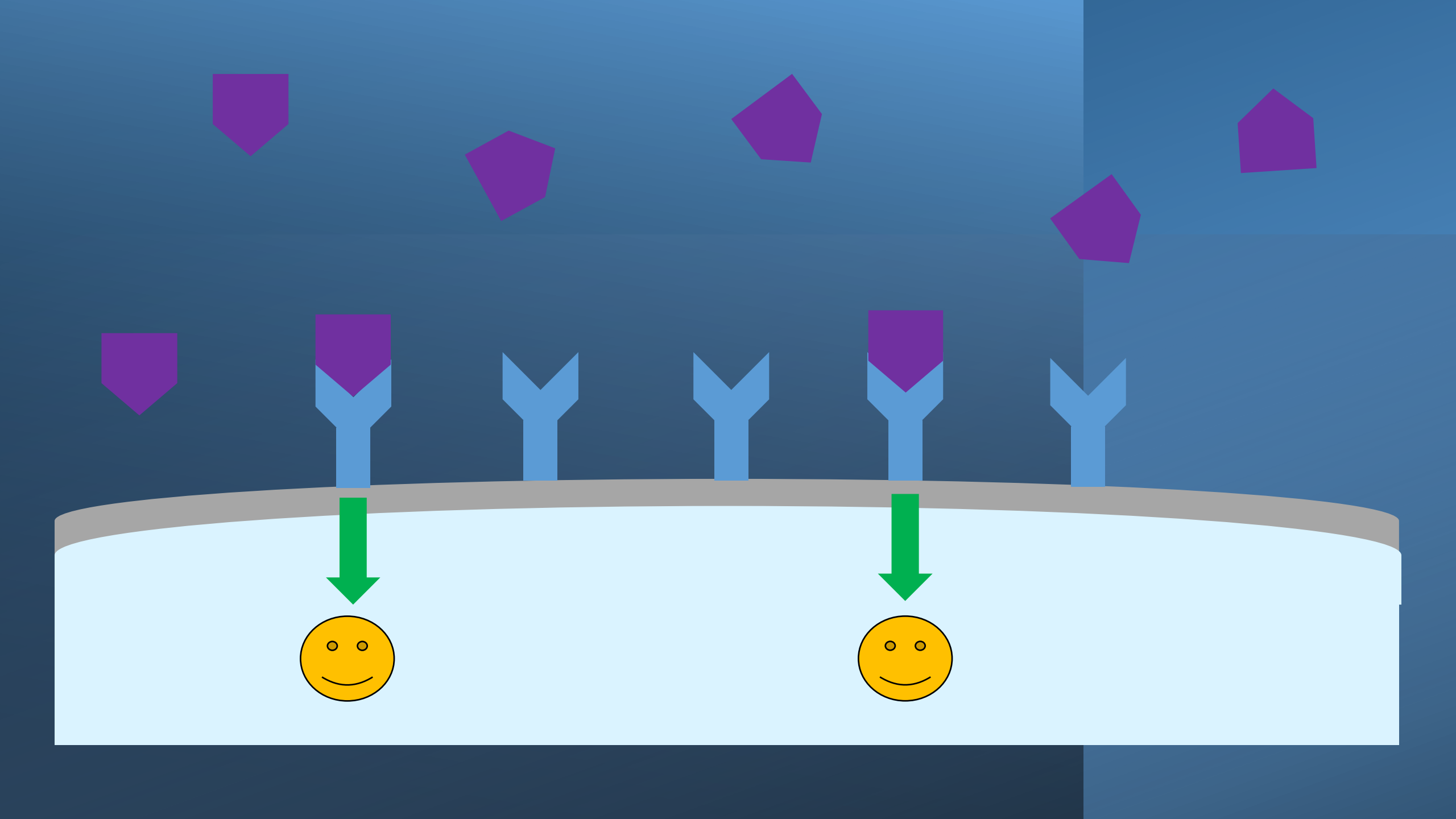
Volkow ND et al. N Engl J Med 2016

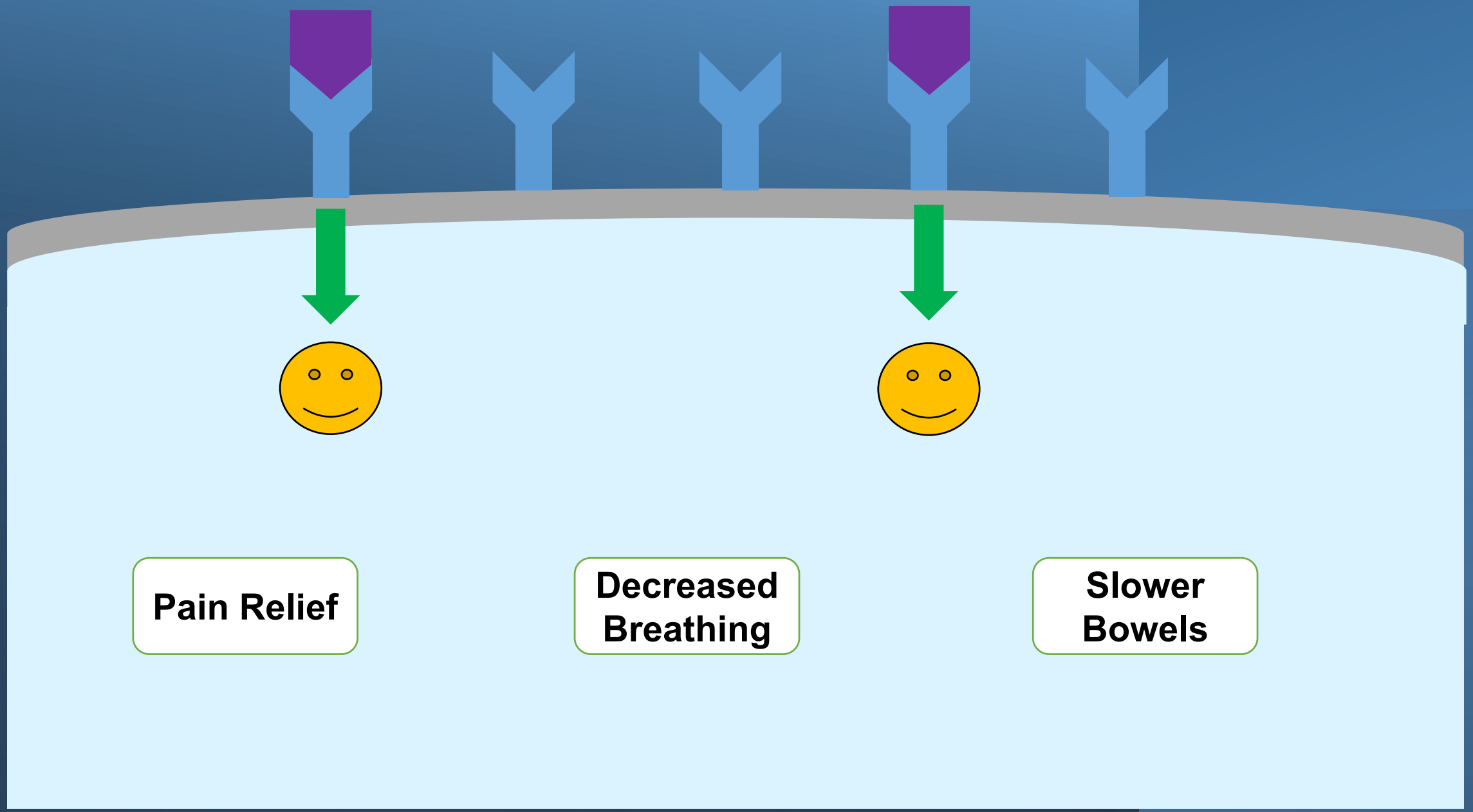
Scientific Basis for Opioid Addiction

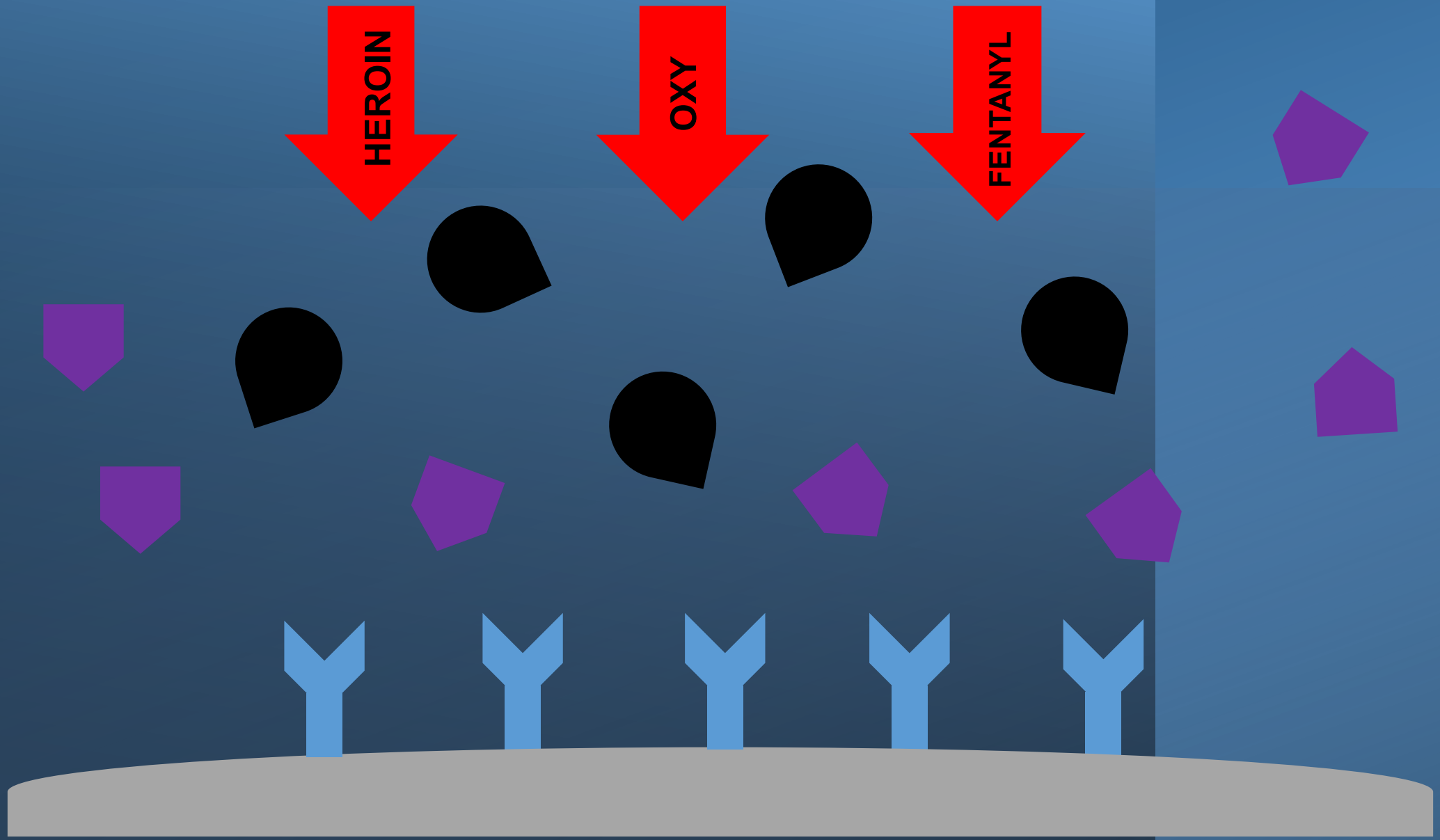
Opioid Receptors

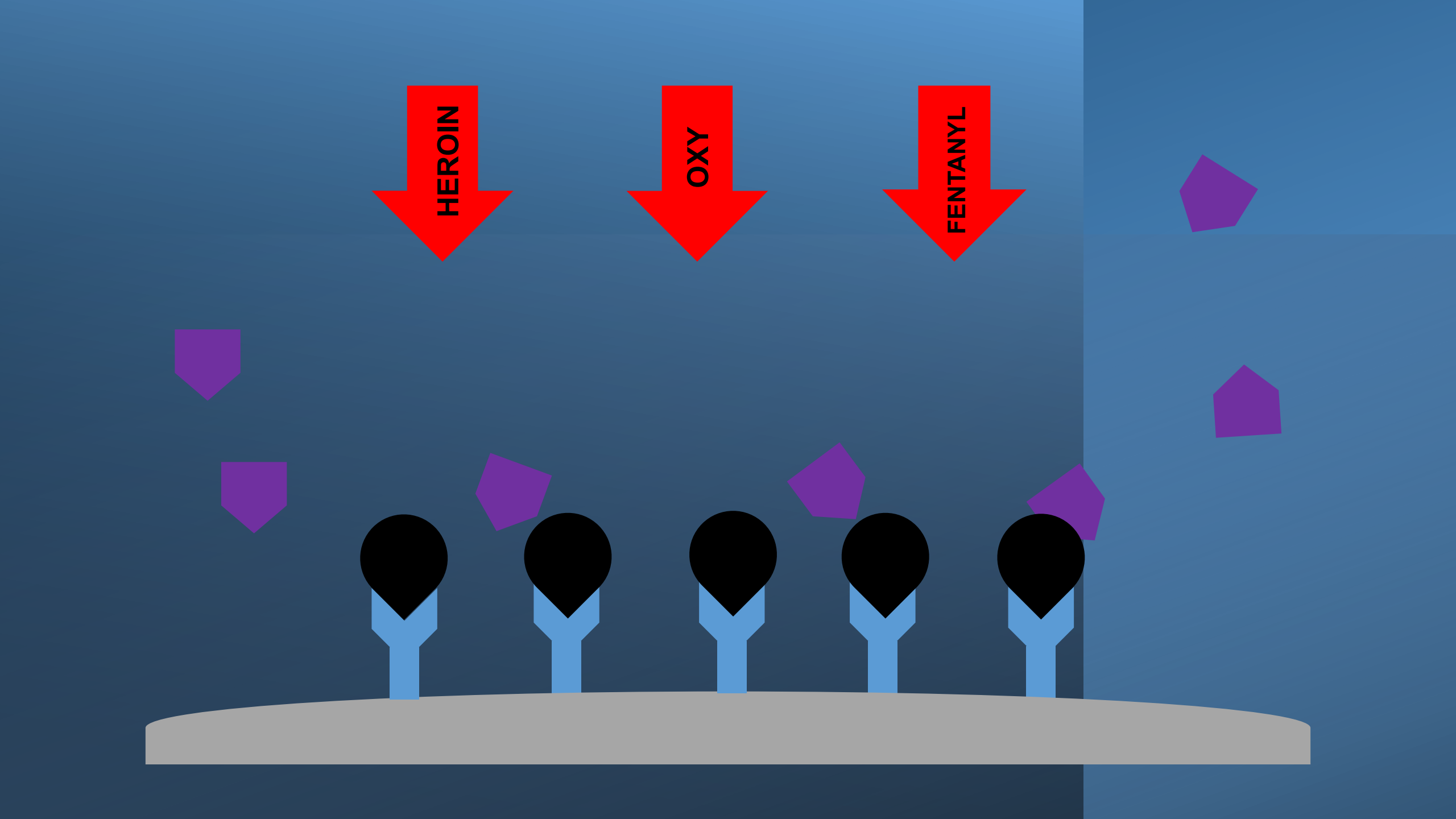

FOOD
SEX
WATER






Pain Relief
Decreased Breathing
Slower Bowels


HEROIN
OXY
FENTANYL


HEROIN
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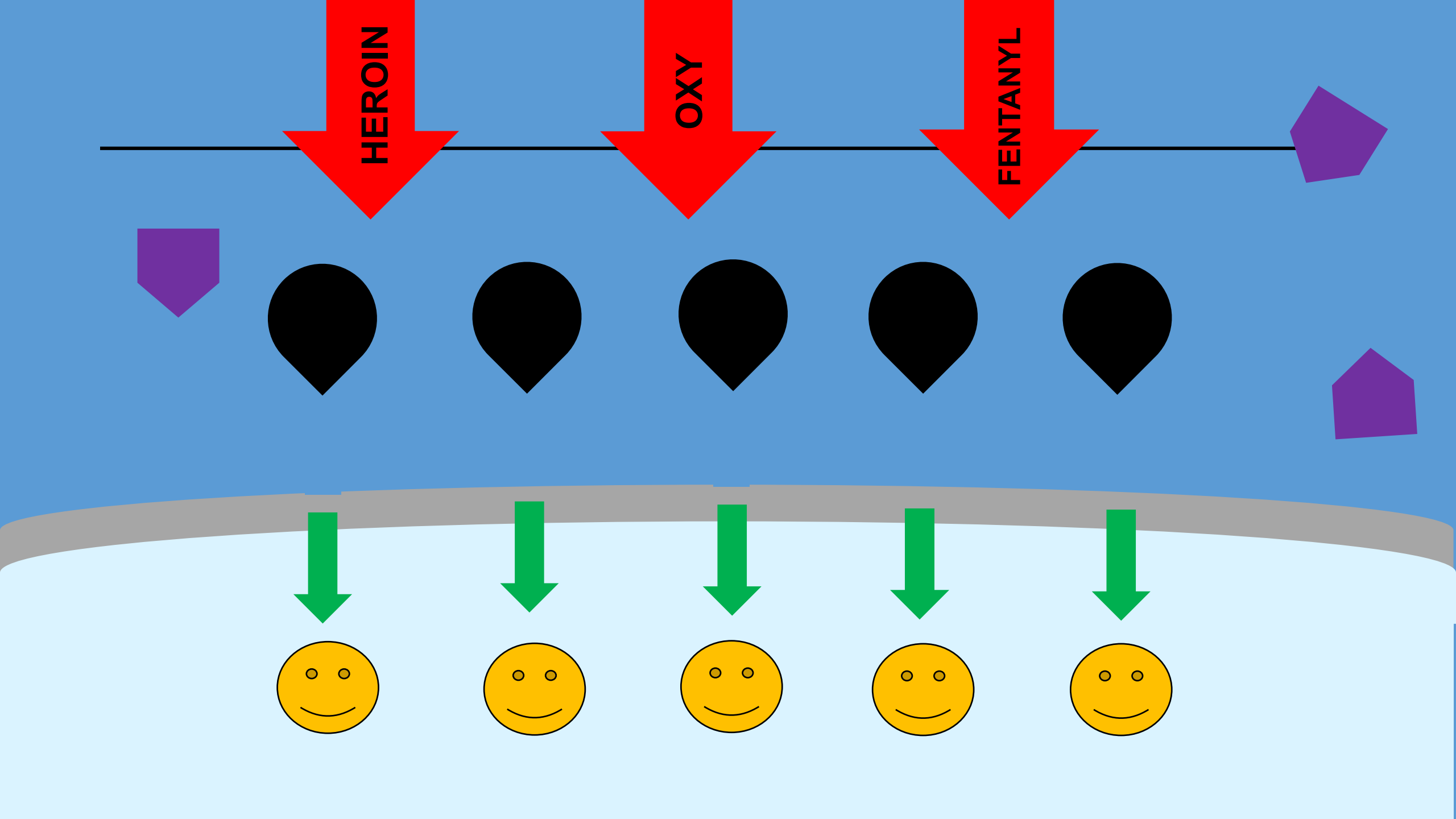
HEROIN
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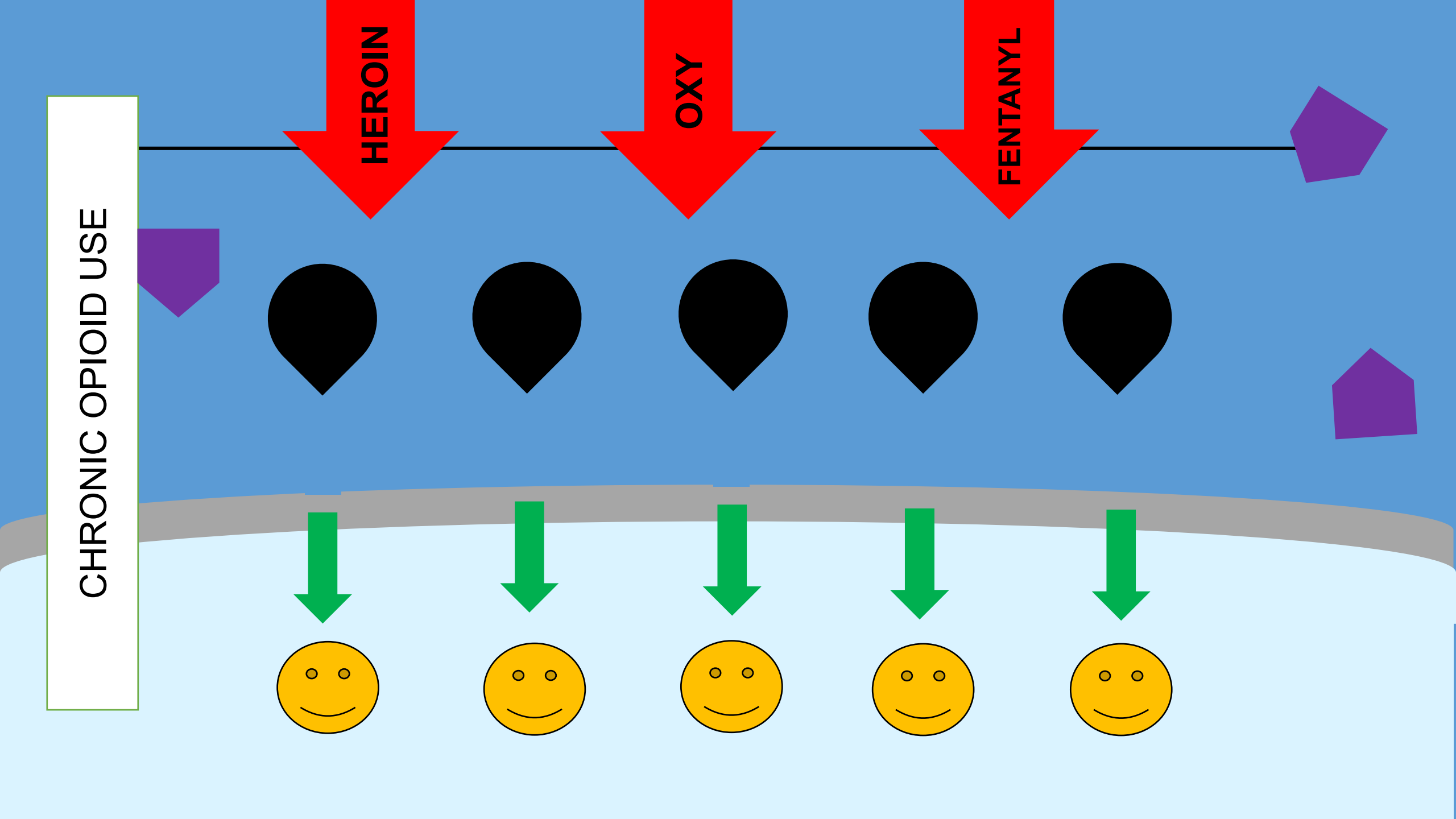
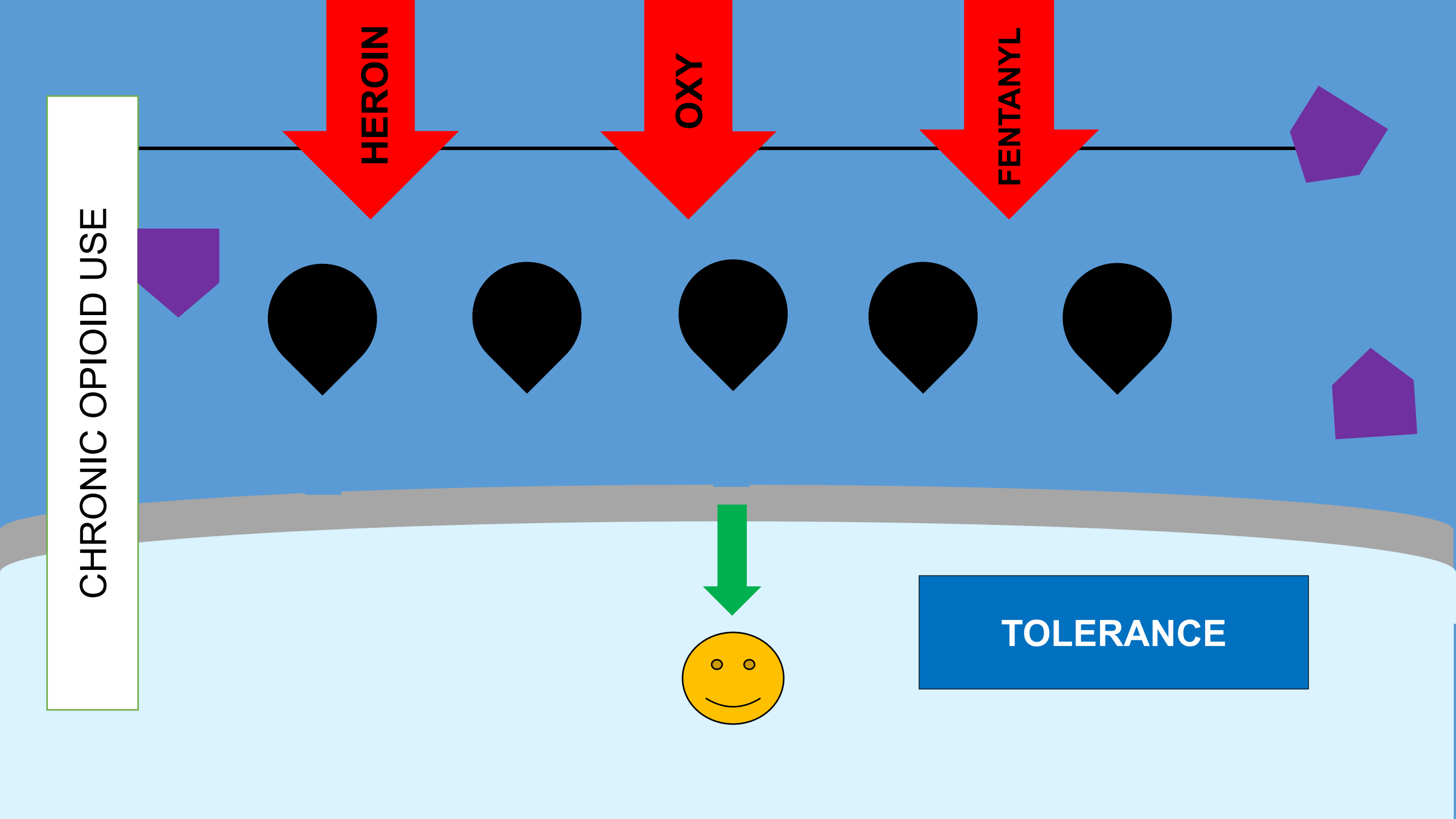
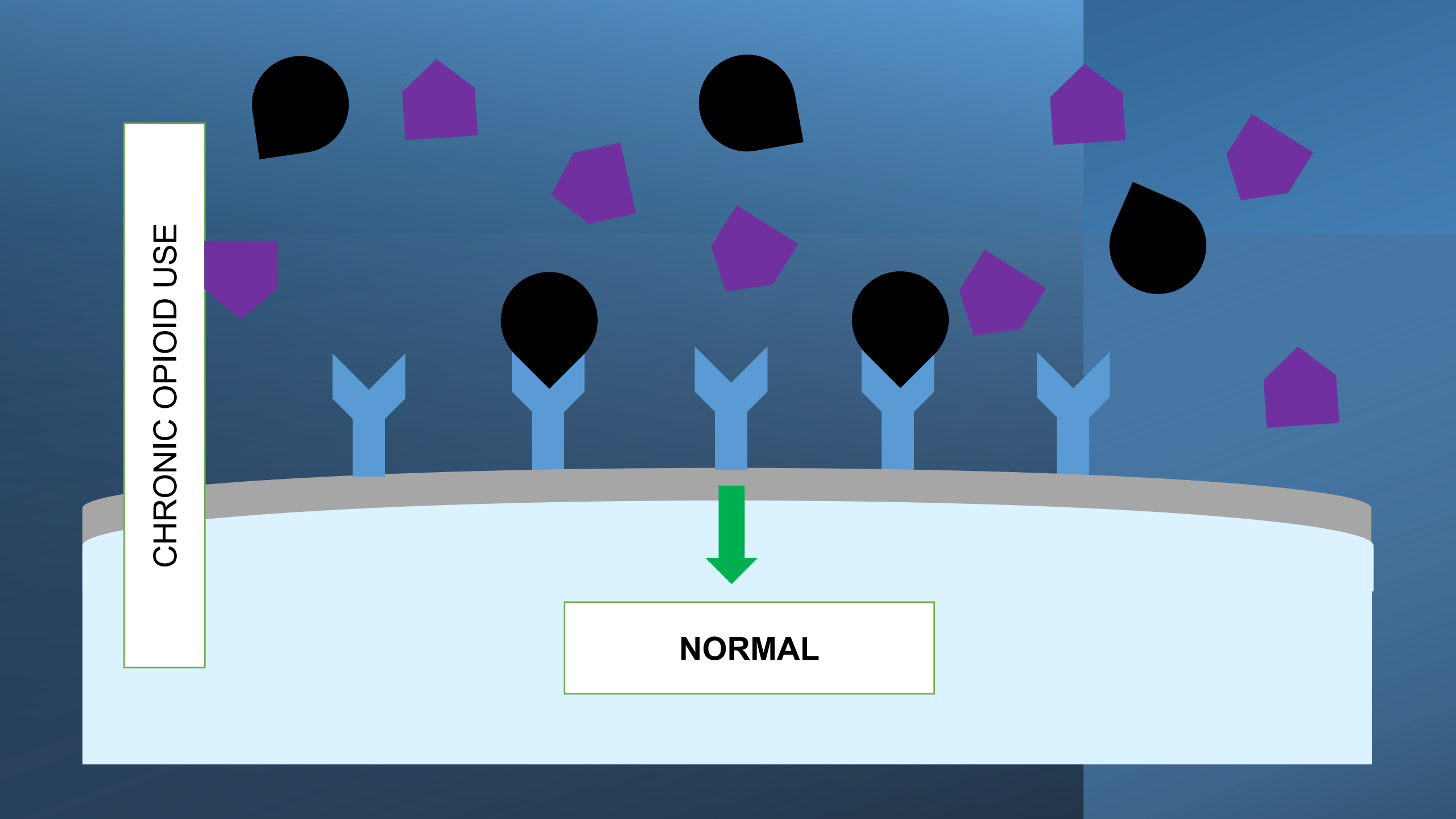
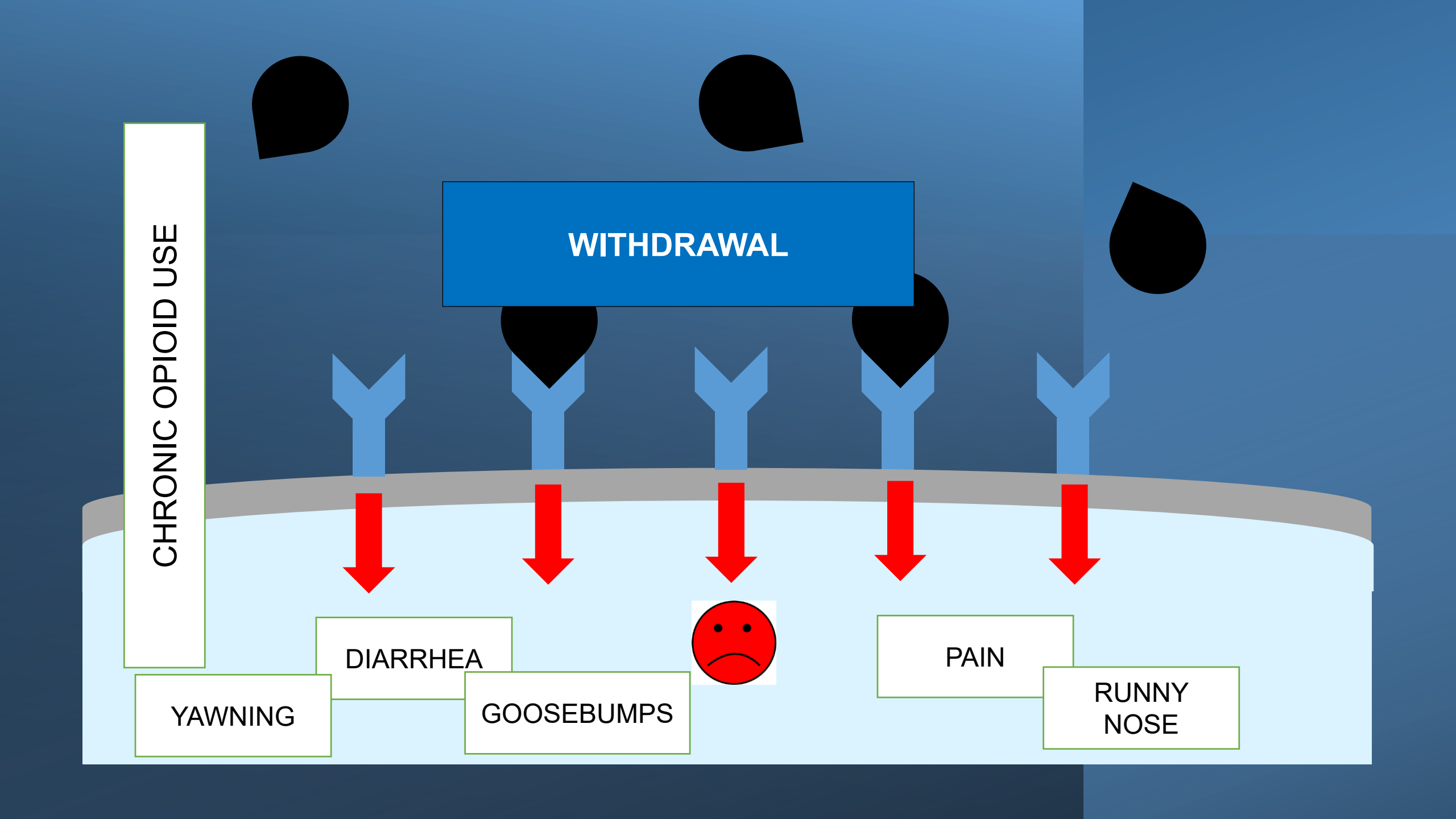
FENTANYL


CHRONIC OPIOID USE
HEROIN
OXY
FENTANYL


CHRONIC OPIOID USE
HEROIN
OXY
FENTANYL
TOLERANCE

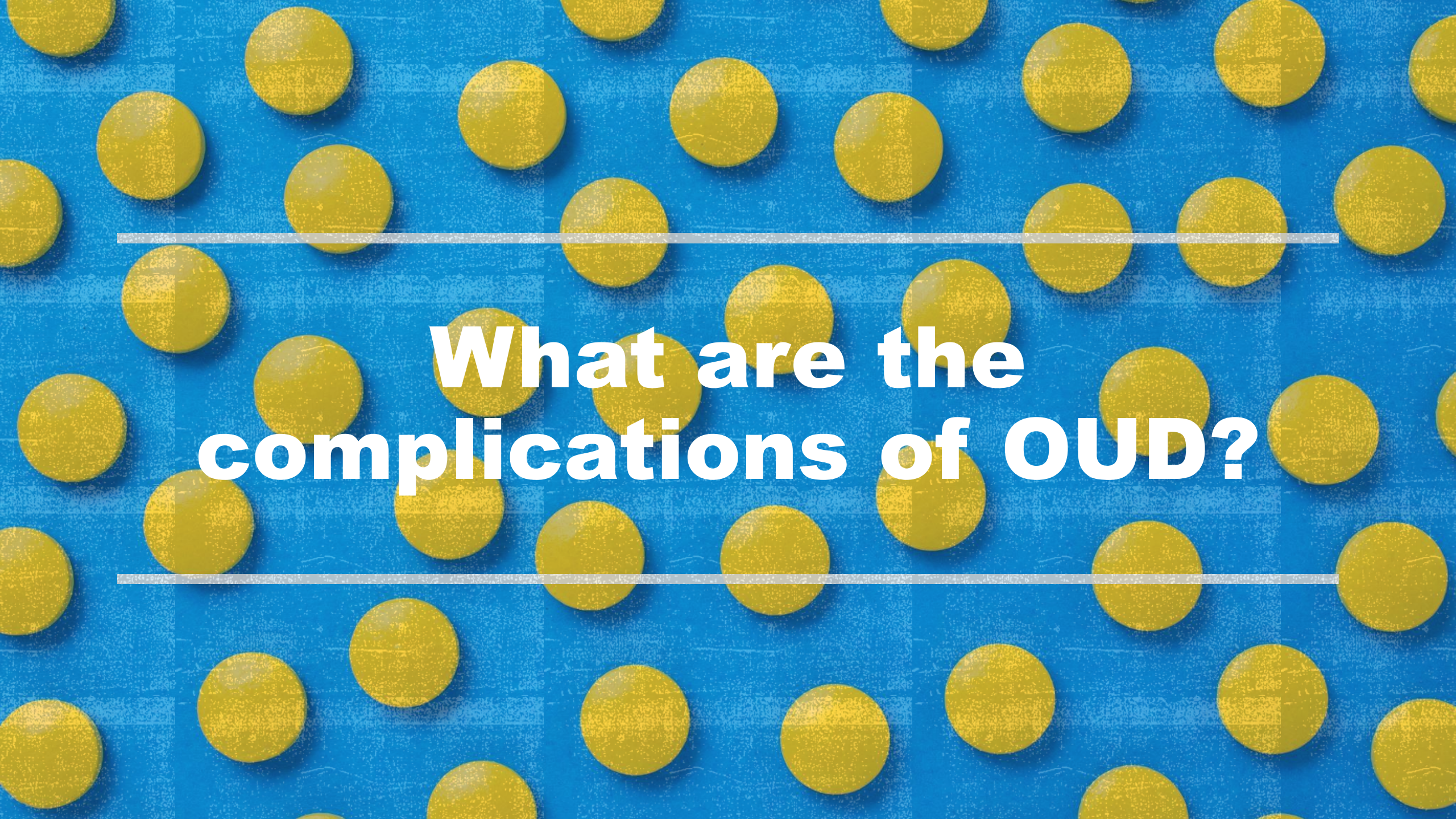

CHRONIC OPIOID USE
NORMAL


CHRONIC OPIOID USE
WITHDRAWAL
DIARRHEA
YAWNING
GOOSEBUMPS
PAIN
RUNNY NOSE

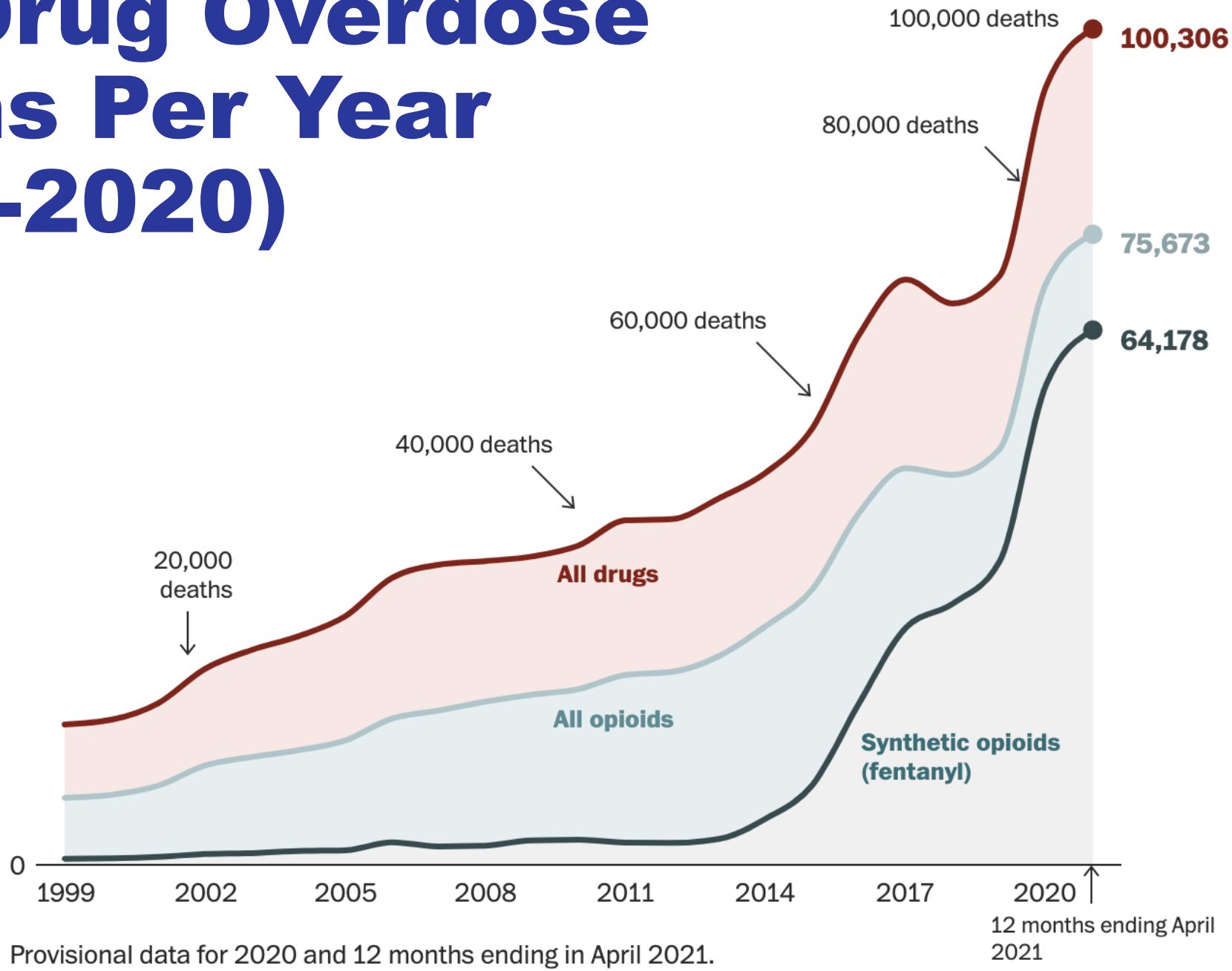
DSM-V Definition of Opioid Use Disorder

A problematic pattern of opioid use leading to clinically significant impairment or distress, manifested by 2 or more criteria within 12 months:

- Taking increasing amounts
- Persistent desire or unsuccessful efforts to cut down
- Spent time obtaining, using, or recovering
- Craving
- Use prevents fulfilling obligations
- Social or interpersonal problems
- Giving up important activities
- Physically harmful situations
- Physical or psychological problems
- Tolerance
- Withdrawal

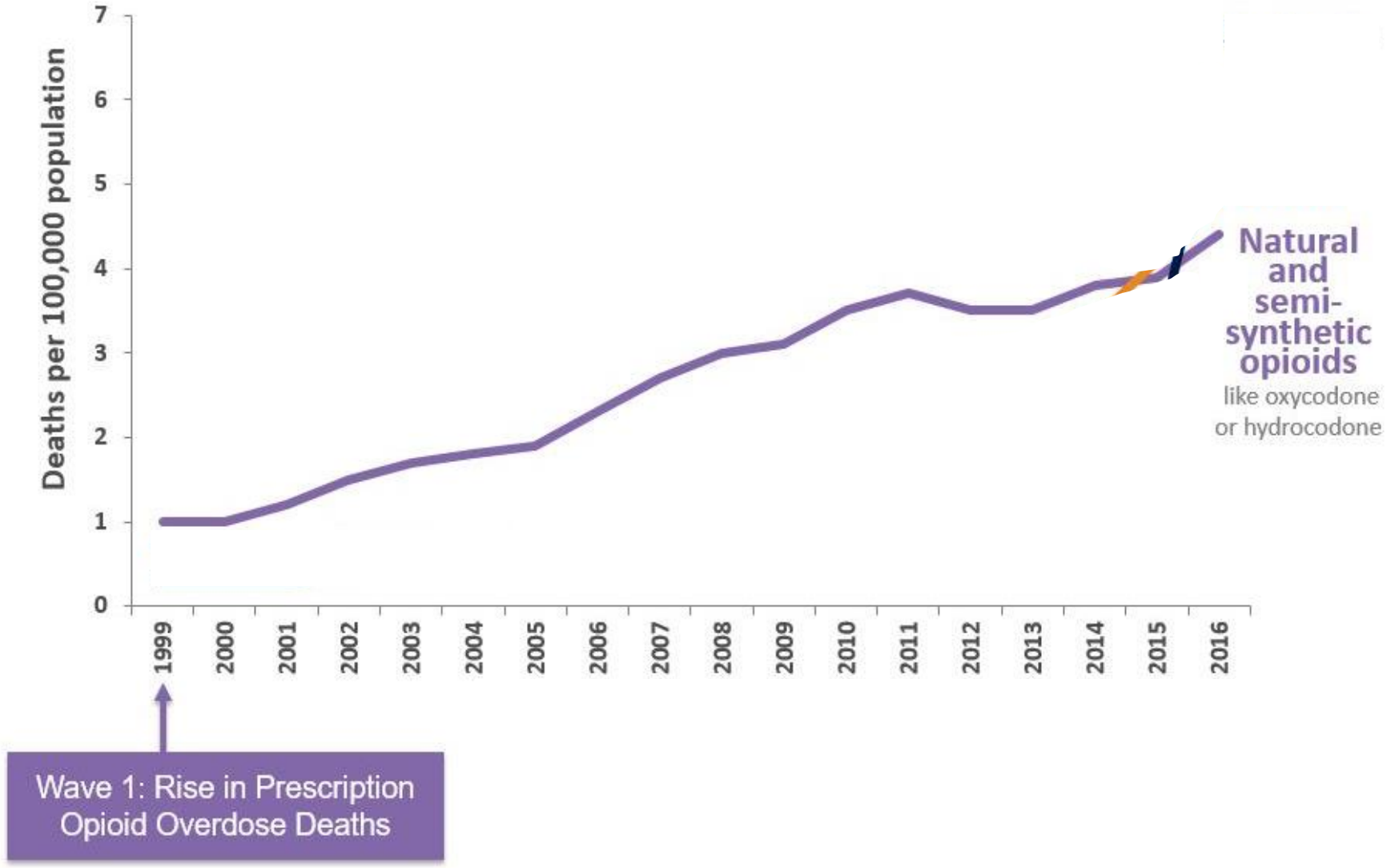

What are the
complications of OUD?

U.S. Drug Overdose Deaths Per Year (1999-2020)



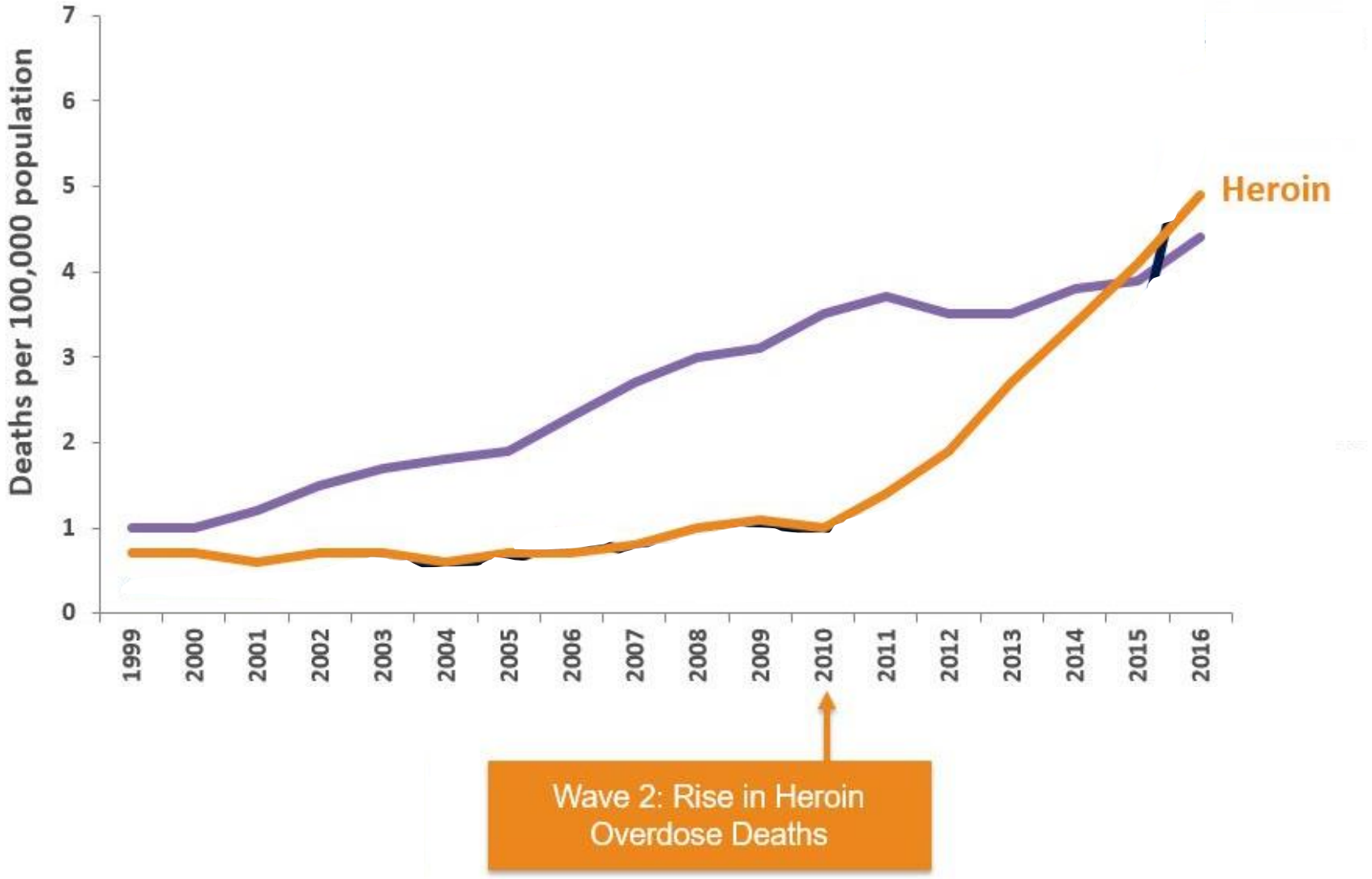
CDC, Washington Post

Overdose Epidemic: Triple Wave



National Vital Statistics
https://www.cdc.gov/drugoverdose/epidemic/index.html
Ciccarone, IJDP 2019

Overdose Epidemic: Triple Wave



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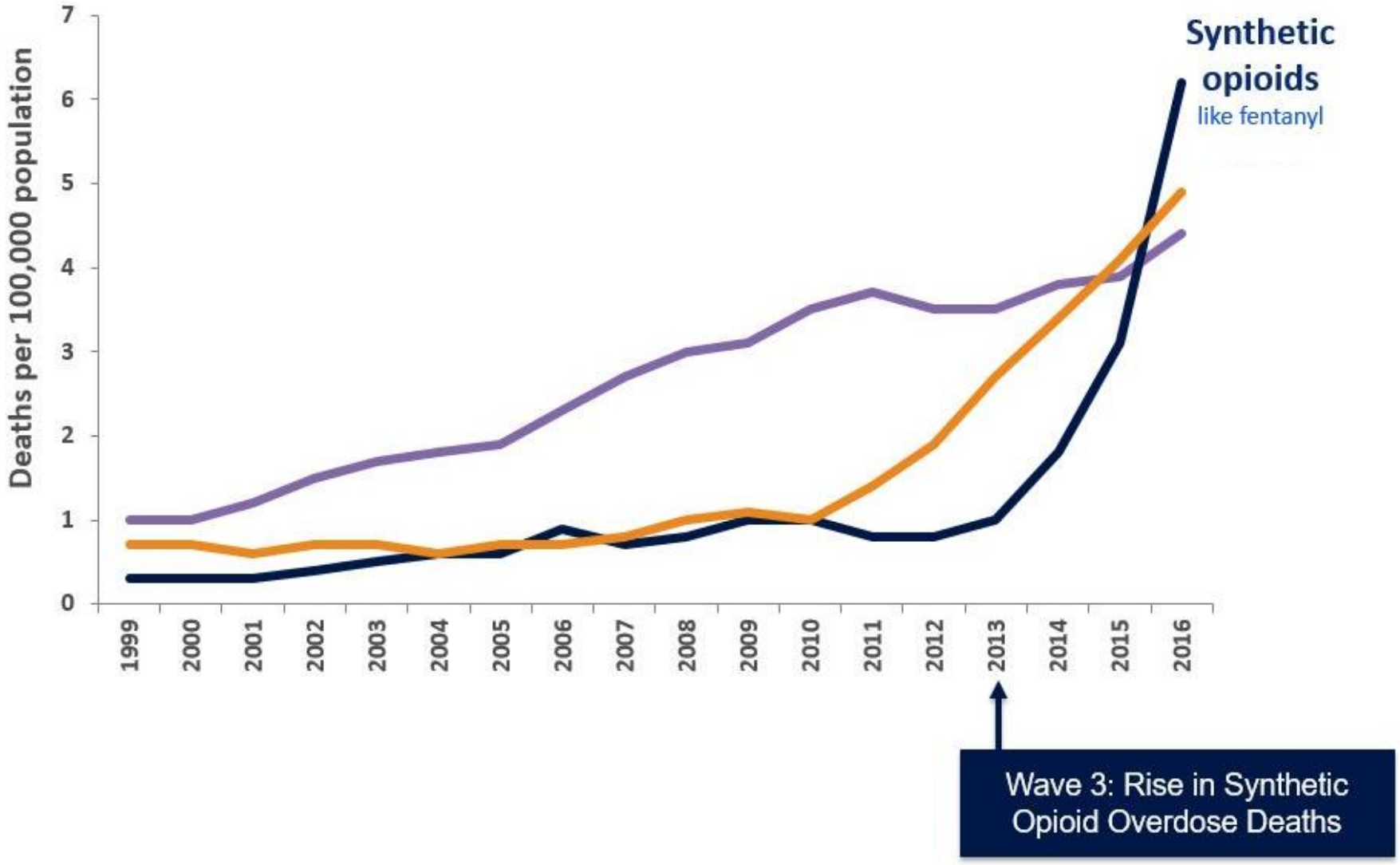
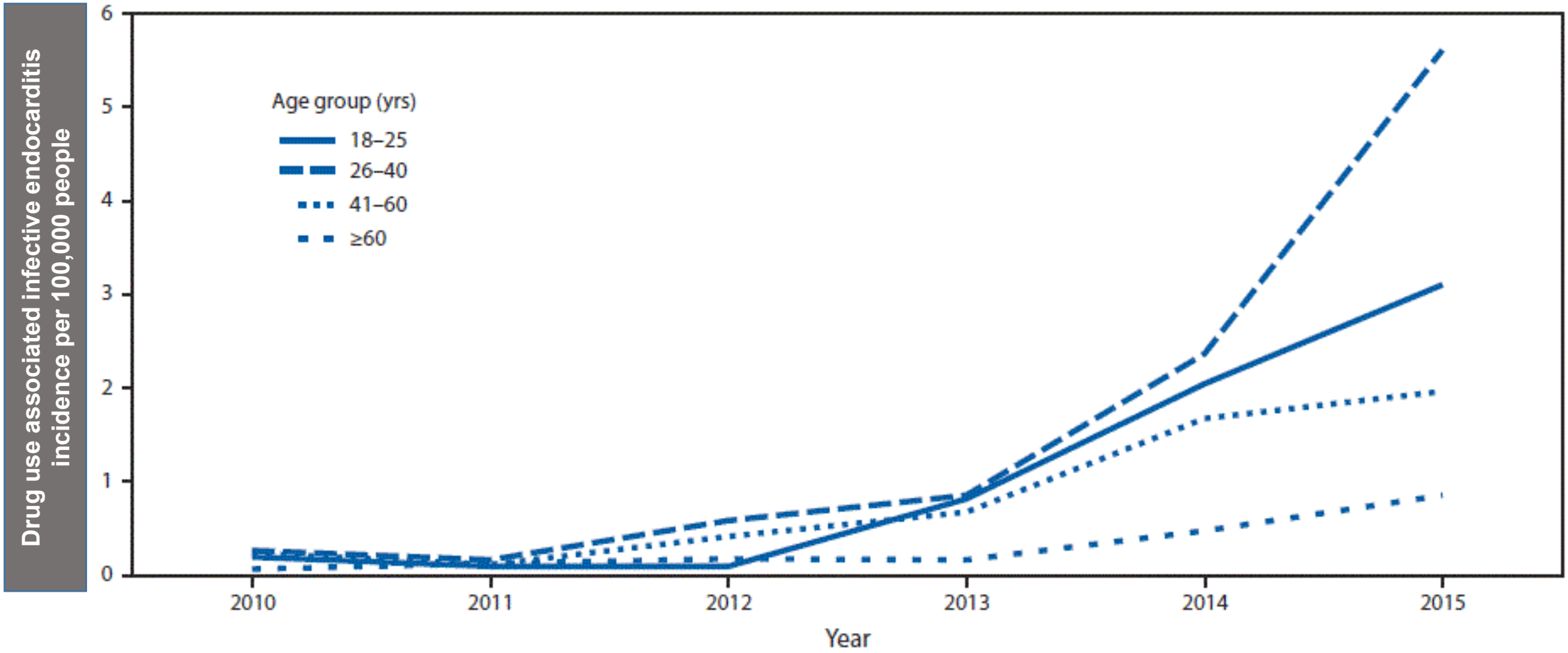


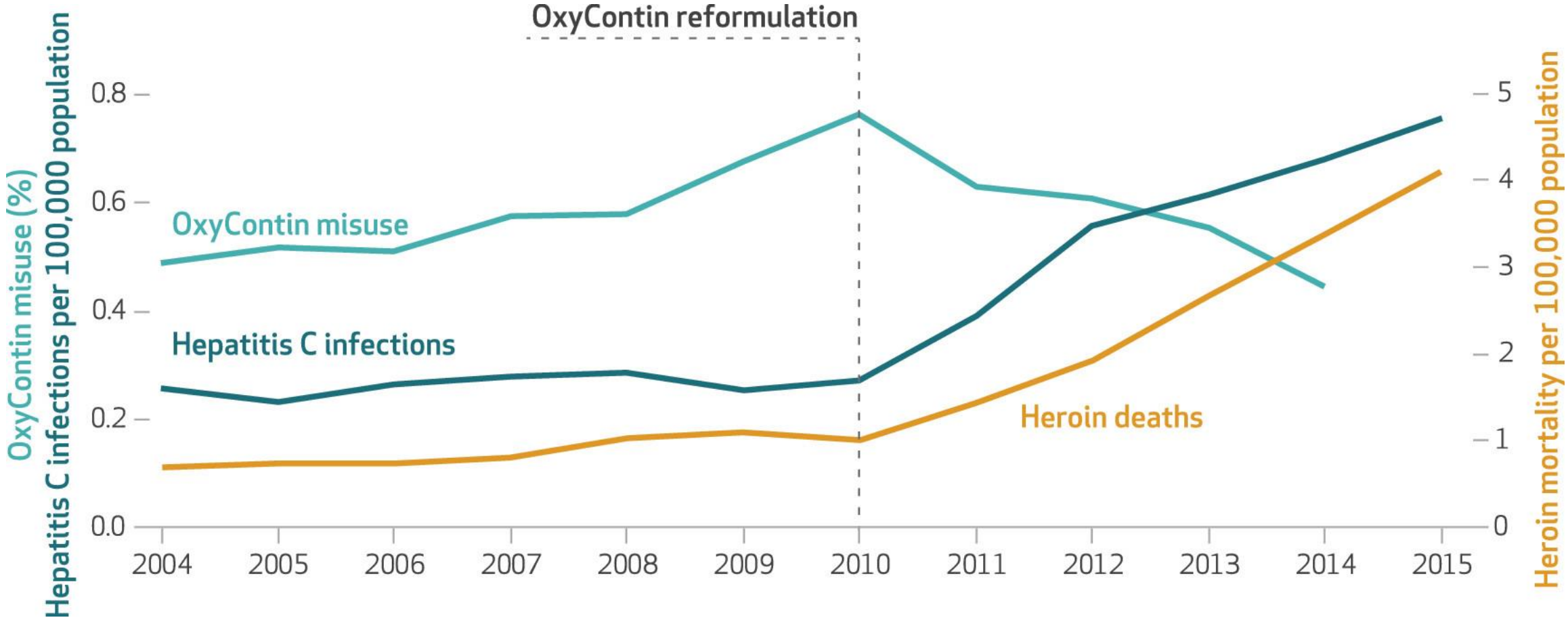
National Vital Statistics
https://www.cdc.gov/drugoverdose/epidemic/index.html
Ciccarone, IJDP 2019

Rise in Infectious Endocarditis in PWID



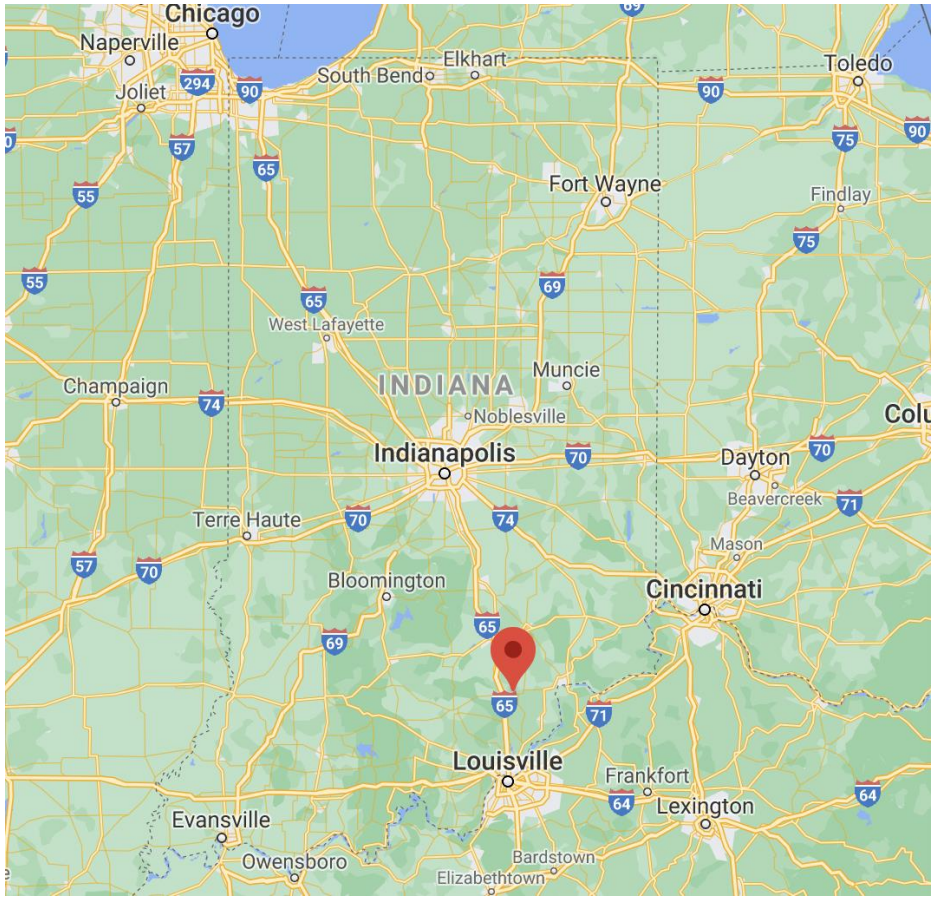
Fleischauer, MMWR 2017

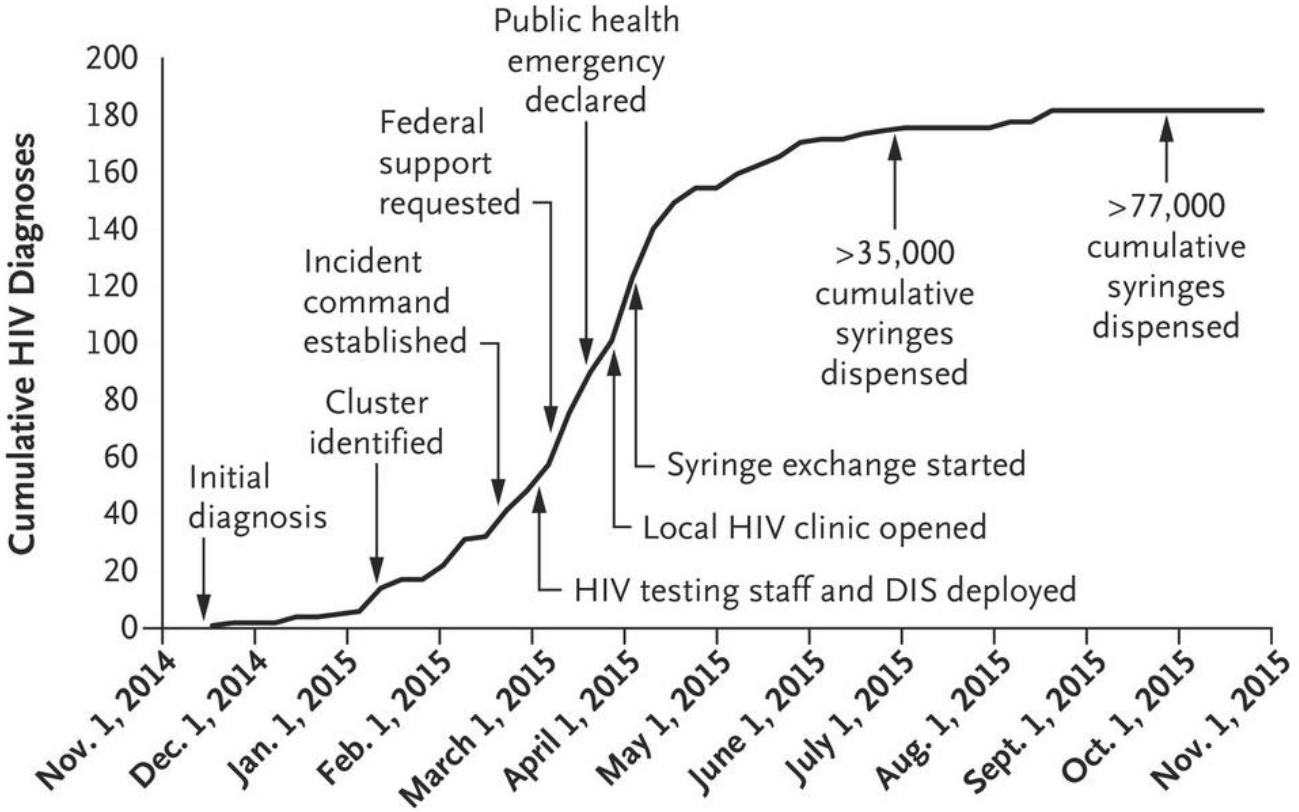
Rise in HCV Associated with Opioid Misuse



Powell, Health Affairs 2019

HIV Outbreaks Associated with Opioid Misuse



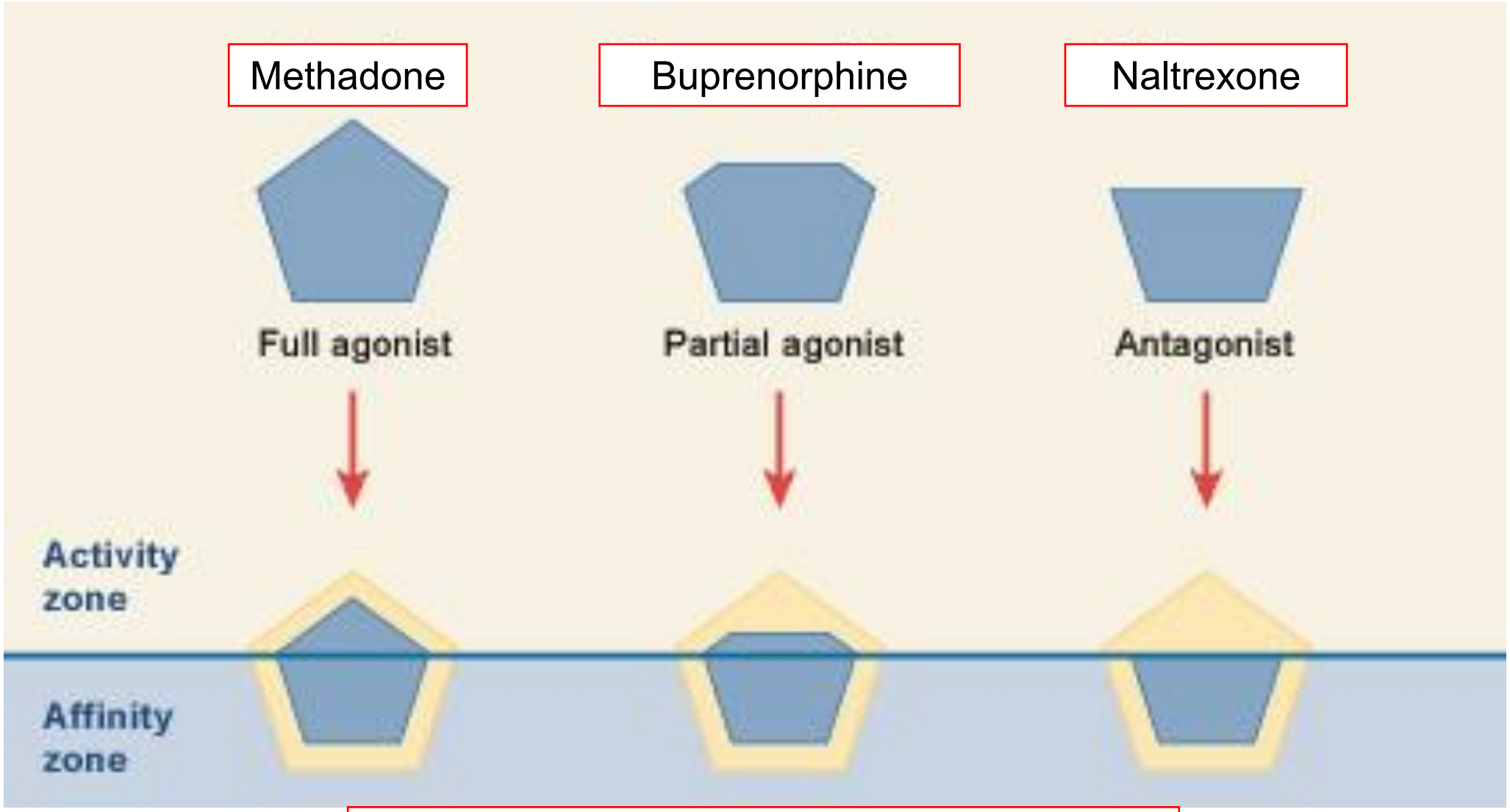


Peters PJ et al. N Engl J Med 2016;375:229-239.

How do we prevent complications from OUD?

Medication for Opioid Use Disorder

Medications for Opioid Use Disorder



Major Features of Methadone

Synthetic opioid

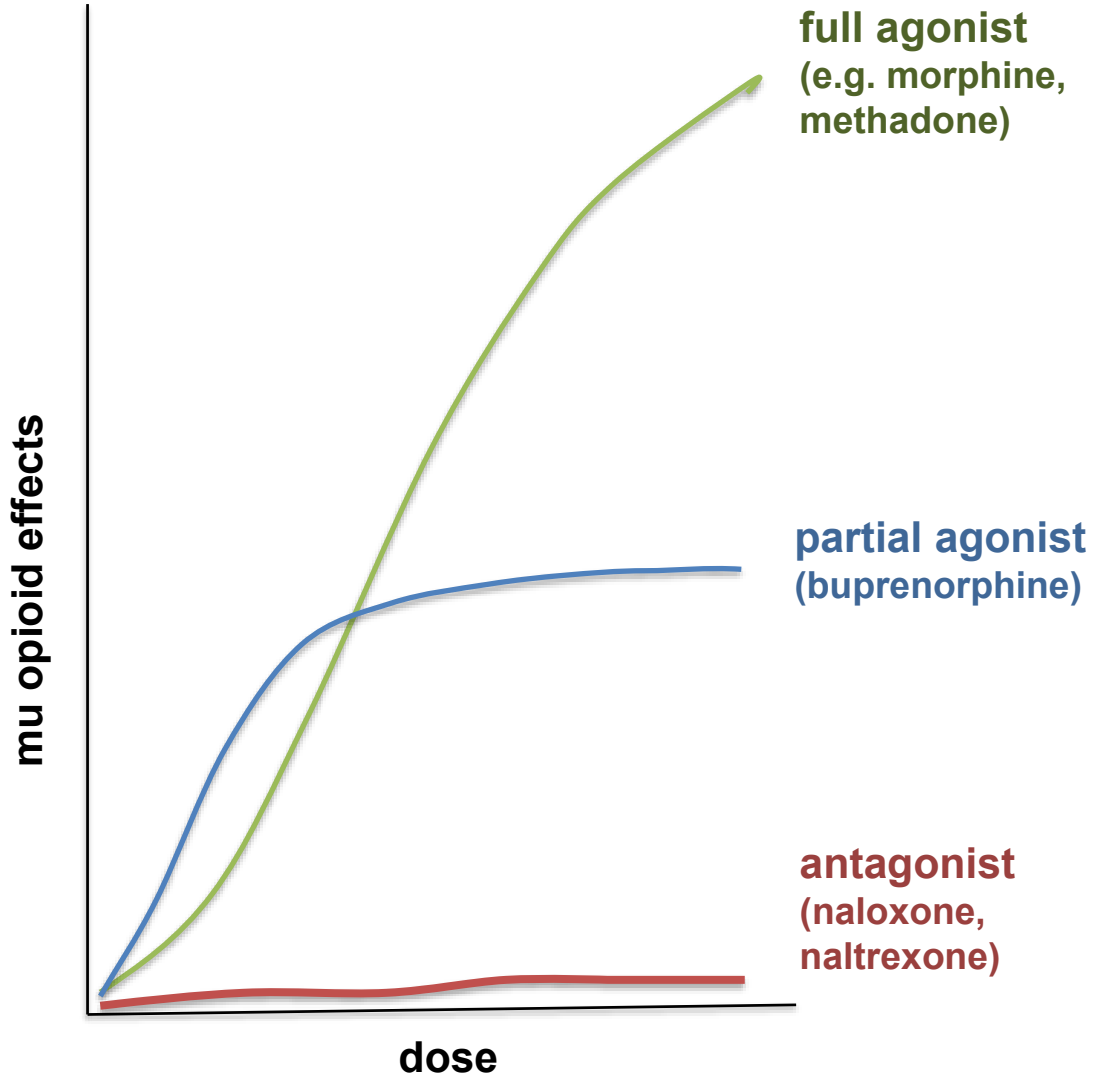
***Full Agonist* at mu receptor**

Long acting

- Half-life ~ 15-60 Hours

Weak affinity for mu receptor

- *Can be displaced by partial agonists (e,g. burprenorphine) and antagonists (e.g.naloxone, naltrexone),* which can both precipitate withdrawal



CSAT, 2005

Methadone

Dosing

- Dosed once per day as a liquid
- Typical doses begin at 30mg and can go up to >200mg
- Most individuals 60-100mg

Intake

- Medical assessment (exam, EKG)
- Initiated same day

Monitoring

- Significant respiratory suppression and potential respiratory arrest in overdose
- QT prolongation

Regulations

- 1974- “Narcotic Addict Treatment Act”
- Require dispensing at “Opioid Treatment Program”

Major Features of Buprenorphine

Semi-synthetic

Partial agonist at mu receptor

- Comparatively minimal respiratory suppression and no respiratory arrest when used as prescribed

Long acting

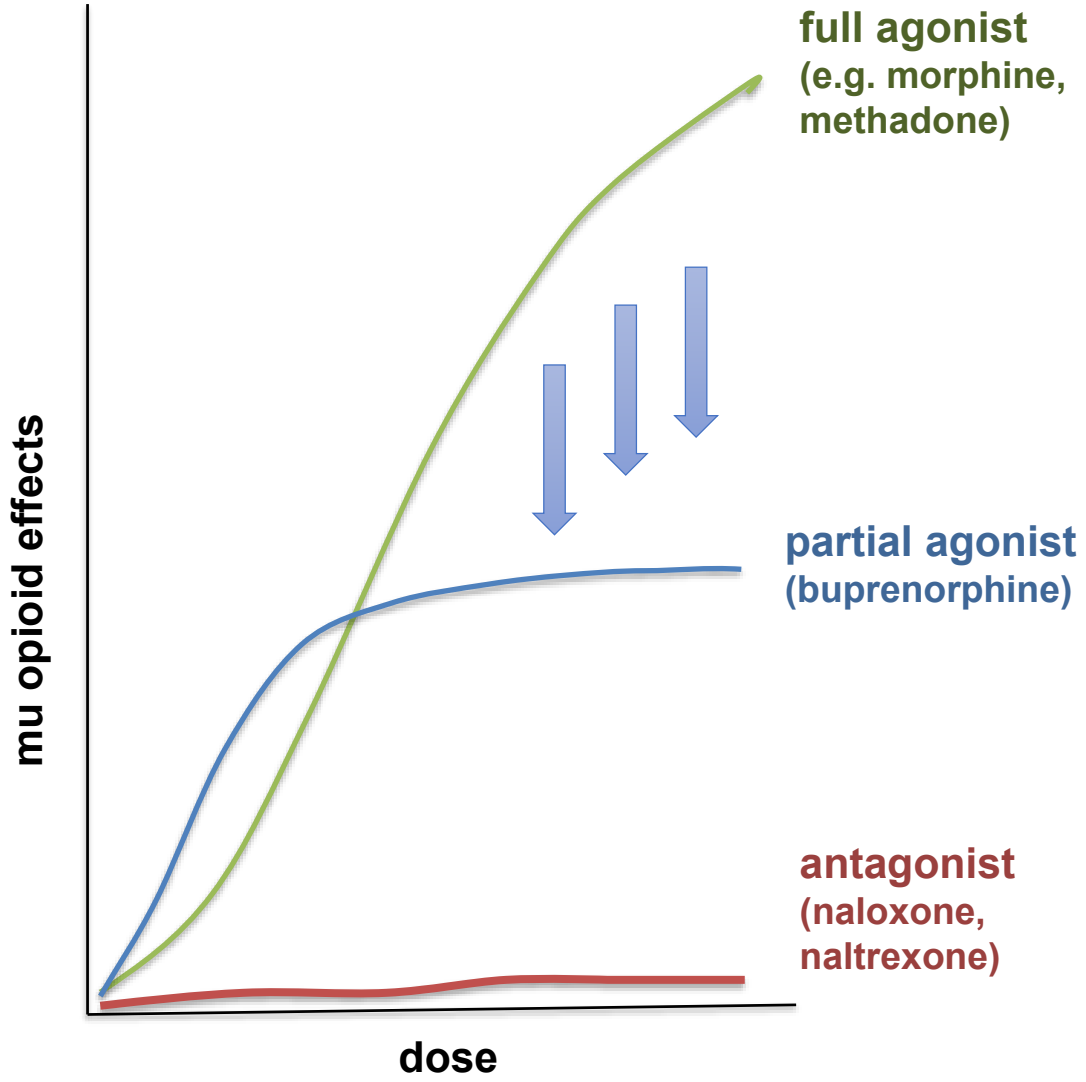
- Half-life ~ 24-36 Hours

High affinity for mu receptor

- *Blocks* other opioids
- *Displaces* other opioids
  - Can precipitate withdrawal

Slow dissociation from mu receptor

- *Stays on receptor for a long time*



SAMHSA, 2018
Orman & Keating, 2009

Buprenorphine

- **Dosing**
  - Dosed once per day as a sublingual strip or sublingual pill
  - Typical doses begin at 8mg and can go up to 32mg
  - Most individuals 16-32mg
- **Intake**
  - Prior authorization might limit same-day dosing
  - No opioids for 12 hours to avoid precipitated withdrawal (for short acting opioids, long acting opioids like fentanyl take longer). Patients need to be in moderate withdrawal (COWS>12).
  - Home inductions > office-based
- **Regulations**
  - DATA (2000)- Buprenorphine can now be prescribed after obtaining waiver
    - 8 hour training for MDs
  - Outpatient (OBOT)

Buprenorphine Intake

Complete intake to assess readiness, discuss other medications, and check PDMP

Prior authorization limits same-day dosing

No opioids for 12-36 hours to avoid precipitated withdrawal

Start with mild to moderate withdrawal

Home induction

Buprenorphine Dosing

- **Dose can be titrated up weekly**
- **8 to 24 mg/d optimal dose**
  - Can go up to 32mg/d**
- **Can take films/tablets at same time or spread apart****
- **Brain mu receptors are 85-92% saturated at a dose of 16 mg/day demonstrated on neuroimaging**

McNicholas L. Department of Health and Human Services. Clinical Guidelines he Use of Buprenorphine in the Treatment of Opioid Addiction: A Treatment Improvement Protocol: TIP 40. 2004. Available at: http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf
Lee JD,Vocci F,Fiellin DA. *J Addict Med*. 2014;8(5):299-308.
Kraus ML, et al.*J Addict* Med.2011;5:254–263.
Greenwald MK, et. al. *Neuropsychopharmacol*..2003;28:2000–2009
Casadonte. PCCS MAT Training. Buprenorphine Induction. 2013. Available at: http://pcssmat.org/wp-content/uploads/2014/02/PCSS-MATGuidanceBuprenorphineInduction.Casadonte.pdf

Buprenorphine/Naloxone Instructions

Moisten mouth before taking film

Hold sublingual film/tablet (for 2 to 8 minutes) until completely dissolved

Do not swallow

If administering 2 films/tablets at the same time, place the second under the tongue on the opposite side. Try to avoid having the films/tablets touch as much as possible

Don’t drink or eat until 20 min after taking bup

Risk for OD:

- Avoid BZD and other potent CNS depressants
- Offer naloxone

Buprenorphine Maintenance

Weekly for 1st few weeks-months

If good response, ↓ to q2wks

If good response, ↓ to monthly

Very rarely, provider may give refill. Most require monthly monitoring

Side Effects

GI: Nausea, Vomiting, Constipation

Drug withdrawal syndrome

Headache

Sweating

Insomnia

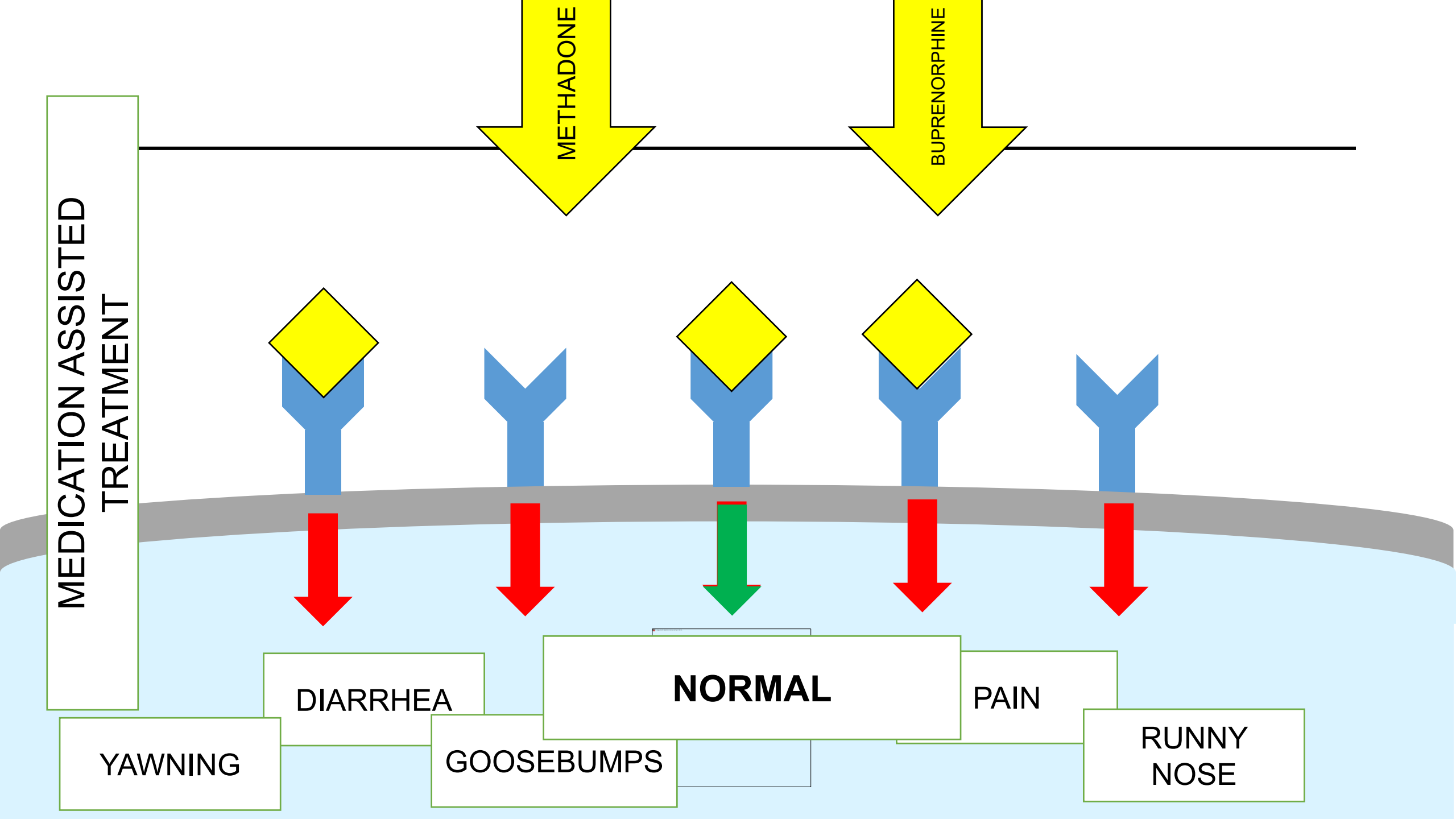
Sedation

Dizziness

Edema

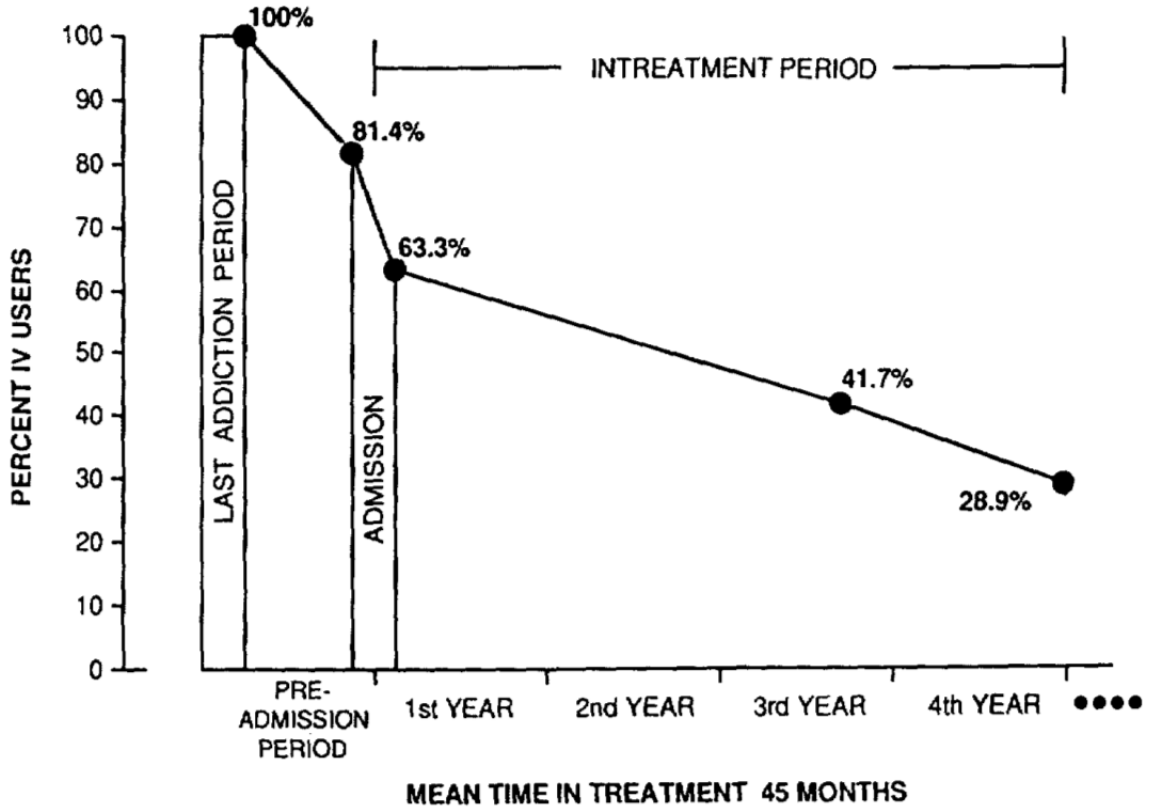
Opioid Agonists for OUD

Methadone	Buprenorphine
Schedule II	Schedule III
Agonist	Partial agonist
Evidenced base efficacy	Comparable efficacy to low dose methadone
Closed distribution system	Office based prescribing
Daily medication supply	Weekly to monthly supply
More severe withdrawal, longer duration	Less severe withdrawal, easier to discontinue

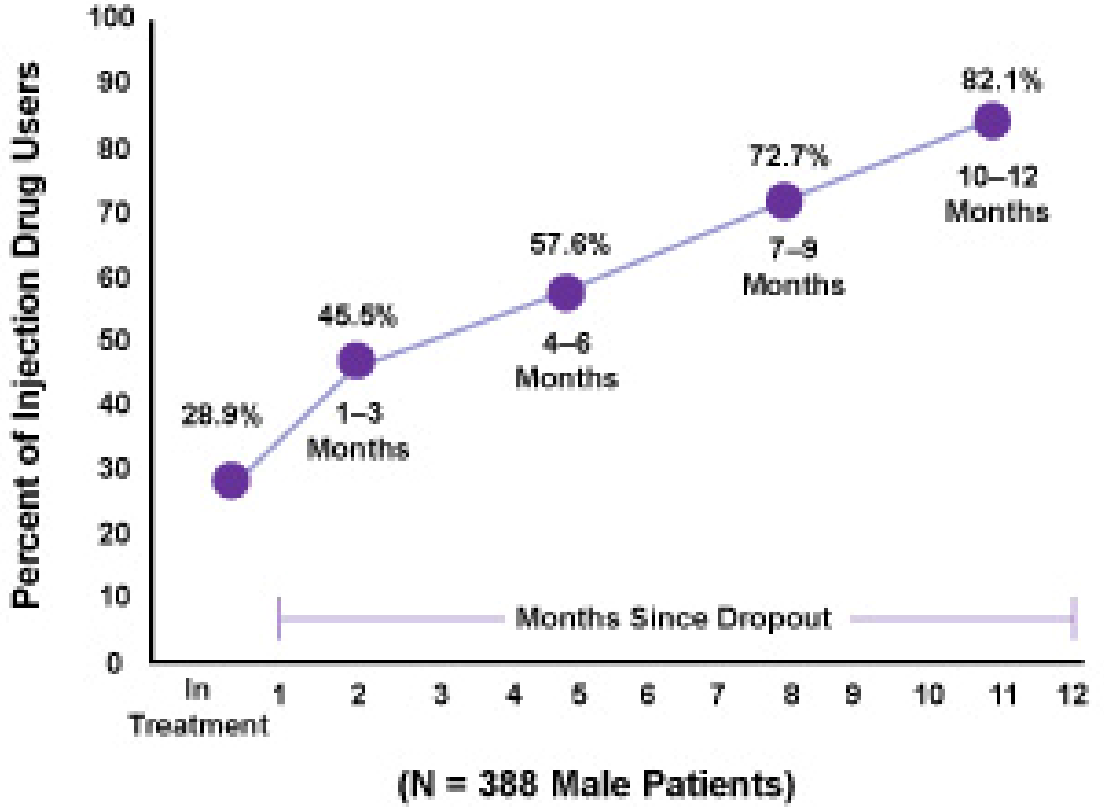

METHADONE
BUPRENORPHINE
MEDICATION ASSISTED TREATMENT
DIARRHEA
YAWNING
GOOSEBUMPS
NORMAL
PAIN
RUNNY NOSE

Opioid Agonist Therapy Decreases IDU

IDU while in methadone

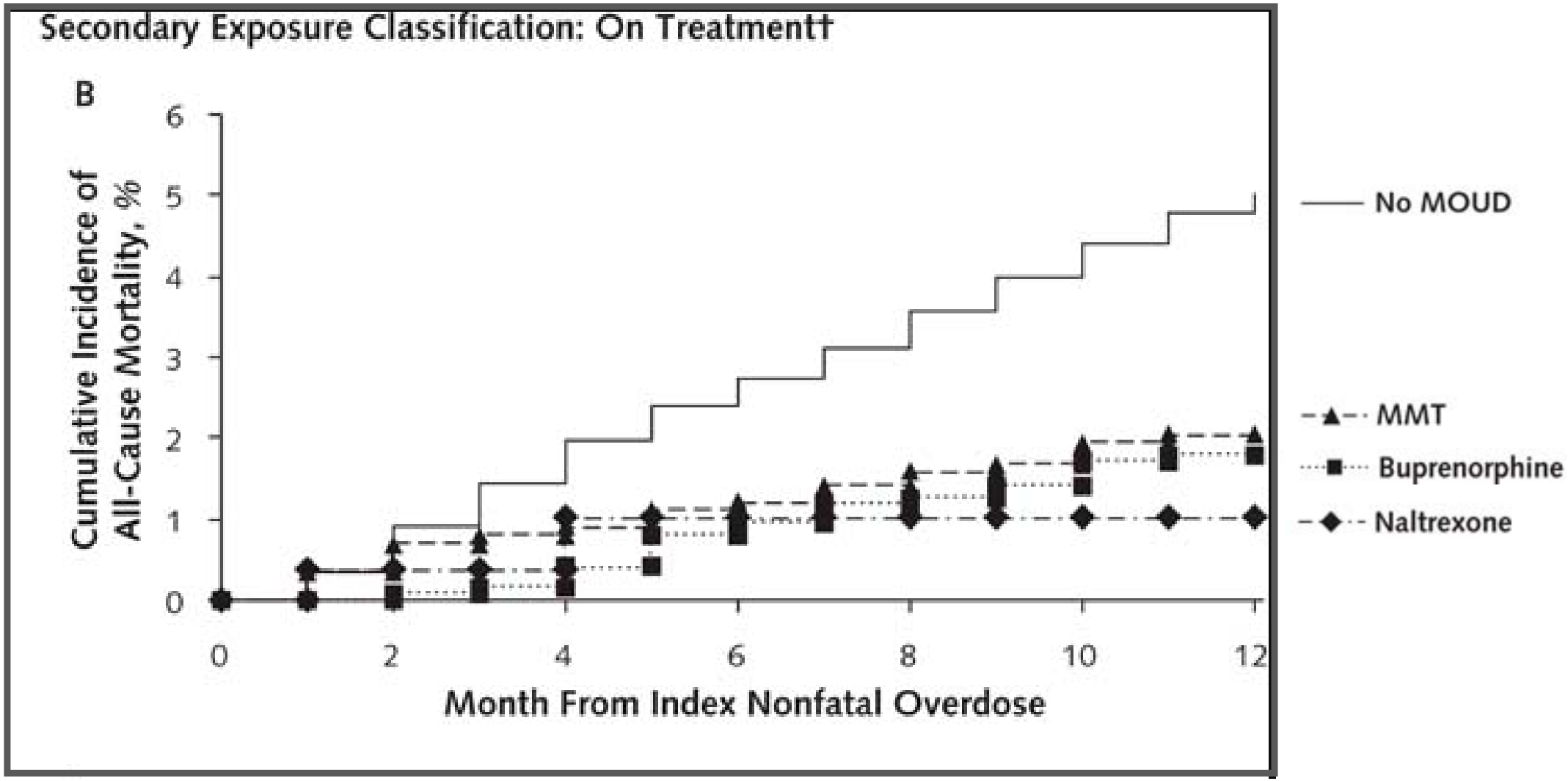


IDU after termination of methadone



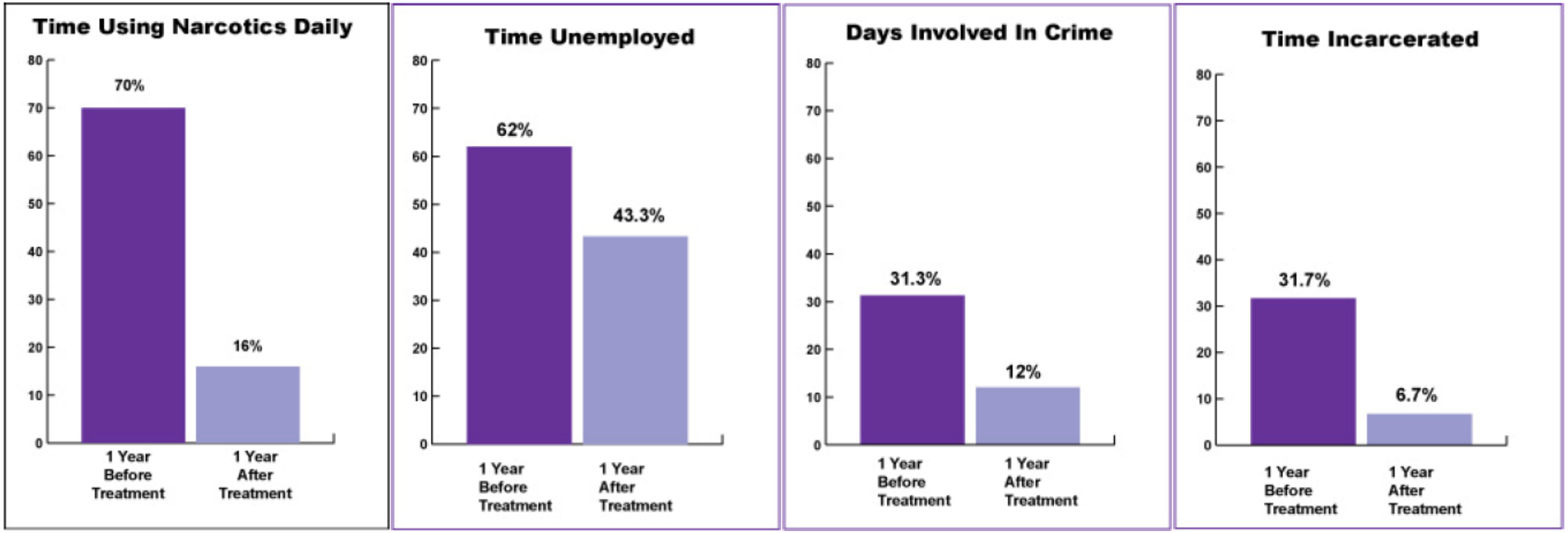
Ball JC, Ross A. The effectiveness of methadone maintenance treatment, 1991

Opioid Agonist Therapy Decreases Mortality



Larochelle, Annals of Internal Medicine 2018

Opioid Agonist Therapy Reduces Harm



NIDA International Program, Methadone Research Web Guide, 2013

Major Features of Naltrexone

Full Antagonist at mu receptor

- Competitive binding at mu receptor

Long acting

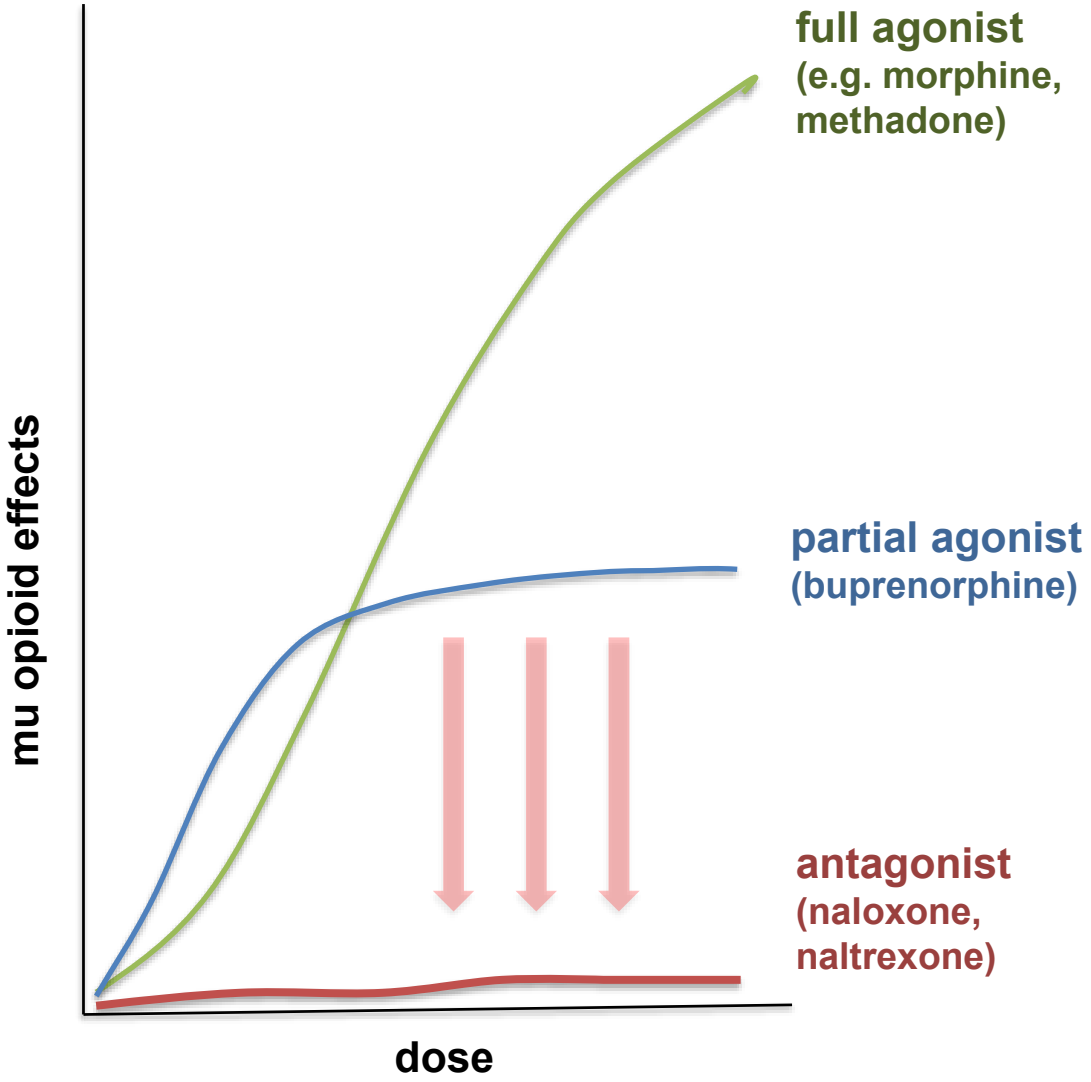
- Half-life:
  - Oral ~ 4 Hours
  - IM ~ 5-10 days

High affinity for mu receptor

- *Blocks* other opioids
- *Displaces* other opioids
  - Can precipitate withdrawal

Formulations

- *Tablets: Revia®: FDA approved in 1984*
- *Extended-Release intramuscular injection: Vivitrol®: FDA approved in 2010*



SAMHSA, 2018

However…

Not all patients want to reduce or stop substance use

Not all patients want to be on medication for substance use

Patients who become abstinent may not stay that way

~~Stigma~~ Discrimination

Disregard for the disease model of addiction

Misconceptions about mOUD

“Replacing one addiction with another”

Criminalization of substance use disorder

What is harm reduction?

A set of practical strategies and concepts aimed at reducing the negative consequences associated with drug use.

A movement for social justice built on the belief in, and respect for, the rights of people who use drugs.

Why engage in harm reduction?

- To focus on where patients are, not where we want them to be
- To empower and support patients in their decisions and goals
- To destigmatize drug use
- To reduce barriers to care
- To keep patients engaged in care

d

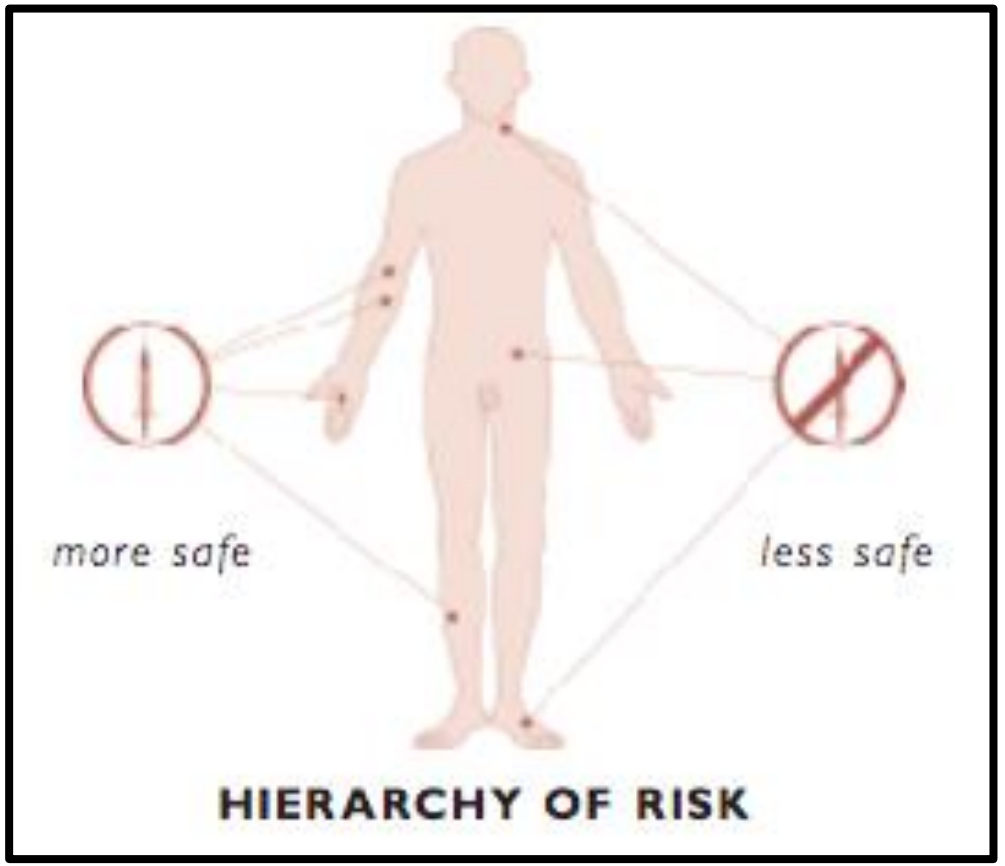
Method	AKA	Risks/Cons	Benefits/Pros
Intranasal	**Snorting**	• Damage to nose • Moderate risk of OD • Sharing straws	• Easier to control high • Less risky than injecting* • No track marks*
Inhalation	**Smoking**	• Irritation to lungs & teeth • Sharing straws or pipes • Wasteful	• Getting a rush • Less OD risk than smoking
Anorectal	**Booty bumping**	• Irritation to anus/rectum • Sharing equipment	• Getting a rush (absorbs quickly)
Oral	**Swallowing**	• Takes longer to feel effect • Difficult to control high	• Less wasteful than smoking

Safer Injection Counseling

Injection Site

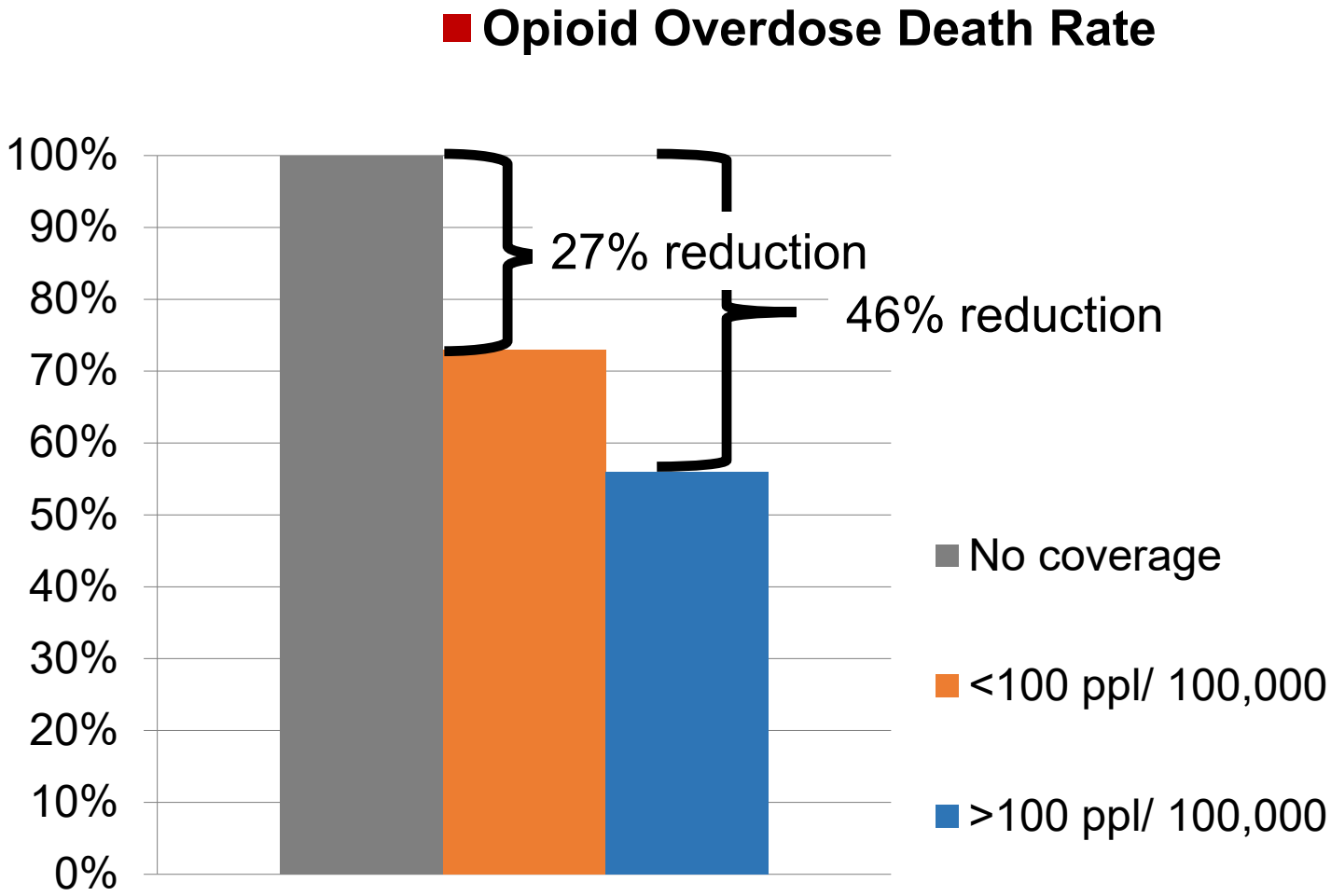
Injection Technique

Sharing Techniques



Harm Reduction Coalition, Getting Off Right,

Naloxone Distribution



Adapted from Alex Walley's slide, CRIT/FIT Program 2014

Overdose Prevention Sites

Safe Consumption Sites

- Increased entry into substance use disorder treatment
- Reduction in the amount and frequency of drug use
- Reduction in public disorder and public injecting
- Reduction in risk behaviors associated with HIV and HCV acquisition
- Increased delivery of medical and social services


THIS SITE SAVES LIVES
ESTE SITIO SALVA VIDAS

Street Names

- Fentanyl: Apache, China Girl , China White, Dance Fever, Friend, Goodfella, Jackpot, Murder 8, Tango and Cash, and TNT.
- Methadone: Amidone, Fizzines with MDMA: Chocolate Chip Cookies
- Heroin: Brown sugar, China White, Dope, H, Horse, Junk, Skag, Skunk, Smack, White Horse

– National Institute of Drug Abuse (NIDA) “Commonly Abused Drugs Chart.” as of July 2017.

Thank You!

MACS

Maryland Addiction Consultation Service

Provides support to prescribers and their practices in addressing the needs of their patients with substance use disorders and chronic pain management.

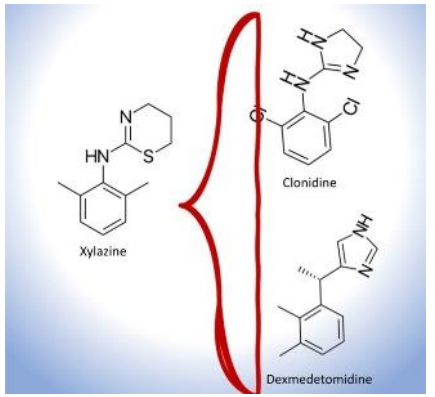
All Services are FREE

- Phone consultation for clinical questions
- Education and training opportunities related to substance use disorders and chronic pain management
- Assistance with addiction and behavioral health resources and referrals
- Technical assistance to practices implementing or expanding office-based addiction treatment services
- MACS TeleECHO Clinics: collaborative medical education through didactic presentations and case-based learning

1-855-337-MACS (6227) • www.marylandMACS.org

XYLAZINE: BASICS

- Synthesized in1962 in Germany
- Partial α-2 agonist
  - Important in sympathetic nervous system
  - Works on pre-synaptic central adrenergic receptors & post-synaptic peripheral receptors
  - Causes decreased release of dopamine and norepinephrine
  - Similar to Clonidine and Dexmedetomidine (Precedex)
  - Structural similarity to phenothiazines and tricyclic antidepressants



- FDA approved in U.S. in 1972 as a sedative, analgesic, & muscle relaxant
  - Only for animals (dogs, cats, horses, elk, fallow deer, mule deer, sika deer, and white-tailed deer)
    - Rompun, Anased, Sedazine, Xylamed, Chanazine
  - A parenteral liquid (20, 100, 300 mg/ml)
- Administered subcutaneously, intramuscularly, intravenously
- Reports of accidental overdose during administration to animals
- Not currently scheduled by DEA

XYLAZINE: “MISUSE”

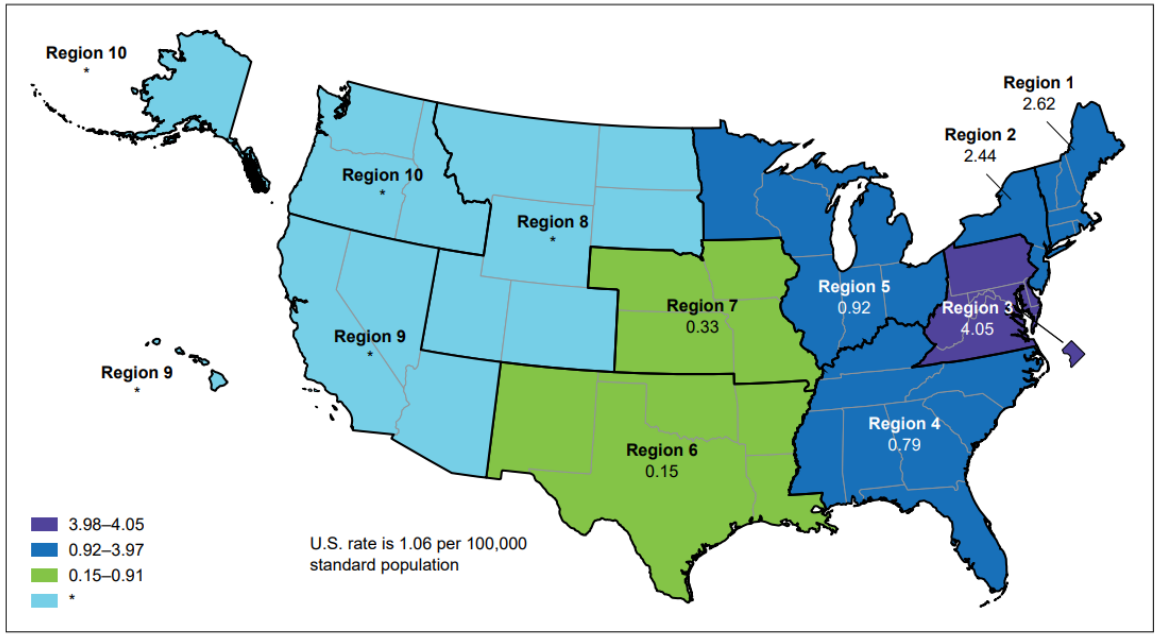
- “Tranq”, “Tranq-Dope”, “Sleep Cut”, “Philly-Dope”, “Zombie Drug”
- “Wipeout”- fentanyl + cocaine+ xylazine
- Vast majority of individuals not seeking it out
- Reported use IV, IN, IM, SC, “smoking”*
  - no reports of actual vaping
- Rapid onset- minutes
- Effects typically last 8 hours but can last for up to 72 hours
- Testing
  - Currently, primarily of drug supply (by syringe services programs, etc.) & post-mortem
  - Immunoassay not very sensitive for detection in urin
  - LC-MS testing by specialty labs

XYLAZINE: "MISUSE"

- Illicit use dating back to late 1970s
- Often by veterinarians or individuals in the equestrian industry
  - Often from diverted veterinary supply
- Popular in Puerto Rico ("Anestesia de Caballo") since early 2000s
- Appeared in continental U.S. in Philadelphia late 2000s
- Increasing adulterant in illicit drug supply
  - Primarily heroin/fentanyl
  - Also in cocaine, methamphetamine, benzodiazepines
- Possibly added to:
  - prolong effects of fentanyl
  - delay withdrawal from fentanyl
  - decrease proportionate amount of opioid w less respiratory depression
- Liquid dried to a powder
- Increasingly coming from China as a powder

XYLAZINE: FATAL OD

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



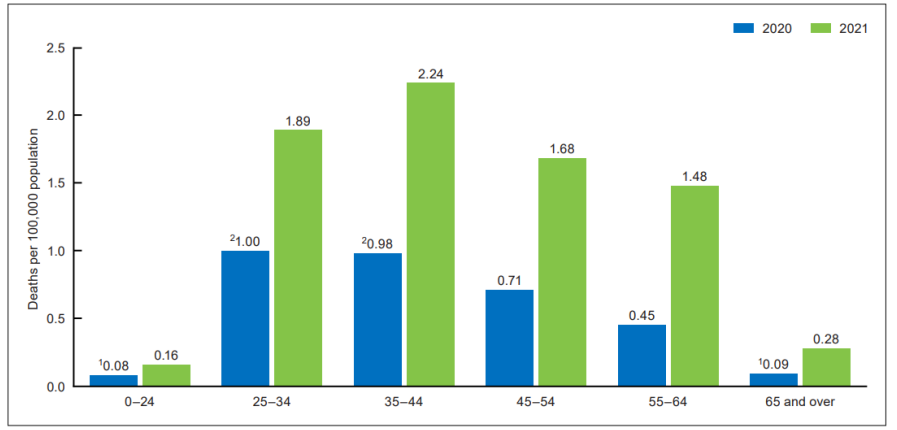
* Rate does not meet the National Center for Health Statistics reliability criteria of 20 deaths or more and as a result is not reported.
NOTES: Drug overdose deaths are identified using *International Classification of Diseases, 10th Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent (listed) drug. Age-adjusted death rates were calculated using the direct method and adjusted to the 2000 U.S. standard population. Regions are the U.S. Department of Health and Human Services public health regions: Region 1 (CT, MA, ME, NH, RI, and VT), Region 2 (NJ and NY), Region 3 (DC, DE, MD, PA, VA, and WV), Region 4 (AL, FL, GA, KY, MS, NC, SC, and TN), Region 5 (IL, IN, MI, MN, OH, and WI), Region 6 (AR, LA, NM, OK, and TX), Region 7 (IA, KS, MO, and NE), Region 8 (CO, MT, ND, SD, UT, and WY), Region 9 (AZ, CA, HI, and NV), and Region 10 (AK, ID, OR, and WA). Except for Regions 1 and 2, differences in rates between all regions were significant ($p < 0.05$).
SOURCE: National Center for Health Statistics, death certificate literal text from the National Vital Statistics System as of May 24, 2023.

Table. Most frequent concomitant drugs for drug overdose deaths involving xylazine: United States, 2018–2021

Year	Referent drug	Number of drug overdose deaths involving referent drug	Most frequent concomitant drug		Second most frequent concomitant drug		Third most frequent concomitant drug	
			Concomitant drug	Number and percent of deaths involving both drugs	Concomitant drug	Number and percent of deaths involving both drugs	Concomitant drug	Number and percent of deaths involving both drugs
2021	Xylazine	3,468	Fentanyl	3,437 (99.1)	Cocaine	1,216 (35.1)	Methamphetamine	652 (18.8)
2020	Xylazine	1,499	Fentanyl	1,490 (99.4)	Cocaine	489 (32.6)	Methamphetamine	232 (15.5)
2019	Xylazine	627	Fentanyl	621 (99.0)	Cocaine	194 (30.9)	Heroin	151 (24.1)
2018	Xylazine	102	Fentanyl	99 (97.1)	Cocaine	41 (40.2)	Heroin	30 (29.4)

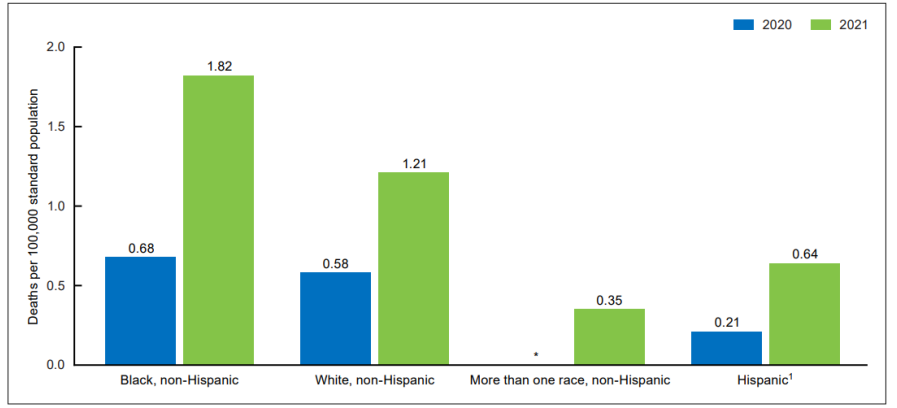
NOTES: Drug overdose deaths are identified using *International Classification of Diseases, 10th Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to xylazine. Age-adjusted death rates were calculated using the direct method and adjusted to the 2000 U.S. standard population. When comparing rates across years, note that trends may be influenced by improvements in drug reporting. The reporting of at least one specific drug or drug class in the literal text, as identified by multiple cause-of-death codes T36–T50.8, improved from 92.0% of drug overdose deaths in 2018 to 95.2% in 2021.

Figure 2. Rate of drug overdose deaths involving xylazine, by age group: United States, 2020–2021



[1]Significantly lower than all other age groups ($p < 0.05$) for 2020.
[2]Significantly higher than all other age groups ($p < 0.05$) for 2020.
NOTES: Drug overdose deaths are identified using *International Classification of Diseases, 10th Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent (listed) drug. When comparing rates across years, note that trends may be influenced by improvements in drug reporting. The reporting of at least one specific drug or drug class in the literal text, as identified by multiple cause-of-death codes T36–T50.8, improved from 94.4% of drug overdose deaths in 2020 to 95.2% in 2021. Differences in rates between 2020 and 2021 were significant for all groups ($p < 0.05$). In 2021, differences in rates were significant between all groups ($p < 0.05$).
SOURCE: National Center for Health Statistics, death certificate literal text from the National Vital Statistics System as of May 24, 2023.

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



* Rate does not meet the National Center for Health Statistics reliability criteria of 20 deaths or more and as a result is not reported.
[1]People of Hispanic origin may be of any race.
NOTES: Drug overdose deaths are identified using *International Classification of Diseases, 10th Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent (listed) drug. Age-adjusted death rates were calculated using the direct method and adjusted to the 2000 U.S. standard population. When comparing rates across years, note that trends may be influenced by improvements in drug reporting. The reporting of at least one specific drug or drug class in the literal text, as identified by multiple cause-of-death codes T36–T50.8, improved from 94.4% of drug overdose deaths in 2020 to 95.2% in 2021. Difference in rates between 2020 and 2021 and within a given year for all groups was significant ($p < 0.05$). Asian non-Hispanic, Native Hawaiian or Other Pacific Islander non-Hispanic, and American Indian or Alaska Native non-Hispanic people are not reported because the 2020 and 2021 rates do not meet the reliability criteria of 20 deaths or more (see https://www.cdc.gov/nchs/data/nvsr/nvsr70/nvsr70-08-508.pdf).
SOURCE: National Center for Health Statistics, death certificate literal text from the National Vital Statistics System as of May 24, 2023.

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Original Investigation | Substance Use and Addiction

January 5, 2024

Xylazine in Overdose Deaths and Forensic Drug Reports in US States, 2019-2022

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Author Affiliations | Article Information

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- 43 states reported at least 1 xylazine-related overdose death from 2019 to 2022
- In 2019, 16 states had zero xylazine reports (NFLIS reports)
- In 2022, only 2 states had zero xylazine reports
- In 2022, all but 3 states had recorded an increase in xylazine's representation in NFLIS reports.
- In 2022, of states with data available (21), xylazine-involved overdose death rates were highest in Vermont (10.5/ 100 000 residents) & Connecticut (9.8/ 100 000 residents)

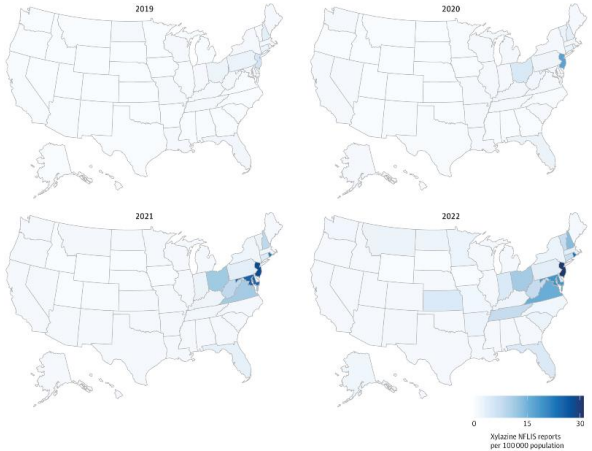


Table. Reported Xylazine-Related Overdose Deaths, 2019-2022

State	No. (rate per 100 000 residents)[a] 2019	2020	2021	2022	Additional information	Source
AK	NR	NR	NR	NR	NA	NA
AL	NR	NR	14 (0.3)	55 (1.1)	NA	Gulf Coast HIDTA,[30] 2023
AR	NR	NR	NR	NR	Jan 2021-June 2022: between 1-9 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
AZ	NR	NR	NR	NR	Jan 2021-June 2022: between 10-99 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
CA	NR	NR	NR	NR	2021: 0.5% of Sampled deaths xylazine-positive, 0.3% xylazine-involved	CA Department of Public Health,[23] 2023
CO	NR	NR	NR	NR	Jan 2021-June 2022: between 1-9 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
CT	71 (2.0)	141 (4.0)	290 (8.2)	354 (9.8)	Xylazine-involved deaths	CT Department of Public Health,[24,25] 2023
DC	NR	3 (0.4)	6 (0.9)	11 (1.6)	Xylazine-involved deaths	DC Office of the Chief Medical Examiner,[26] 2023
DE	NR	NR	NR	NR	Jan 2021-June 2022: between 1-9 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
FL	NR	NR	NR	(1.1)[b,c]	Xylazine-involved; based on first half of year	FL Department of Law Enforcement,[28] 2023
GA	NR	15 (0.1)	116 (1.1)	222 (2.1)	Xylazine-involved	GA Department of Public Health,[29] 2023
HI	NR	NR	NR	NR	NA	NA
IA	NR	NR	NR	NR	Jan 2021-June 2022: between 1-9 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
ID	NR	NR	NR	NR	NA	NA
IL	53 (0.4)	64 (0.5)	188 (1.5)	NA (2.3)[b,c]	Xylazine-involved; 2022 rate based on first half of year	Feinberg School of Medicine,[27] 2023
IN	NR	NR	NR	NR	Jan 2021-June 2022: 82 IMF deaths xylazine-involved	Kariisa et al,[7] 2023
KS	NR	NR	NR	NR	Jan 2021-June 2022: between 1-9 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
KY	NR	NR	NR	NR	In 2022: 1-5 xylazine-positive deaths	KY Office of Drug Control Policy,[31] 2023
LA	3 (0.1)	21 (0.5)	39 (0.8)	25 (0.5)[d]	Xylazine-involved	LA State Board of Medical Examiners,[32] 2023
MA	NR	NR	NR	NR	In 2022: of opioid deaths with toxicology, 5% xylazine-positive	MA Department of Public Health,[33] 2023
MD	103 (1.7)	344 (5.7)	495 (8.0)	NR	Xylazine-positive	Friedman et al,[8] 2022
ME	NR	NR	53 (3.9)	46 (3.4)	Xylazine-involved	Sorg et al,[45] 2022; Sorg et al,[46] 2023
MI	NR	NR	60 (0.6)	92 (0.9)	Xylazine-positive	MI Department of Health and Human Services,[34] 2023
MN	4 (0.1)	8 (0.1)	24 (0.4)	34 (0.6)[d]	Xylazine-involved	MN Department of Health,[35] 2023
MO	4 (0.1)	2 (0.0)	39 (0.6)	109 (1.8)[d]	Xylazine-involved	Nickelson,[40] 2023
MS	NR	NR	NR	NR	Jan 2020-Jun 2022: 19 Xylazine-involved deaths	MS State Department of Health,[36] 2023
MT	NR	NR	NR	NR	NA	NA
NC	NR	NR	NR	NR	NA	NA
ND	NR	NR	NR	NR	Jan 2019-July 2023: 9 Xylazine-positive deaths	ND Department of Health and Human Services,[41] 2023
NE	NR	NR	NR	NR	2021-2022: 4 Xylazine-involved deaths	NE Department of Health and Human Services,[37] 2023
NH	NR	NR	NR	3 (0.2)[d]	Xylazine-involved	NH Office of Chief Medical Examiner,[38] 2023
NJ	13 (0.1)	34 (0.4)	226 (2.4)[d]	210 (2.3)[d]	NA	Bureau of Justice Assistance,[27] 2023
NM	NR	NR	NR	NR	Jan 2021-June 2022: between 1-9 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
NV	NR	NR	NR	NR	Jan 2021-June 2022: between 1-9 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
NY	NR	NR	NR	NR	2021: 429 xylazine-involved opioid deaths in NYC; 135 in New York State outside NYC	NY State Department of Health,[39] 2023
OH	15 (0.1)	45 (0.4)	75 (0.6)	119 (1.0)[d]	Xylazine-involved	OH Department of Health,[42] 2023
OK	NR	NR	NR	NR	Jan 2021-June 2022: between 1-9 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
OR	NR	2 (0.0)	9 (0.2)	9 (0.2)[d]	Xylazine-positive	OR Health Authority,[43] 2023
PA	259 (2.0)	377 (2.9)	576 (4.4)	760 (5.9)	Xylazine-involved	PA Department of Health,[44] 2023
RI	NR	NR	NR	NR	Jan 2021-June 2022: between 10-99 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
SC	NR	NR	NR	NR	Jan 2021-June 2022: 178 IMF deaths involving xylazine	Kariisa et al,[7] 2023
SD	NR	NR	NR	NR	NA	NA
TN	NR	56 (0.8)	94 (1.3)	NR	Xylazine-involved	TN Department of Health,[47] 2022
TX	NR	NR	11 (0.0)	19 (0.1)	Xylazine-involved	TX Department of State Health Services,[48] 2023
UT	NR	NR	NR	NR	NA	NA
VA	NR	NR	NR	NR	Jan 2021-June 2022: between 10-99 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
VT	6 (1.0)	5 (0.8)	29 (4.5)	68 (10.5)	Xylazine-involved	VT Department of Health,[49] 2023
WA	NR	NR	NR	NR	Jan 2021-June 2022: between 1-9 IMF deaths xylazine-positive	Kariisa et al,[7] 2023
WI	NR	NR	NR	NR	2019-2020: 6 xylazine-positive deaths reported in Milwaukee	Friedman et al,[8] 2022
WV	10 (0.6)	67 (3.8)	(4.5)[b,c]	NR	Xylazine-positive	Sibbesen et al,[5] 2023
WY	NR	NR	NR	NR	NA	NA

Abbreviations: IMF, illicitly manufactured fentanyl; NA, not available; NR, not reported.

[a] Death counts were most recently accessed from each source October 27 to 30, 2023. Rates are per 100 000 population and calculated using population estimates from the National Center for Health Statistics.

[b] Totals provided for a half-year period, and not included.

[c] Data provided for half of year only.

[d] Data source indicates this figure is based on provisional data.

XYLAZIN

Maryland
OPIOID OPERATIONAL COMMAND CENTER

OIT Alert!

JULY 31, 2020

UNKNOWN SUBSTANCE REPORTED IN FREDERICK, CECIL & HARFORD COUNTIES

On Thursday, July 23, our office received reports of an unknown substance in Frederick, Cecil, and Harford Counties that can cause very serious wounds at the site of injection.

In Frederick County, the substance is being sold under the name "No Shorts" and distributed in capsule form. Reports indicate that individuals purchasing the substance believe that they are purchasing heroin. After injecting the substance, individuals report injuries that begin as a small discoloration and progress into an open wound. An article citing a warning from Frederick County Health Department can be found here: https://wtop.com/frederick-county/2020/07/frederick-county-warns-of-possibly-fake-heroin-causing-gangrene/.

The High Intensity Drug Trafficking Area program is currently awaiting results from a forensic lab analysis from Frederick County. HIDTA's initial concern is related to a substance called "krokodil" (desomorphine), but lab results are required before any final determination is made. Read more about krokodil here: https://www.drugs.com/illicit/krokodil.html.

The Cecil County Health Department believes that a similar substance, branded as "Don't Make Me Mad," is present in Cecil County, where two confirmed cases have been reported. Both of the cases involved individuals engaged in wound-care services. CCHD will continue to monitor the situation and share information with the community as it becomes available.

Harford County has issued the following public health alert:

"The Harford County Health Department Harm Reduction Program has received reports of soft tissue injuries, including abscesses and development of gangrene, associated with injection drugs recently in circulation. Similar reports have also been made in Frederick and Cecil Counties, MD.

Development of abscesses and cellulitis after injecting heroin cut with xylazine (commonly used as a horse tranquilizer) has been seen. Bags containing this substance are stamped "Ohh yeah."

Reports also include development of gangrene after injecting contents of a gel capsule containing what was believed to be heroin, sold under the name "No Shorts." The powder turns pink/red when water is added. The injury starts as a small discoloration (purplish) at the injection site and progresses outward into an open wound, sometimes almost black in color.

If you have an injection-related wound that shares any of the similarities above it is recommended you seek immediate medical attention.

Call the Harm Reduction Program at (410) 612-1779 for information on overdose prevention (including free Narcan®) and wound care. Contact Behavioral Health at (410) 877-2340 for information on substance use treatment and peer recovery services."

Please report any further information related to the above to Help.OOCC@Maryland.gov.

XYLAZINE: INTOXICATION

- Clinical effects:
  - Primarily- hypotension, bradycardia, sedation (with immobility)
  - Less effect on respiration
  - Some reports of hyperglycemia & anemia (primarily in animals)
- Does not respond to naloxone but should always be given as usually mixed w opioids
- Activated charcoal, IV fluids, atropine(?), intubation (if with respiratory distress)
- Atipamezole
  - Selective α-2 antagonist
  - FDA approved for animals anesthetized with α-2 agonists
  - Some proposal to use in humans
- Very few fatalities from Xylazine alone reported
  - 1 suicide used IV with serum level 2,900 ng/ml

XYLAZINE: WITHDRAWAL

- Clinical effects
  - Primarily from rebound adrenergic effects
  - Increased blood pressure, heart rate, diaphoresis
  - May appear as worsened opioid withdrawal
    - Locus ceruleus
- IMPORTANT TO TREAT THE OPIOID WITHDRAWAL!!!
- No standardized management.
- Reports of use of:
  - Clonidine
  - Dexmedetomidine (Precedex)
  - Benzodiazepines
  - Tizanidine
  - Guanfacine

XYLAZINE: WOUNDS

- ~~The vast majority not confirmed by toxicology~~
- May develop rapidly and resolve slowly
- Reported in those who deny IV use
- Reported at sites other than where person injected

- Often large, granular, w/ a necrotic center
  - Common course of progression-several small “punch-hole” wounds appearing in a cluster, then coalesce into a single larger wound
  - Not typically purulent
- Unclear pathophysiology
  - Likely related to decreased oxygenation of tissues
- Management more like managing burns
  - Clean well w/ soap & water or saline
  - Keep moist
  - Cover w/ non-adherent dressing (Xeroform)
  - Antibiotics may not be needed

"DESIGNER" OPIOIDS

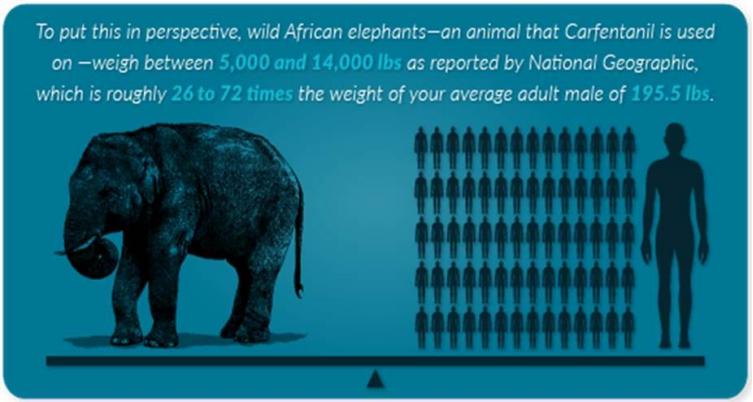
- AKA:
  - NPFs (Non-Pharmaceutical Fentanyls)
  - IMFs (Illicitly-Manufactured Fentanyls)
  - FASH (Fentanyl Adulterated/Substituted
  - HPSO (High Potency Synthetic Opioids)
  - NPOs (Novel Potent Opioids)
- >30 different <u>fentanyl analogues</u>
  - alpha-methylfentanyl (AMF)
  - 3-methylfentanyl (TMF)
  - carfentanil

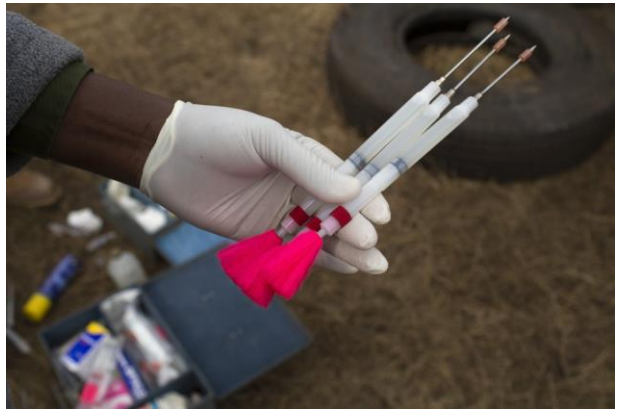
- 3-Methylbutyrfentanyl, 3-MBF
- 3-Methylfentanyl, 3-MF
- 4-Chloroisobutyrfentanyl, 4-ClBF, p-ClBF
- 4-Fluorobutyrfentanyl, 4-FBF, p-FBF
- 4-Fluoroisobutyrfentanyl, 4-FiBF, p-FiBF
- 4-Methoxybutyrfentanyl, 4-MeO-BF, p-MeO-BF
- 4-Fluorofentanyl, 4-FF, p-FF
- Acetylfentanyl, AF
- Acrylfentanyl
- AH-7921
- α-Methylfentanyl, "China White"
- Butyrfentanyl, BF
- Cyclopentylfentanyl, CP-F
- Desmethylprodine, MPPP
- Furanylfentanyl, Fu-F
- MT-45
- O-Desmethyltramadol
- Tetrahydrofuranylfentanyl, THF-F
- U-47700
- U-51754[62]
- Valerylfentanyl, VF

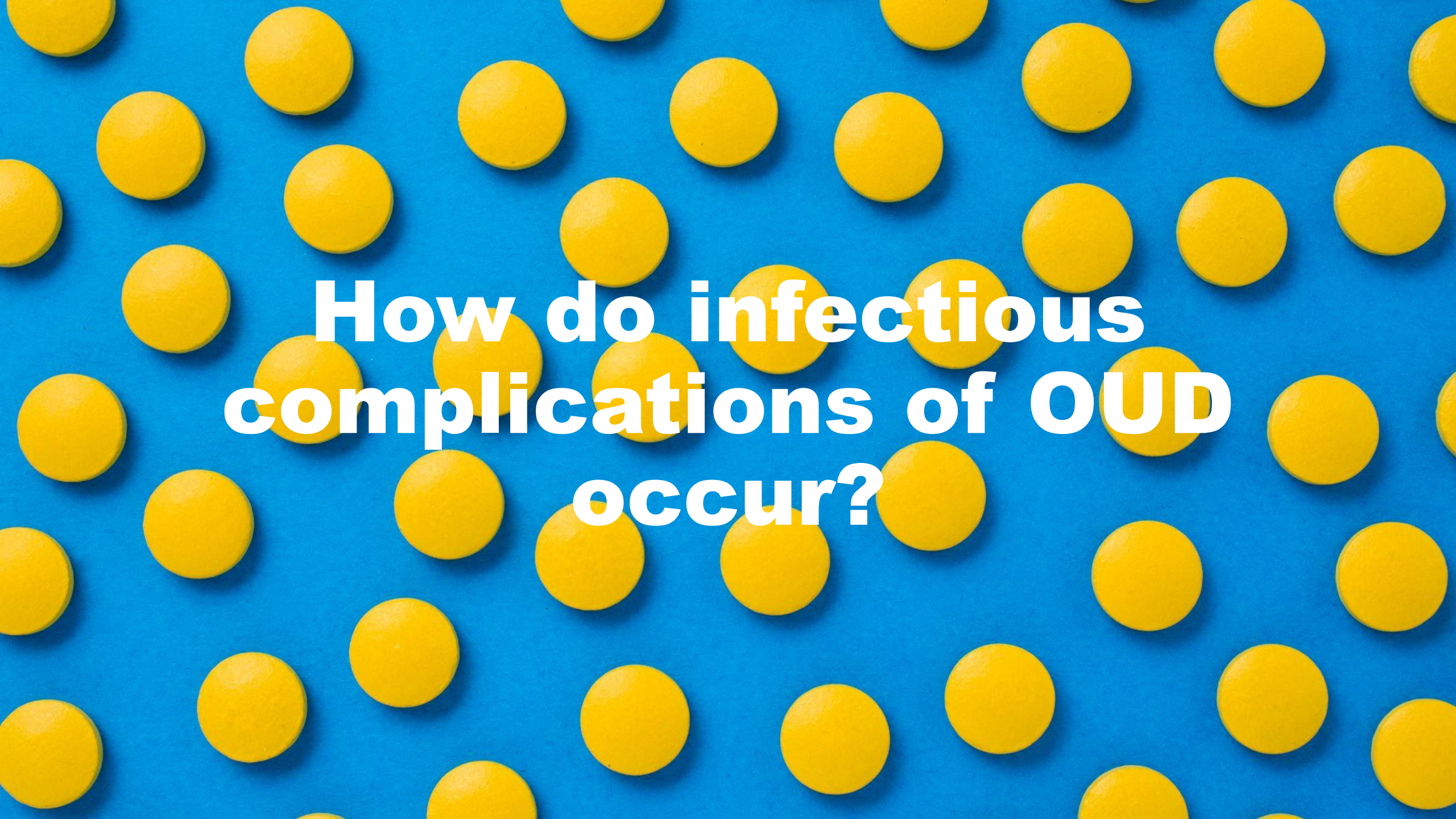
- Originally (1970s-80s) referred to as "China White" (the term reserved for very pure heroin), "Tango & Cash", "Persian White", "Goodfella"
  - "Gunpowder heroin"- newer term
- TMF & carfentanil 1000s of times more potent than morphine

CARFENTANIL

- Fentanyl analog
- Synthetized by Jansen Pharmaceuticals in 1974
- One of the most potent opioids known
- Used commercially as a large animal tranquilizer (*Wildnil*)
- On illicit opioid scene in N. America since 2(






How do infectious complications of OUD occur?

Heroin Forms and Modes of Use

How to Inject Opioids

- Obtain drug
- Place powder into sterile cooker
- Add water to cooker
- Heat cooker to dissolve
- Place filter into solution
- Draw up solution into syringe
- Clean injection site
- Inject

Infections through Drug Contamination

- **Obtain drug**
  - Contaminated drug from supply chain
  - Tablets crushed into powder using teeth

Risks of Drug Contamination

- Obtain drug
- **Place powder into sterile cooker**
  - Non-sterile cookers
  - spoon, bottom of a soda can, bottle cap

Risks of Drug Contamination

- Obtain drug
- Place powder into sterile cooker
- **Add water to cooker**
  - Non-sterile water
    - Sink tap
    - Toilet bowl
    - Puddle

Risks of Drug Contamination

- Obtain drug
- Place powder into sterile cooker
- Add water to cooker
- **Heat cooker to dissolve**

  - Must add acid to dissolve black tar heroin
    - Lemon juice
    - Vinegar

Risks of Drug Contamination

- Obtain drug
- Place powder into sterile cooker
- Add water to cooker
- Heat cooker to dissolve
- **Place filter into solution**

- Makeshift filters are often used
  - Pieces of cotton balls
  - Q-tips
  - Cigarette filters
- Filters are often reused

Risks of Drug Contamination

- Obtain drug
- Place powder into sterile cooker
- Add water to cooker
- Heat cooker to dissolve
- Place filter into solution
- Draw up solution into syringe
- **Clean injection site**
- **Inject**

- Licking the needle tip before injecting
- Injecting into unclean/licked skin
- Reusing needles/syringes