Brigham and Women's Hospital
Founding Member, Mass General Brigham

Management of Substance Use Disorders in the Medical Setting

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Disclosures

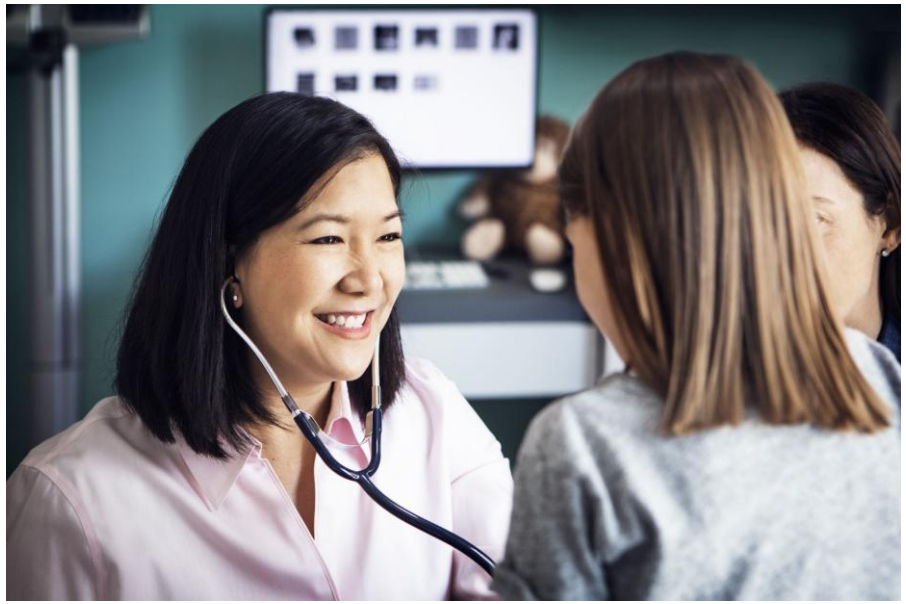
No relevant disclosures

Learning Objectives

By the end of this talk, the audience will:

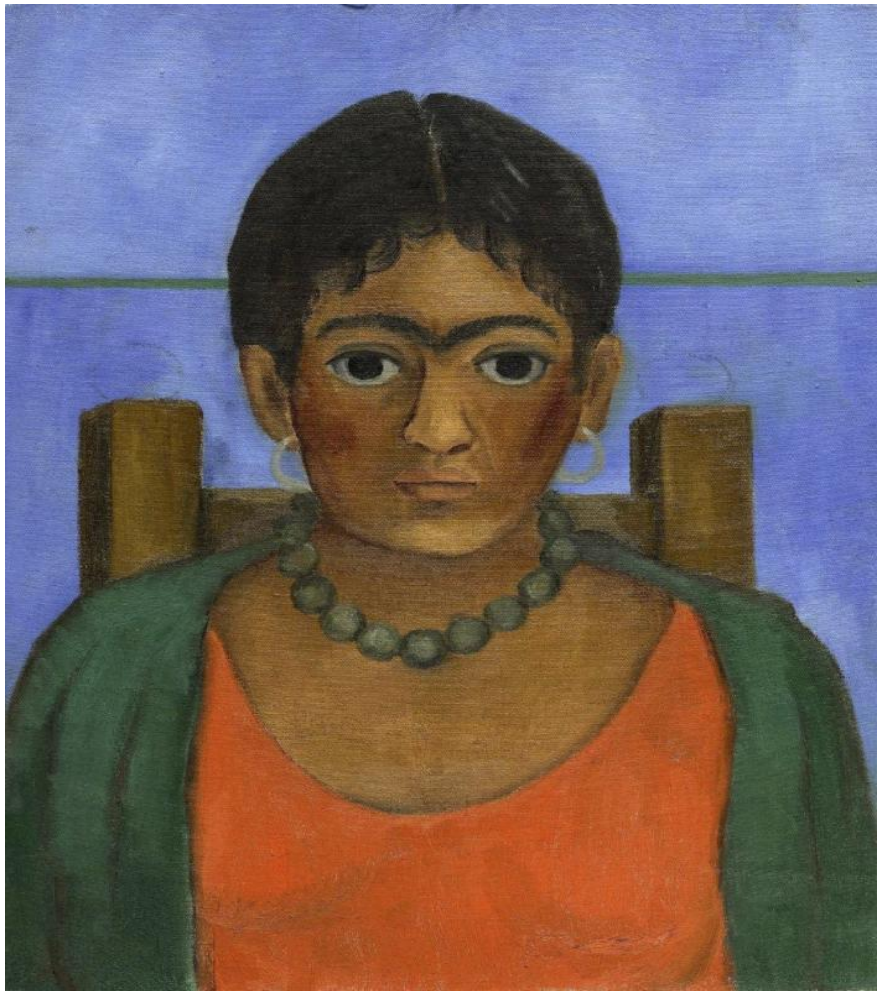
Recognize and manage **alcohol withdrawal** and initiate evidence-based pharmacotherapy to support recovery.

Diagnose opioid use disorder and implement guideline-based **opioid agonist therapy**, and harm reduction strategies.



Learning Objective #1

Recognize and manage **alcohol withdrawal** and initiate evidence-based pharmacotherapy to support recovery.



"I tried to drown my sorrows in alcohol, but [they] learned how to swim."
(Frida Kahlo)

A 38-year-old woman arrives with a two-week history of daily tension-type headaches—dull, band-like pressure that worsens by evening and only partially responds to over-the-counter analgesics, and she recently received a short course of narcotic analgesics when offered for breakthrough pain. Past records are notable for her reporting a long-standing pattern of heavy weekend drinking (last AUDIT-C: 6), several recent ED visits for intoxication followed by her no-showing to outpatient PCP follow up appointments. She lives with her mother and 8-year-daughter, works intermittently as a retail manager. Her physical exam is unremarkable. Headache prophylaxis with low-dose amitriptyline is initiated, sleep hygiene is reviewed, but she declines to be referred to addiction services after discharge.

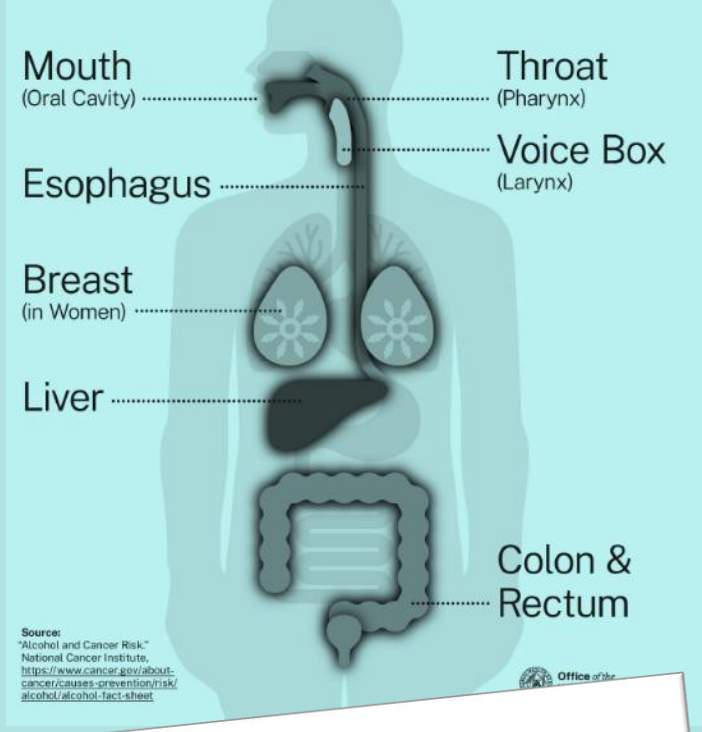
**hypothetical case vignette for teaching purposes*

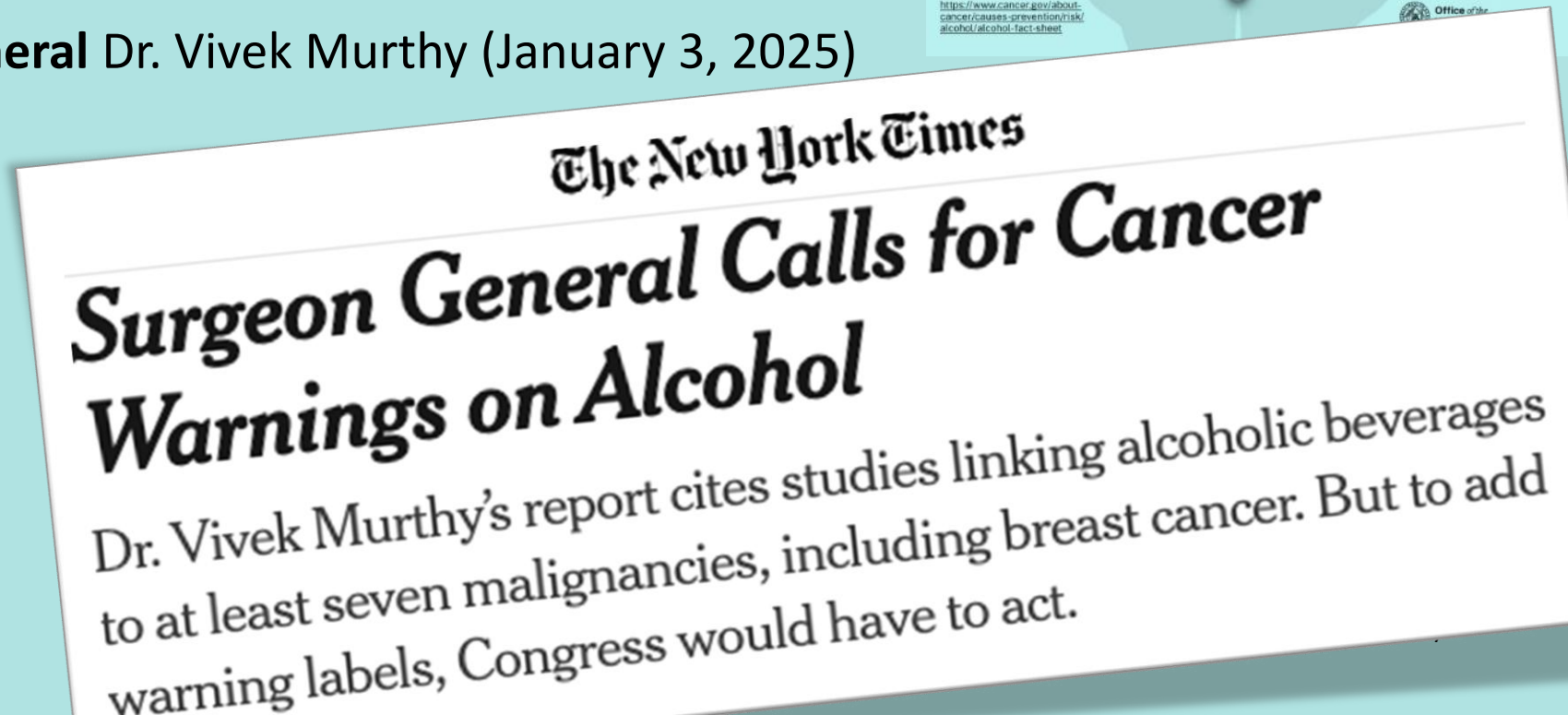
178,000

Number of deaths attributable to alcohol in 2021 (CDC)

“Alcohol Consumption is the Third Leading Preventable Cause of Cancer in the [US].”

– **United States Surgeon General** Dr. Vivek Murthy (January 3, 2025)




The New York Times

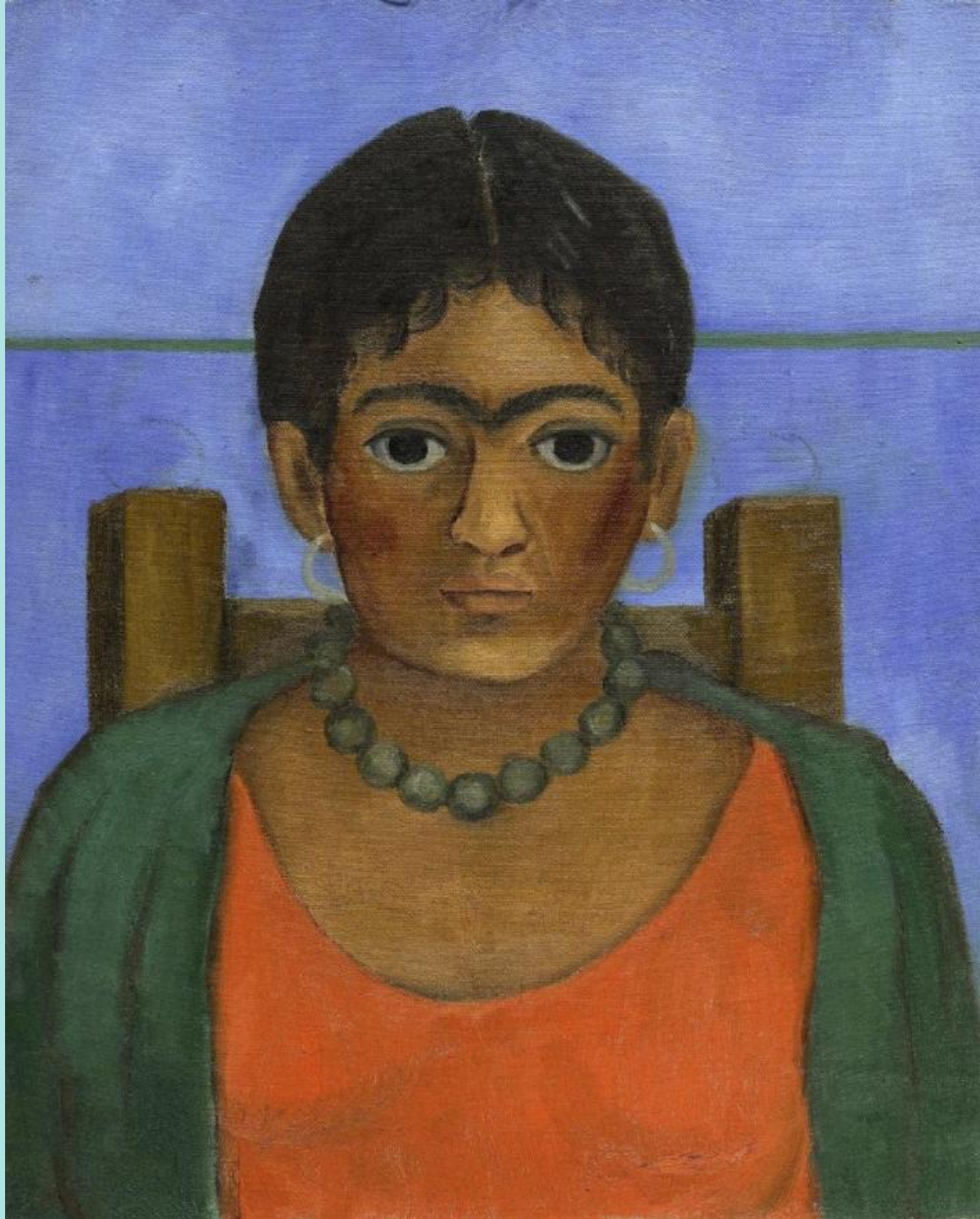
Surgeon General Calls for Cancer Warnings on Alcohol

Dr. Vivek Murthy's report cites studies linking alcoholic beverages to at least seven malignancies, including breast cancer. But to add warning labels, Congress would have to act.

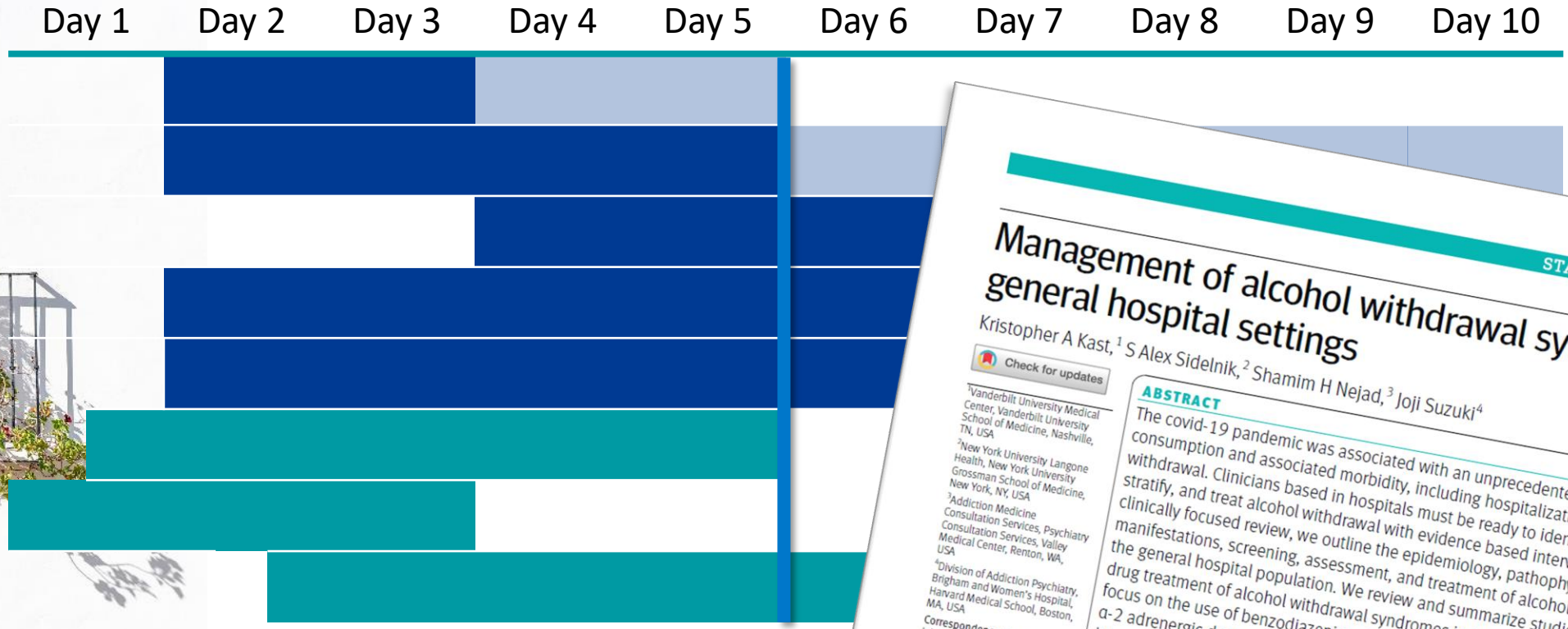
Case 1

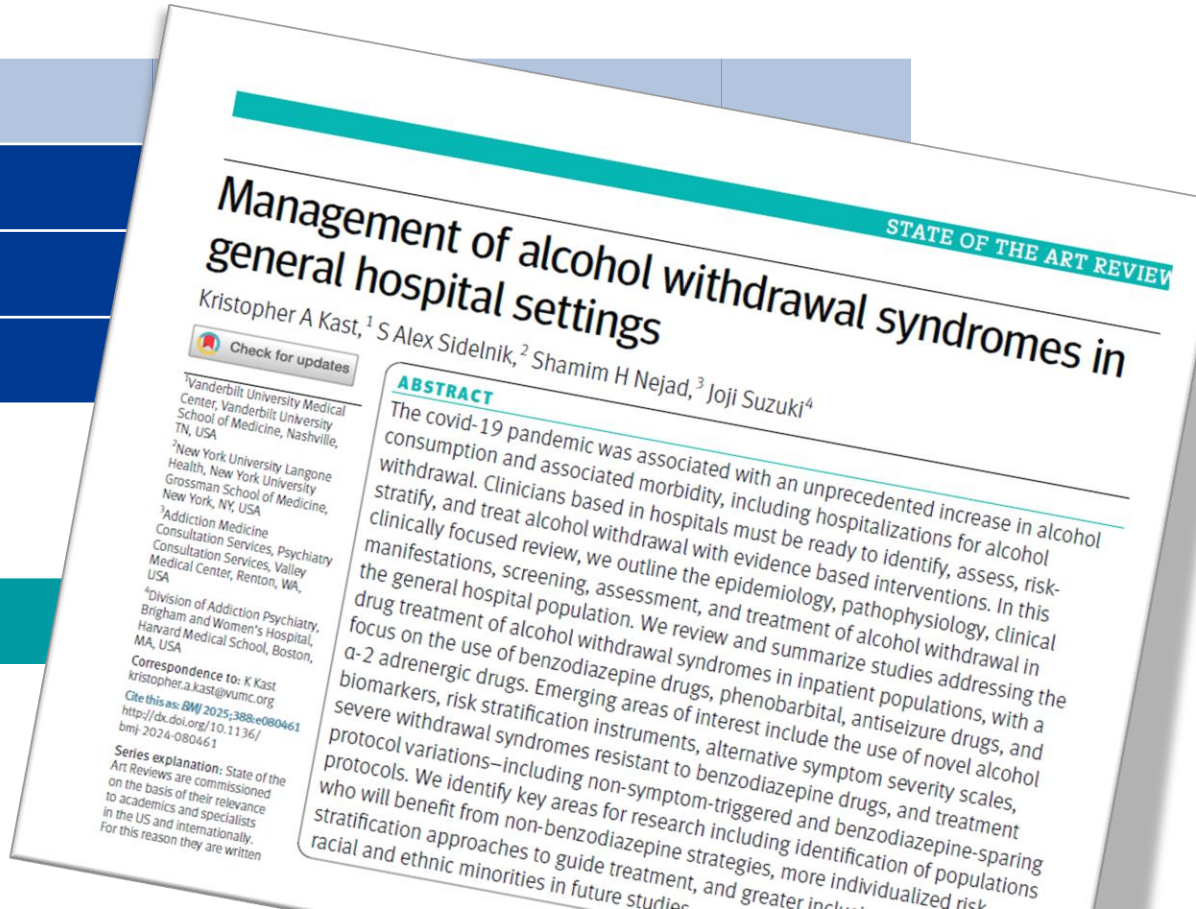
"I tried to drown my sorrows in alcohol, but the bastards learned how to swim."

- Frida Kahlo



Hospitalization is a window of “iatrogenic opportunity,” interrupting alcohol use for an average of 5.9 days





STATE OF THE ART REVIEW

Management of alcohol withdrawal syndromes in general hospital settings

Kristopher A Kast,[1] S Alex Sidelnik,[2] Shamim H Nejad,[3] Joji Suzuki[4]

Check for updates

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Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written

ABSTRACT

The covid-19 pandemic was associated with an unprecedented increase in alcohol consumption and associated morbidity, including hospitalizations for alcohol withdrawal. Clinicians based in hospitals must be ready to identify, assess, risk-stratify, and treat alcohol withdrawal with evidence based interventions. In this clinically focused review, we outline the epidemiology, pathophysiology, clinical manifestations, screening, assessment, and treatment of alcohol withdrawal in the general hospital population. We review and summarize studies addressing the drug treatment of alcohol withdrawal syndromes in inpatient populations, with a focus on the use of benzodiazepine drugs, phenobarbital, antiseizure drugs, and α-2 adrenergic drugs. Emerging areas of interest include the use of novel alcohol biomarkers, risk stratification instruments, alternative symptom severity scales, severe withdrawal syndromes resistant to benzodiazepine drugs, and treatment protocol variations—including non-symptom-triggered and benzodiazepine-sparing protocols. We identify key areas for research including identification of populations who will benefit from non-benzodiazepine strategies, more individualized risk stratification approaches to guide treatment, and greater inclu… racial and ethnic minorities in future studies

Kast KA, Sidelnik SA, Nejad SH, Suzuki J. Management of alcohol withdrawal syndromes in general hospital settings. *BMJ*. 2025;388:e080461. Published 2025 Jan 8. doi:10.1136/bmj-2024-080461 (used as a source throughout this presentation), citing https://data.oecd.org/healthcare/length-ofhospital-stay.htm#indicator-chart

Alcohol Use Disorder

DSM-5-TR Diagnostic Criteria

2 = mild

4 = moderate

6 = severe

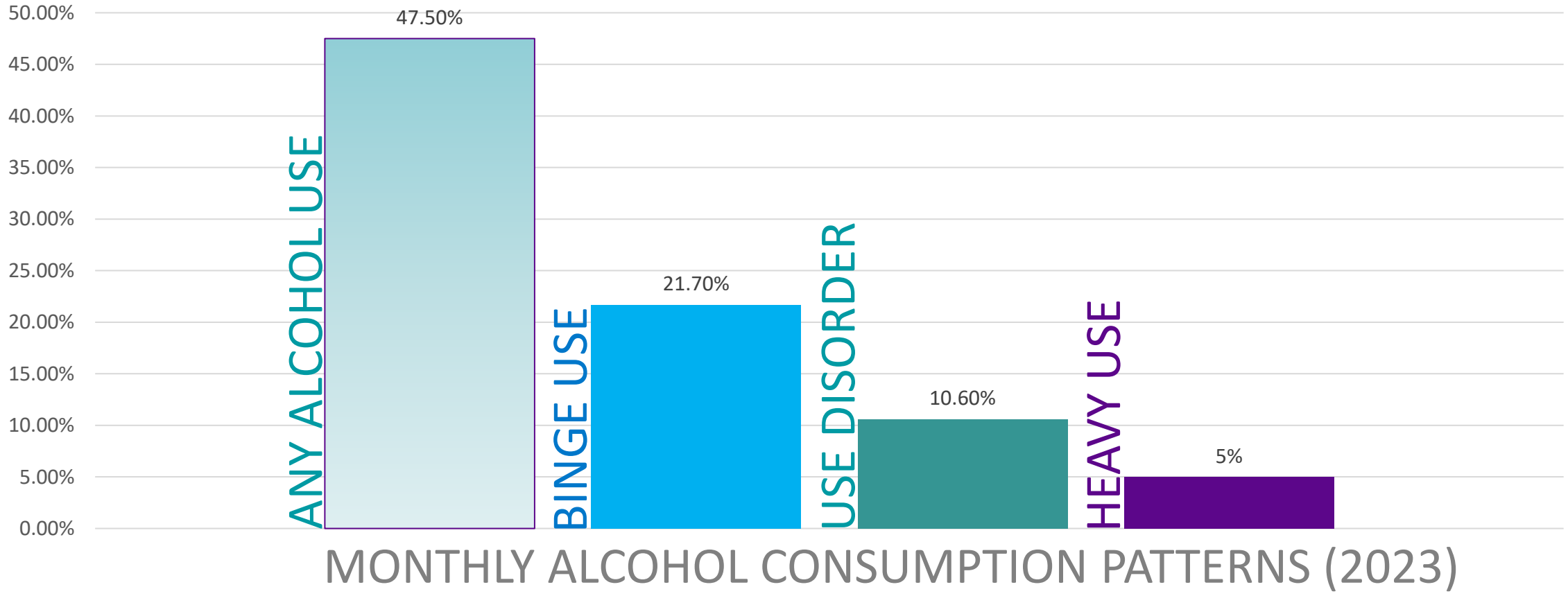
DSM 5 Substance Use Disorder Diagnostic Criteria

A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least **two** of the following, occurring within a 12-month period:

	Alcohol	Opioid	Cocaine	Marijuana
1. Substance is often taken in **larger amounts** or **over a longer period than was intended**.				
2. There is a **persistent desire** or **unsuccessful efforts** to **cut down or control** substance use.				
3. A **great deal of time is spent in activities necessary to obtain** substance, **use** substance, or **recover** from its effects.				
4. **Craving**, or a strong desire or urge to use substance.				
5. Recurrent substance **use resulting in a failure to fulfill major role obligations** at work, school, or home.				
6. Continued substance **use despite having persistent or recurrent social or interpersonal problems** caused or exacerbated by the effects of substance.				
7. Important **social, occupational, or recreational activities are given up or reduced** because of substance use.				
8. Recurrent substance **use in situations in which it is physically hazardous**.				
9. Substance use is continued despite knowledge of having a persistent or recurrent **physical or psychological problem that is likely to have been caused or exacerbated** by substance.				
10. **Tolerance**, as defined by either of the following:				
- A need for markedly increased amounts of substance to achieve intoxication or desired effect.				
- A markedly diminished effect with continued use of the same amount of substance.				
11. **Withdrawal**, as manifested by either of the following:				
- The characteristic withdrawal syndrome for substance (refer to Criteria A and B of the criteria set for substance withdrawal, pp. 499–500).				
-Substance (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.				
Meets Diagnostic Criteria? Severity?				

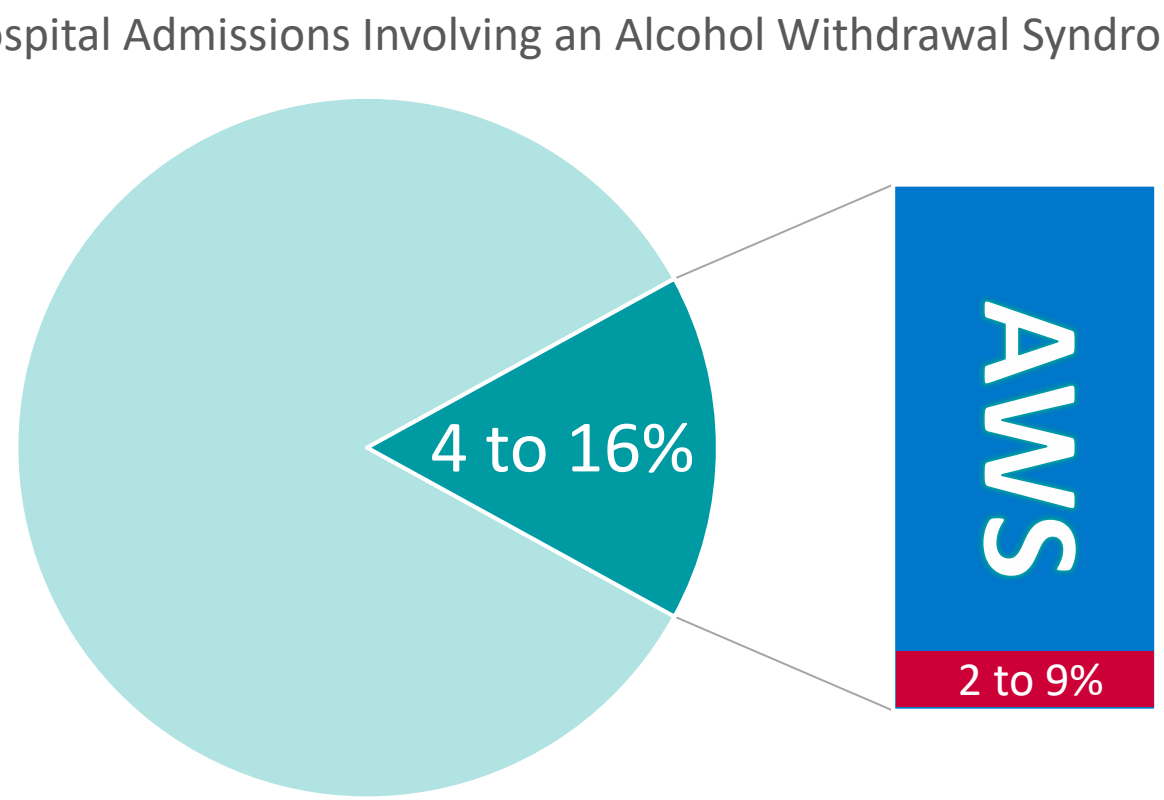
Source: DSM-5

15 to 50% of persons who have an alcohol use disorder or drink heavily will develop **symptoms** of alcohol withdrawal



https://pubmed.ncbi.nlm.nih.gov/35275407/
https://pubmed.ncbi.nlm.nih.gov/15706737/

Among all hospital admissions, **approximately 1 in 10** entail an alcohol withdrawal syndrome (**AWS**)



Severe AWS

Seizures

Alcohol withdrawal ***delirium***

Hallucinosis

https://pubmed.ncbi.nlm.nih.gov/31609866/
https://pubmed.ncbi.nlm.nih.gov/27586815/
https://pmc.ncbi.nlm.nih.gov/articles/PMC8522287/

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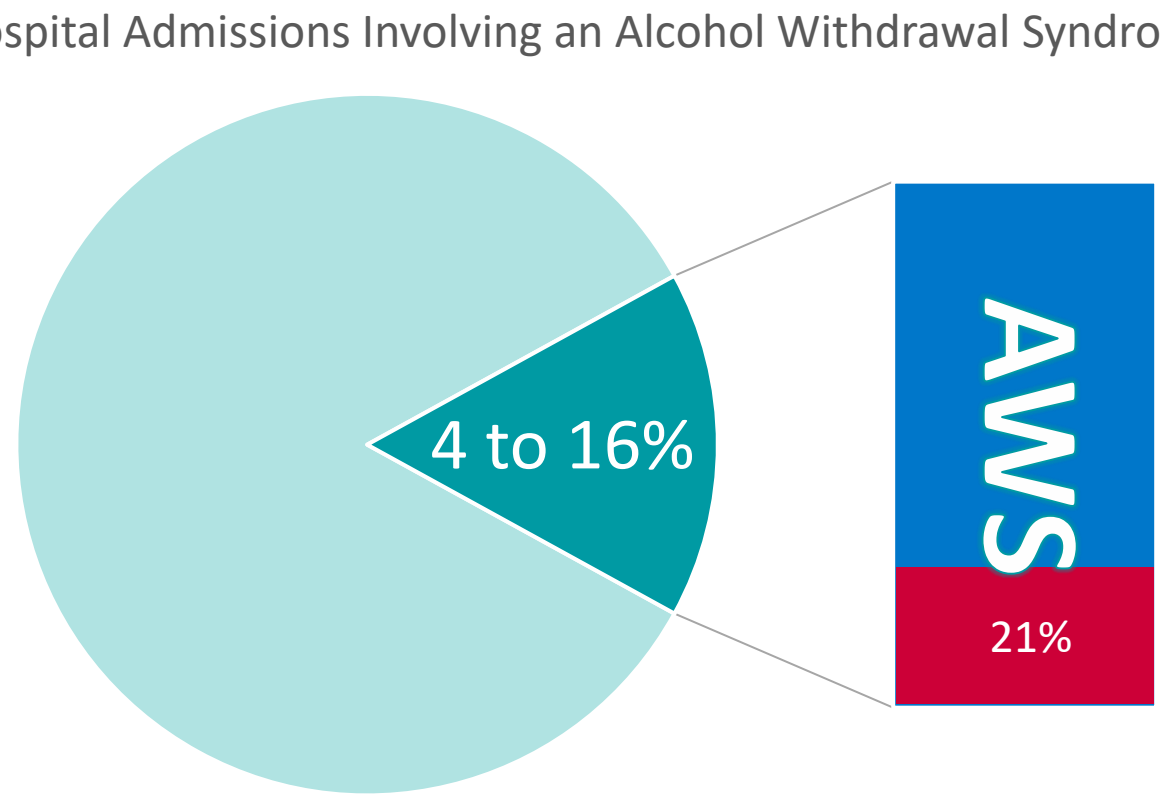

Severe AWS in the ICU
Seizures
Alcohol withdrawal ***delirium***
(higher morbidity, ***1-8% mortality****)*
Hallucinosis

https://pubmed.ncbi.nlm.nih.gov/31609866/
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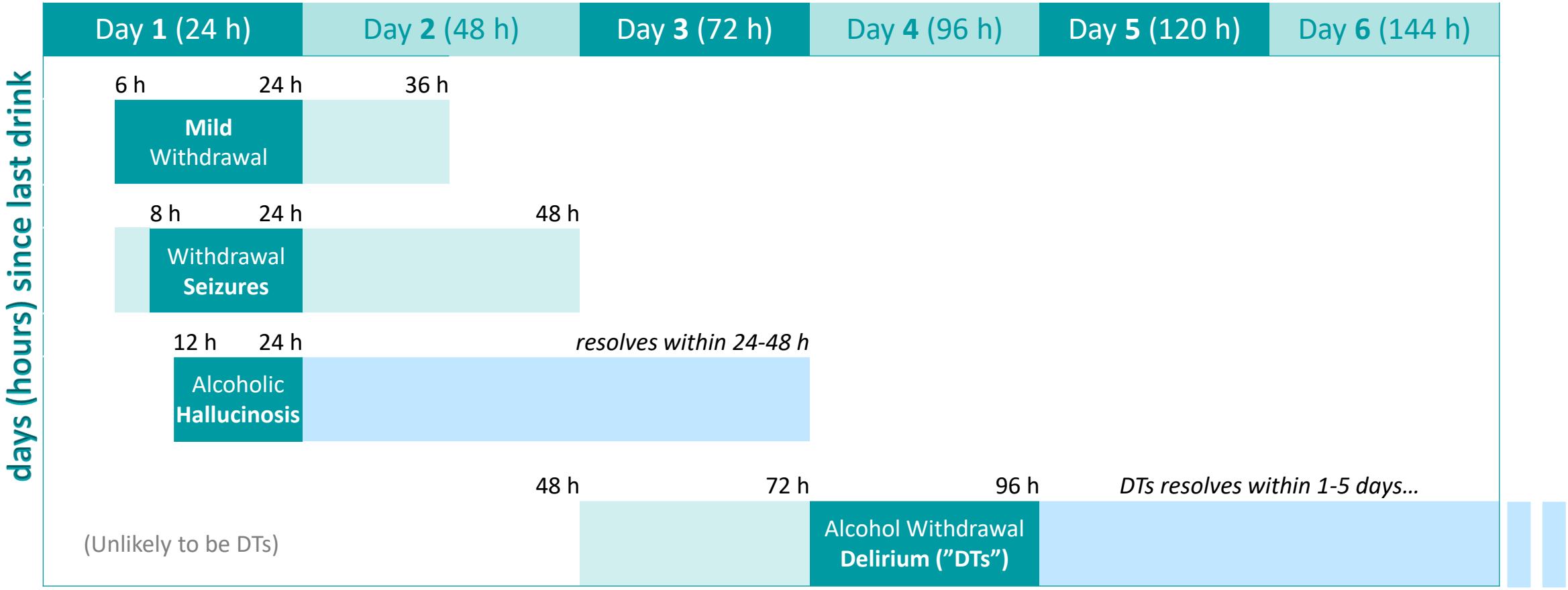
Hospitalization is a window of “iatrogenic opportunity,” interrupting alcohol use for an average of 5.9 days



Kast KA, Sidelnik SA, Nejad SH, Suzuki J. Management of alcohol withdrawal syndromes in general hospital settings. *BMJ*. 2025;388:e080461. https://www.uptodate.com/contents/management-of-moderate-and-severe-alcohol-withdrawal-syndromes?search=alcohol%20withdrawal%20syndromes&topicRef=7800&source=related_link

DSM-5-TR Alcohol Withdrawal

Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) [heavy & prolonged] alcohol use….

autonomic hyperactivity

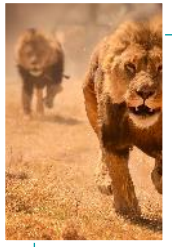
increased hand tremor

insomnia

nausea or vomiting

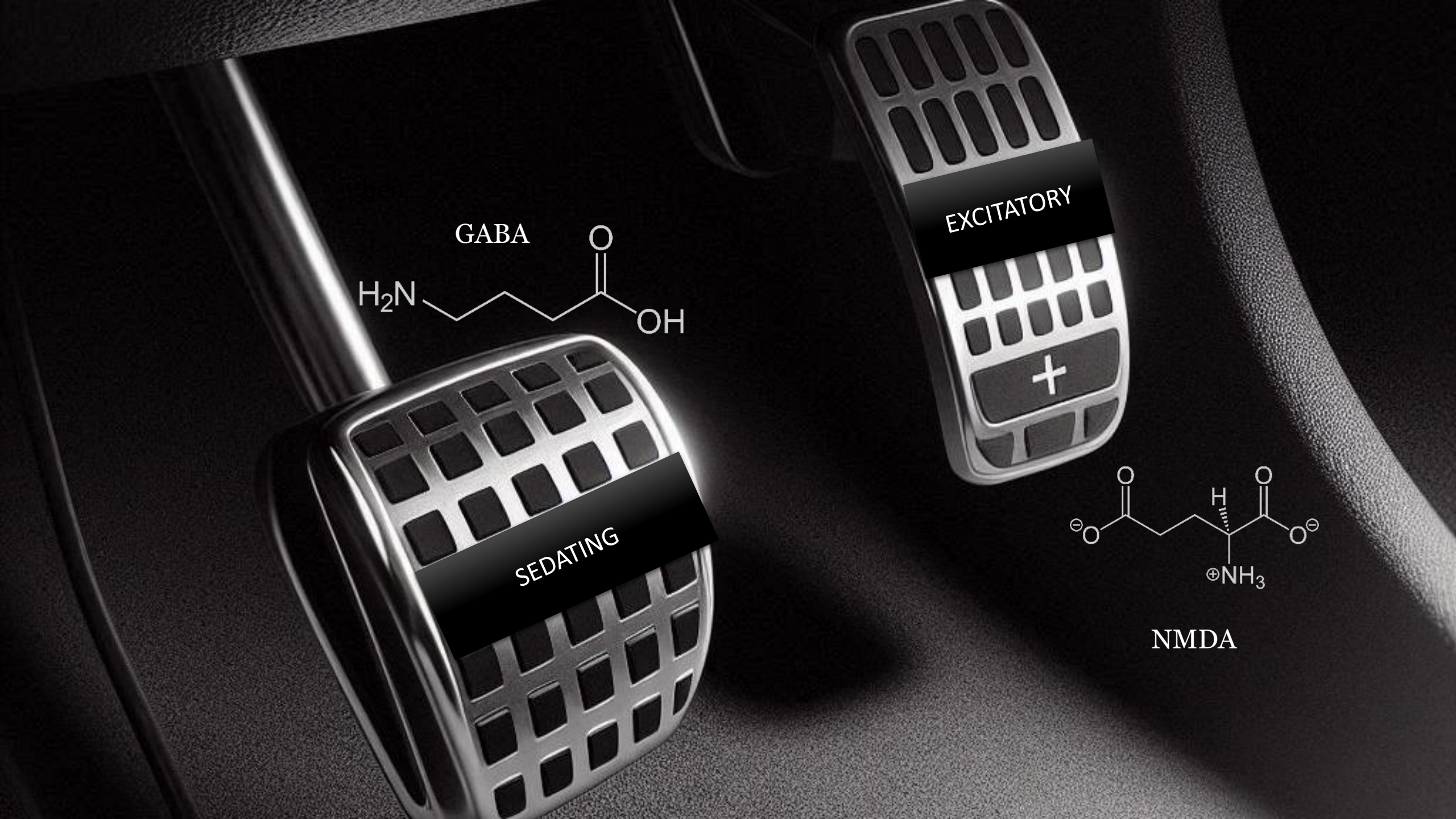
transient VH, TH, AH or illusions

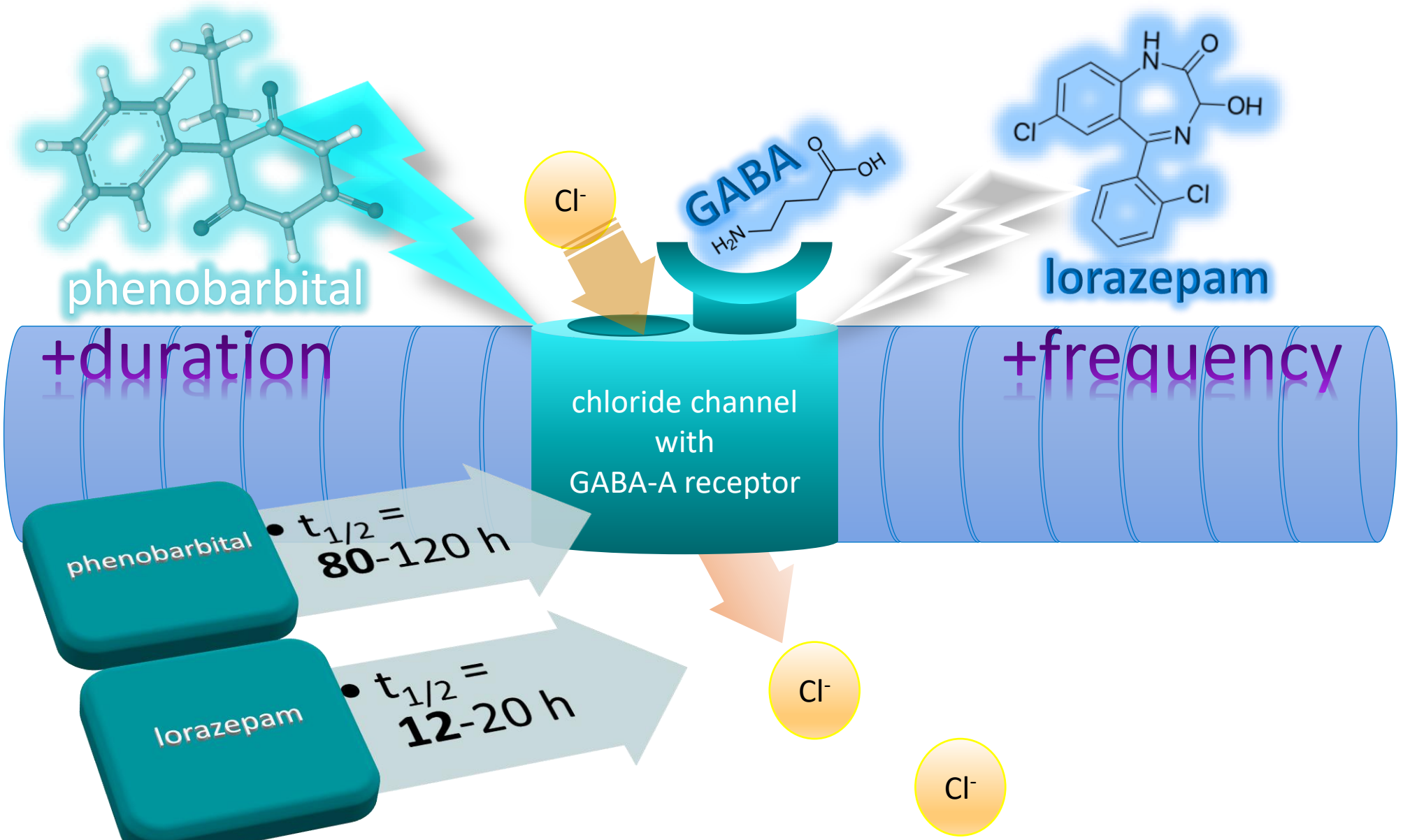
psychomotor agitation



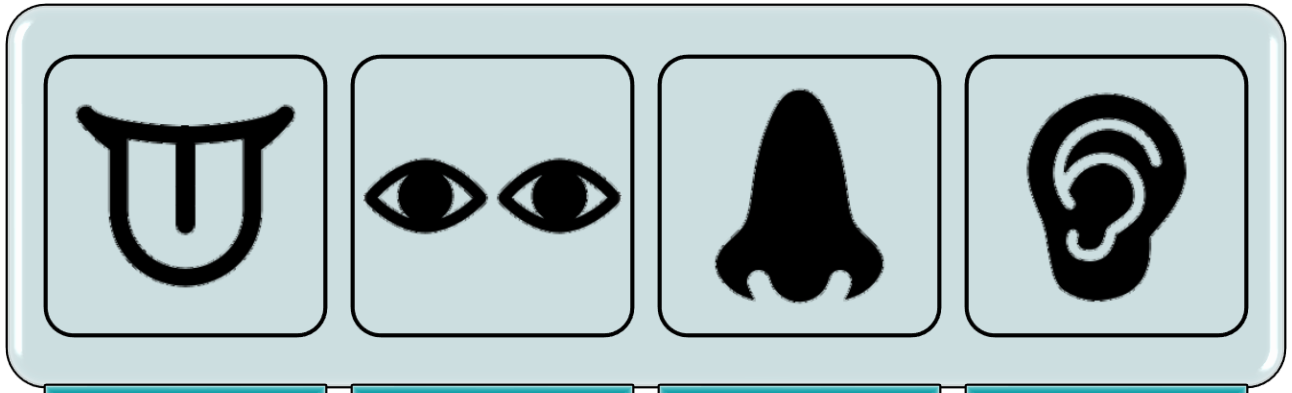
anxiety

generalized tonic-clonic seizures


GABA
O
H_2N
OH
EXCITATORY
SEDATING
O
H
O
O
O
$\oplus NH_3$
NMDA


phenobarbital
Cl-
GABA
OH
H2N
lorazepam
+duration
+frequency
chloride channel
with
GABA-A receptor
phenobarbital
• t1/2 =
80-120 h
lorazepam
• t1/2 =
12-20 h
Cl-
Cl-

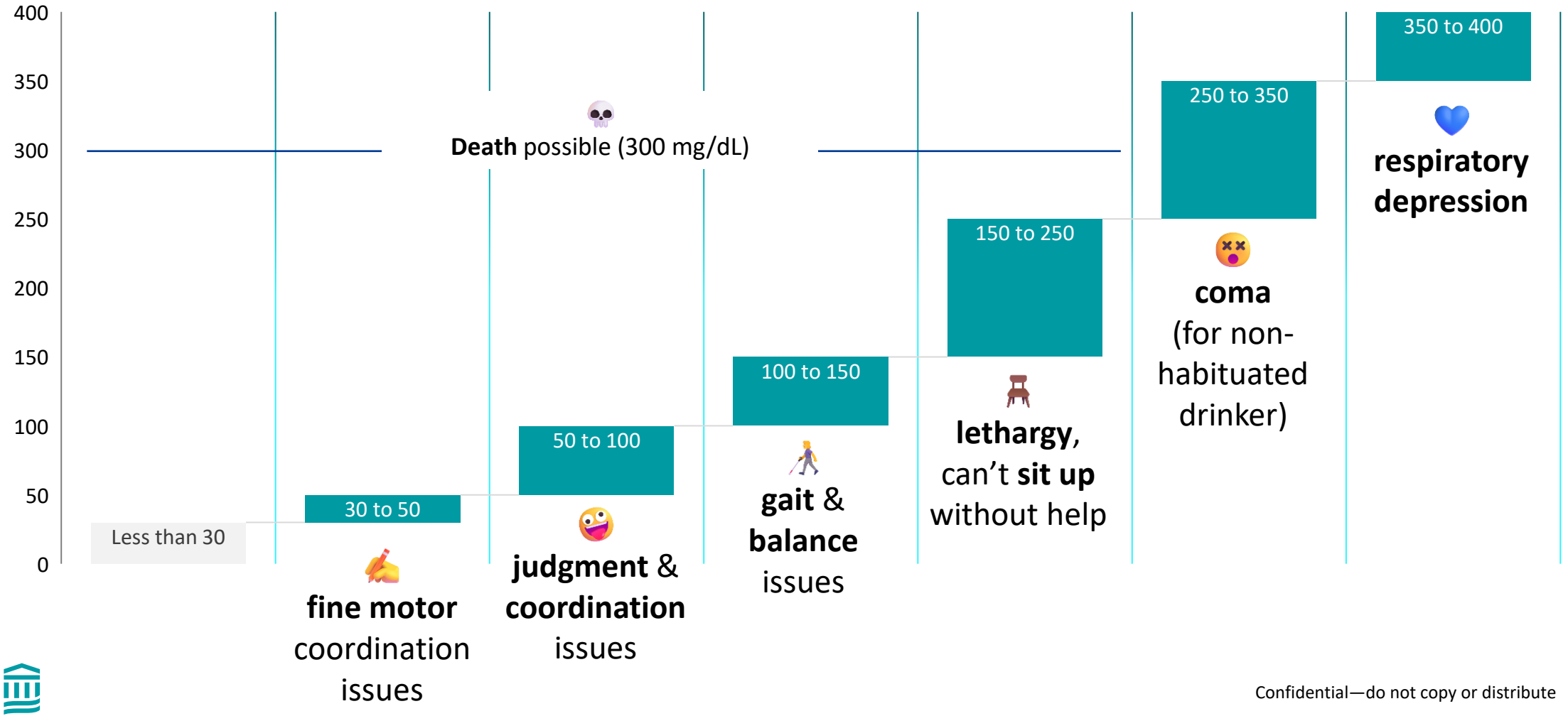
Caine Criteria



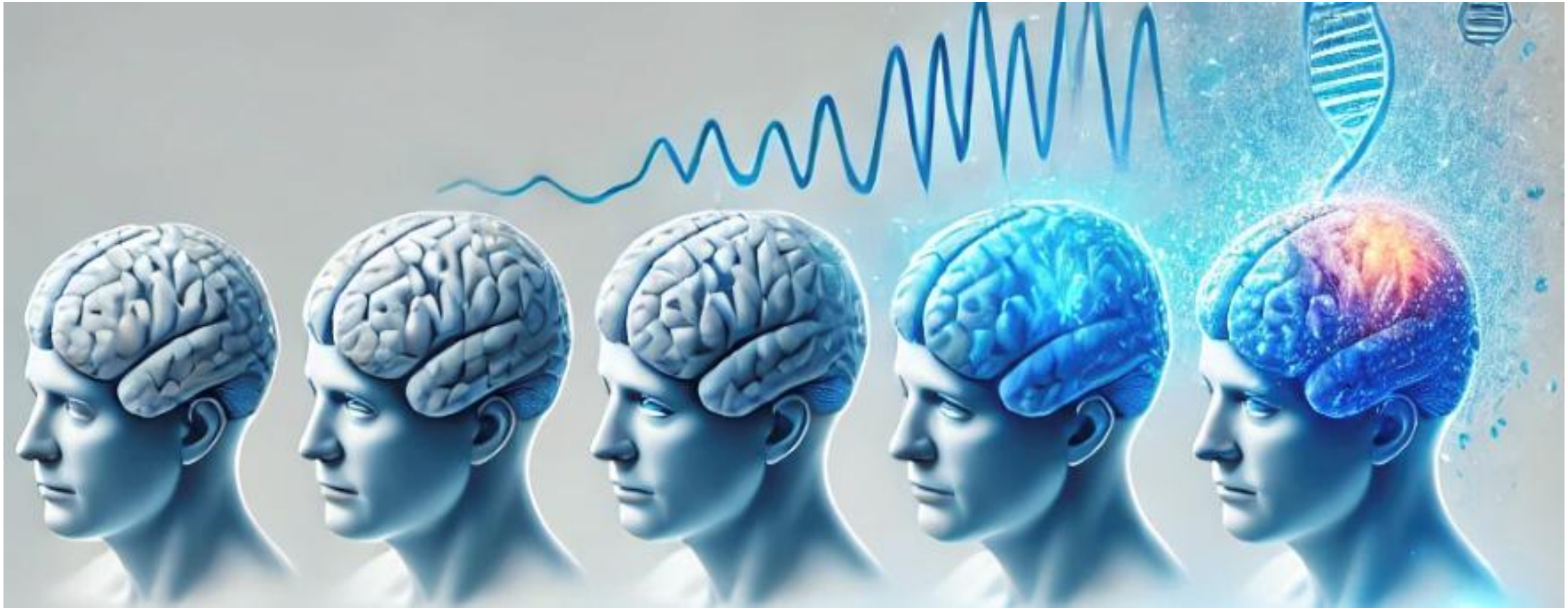
dietary deficiencies	eye signs	cerebellar dysfunction	either an altered mental state or mild memory impairment

2+ → Caine-Positive

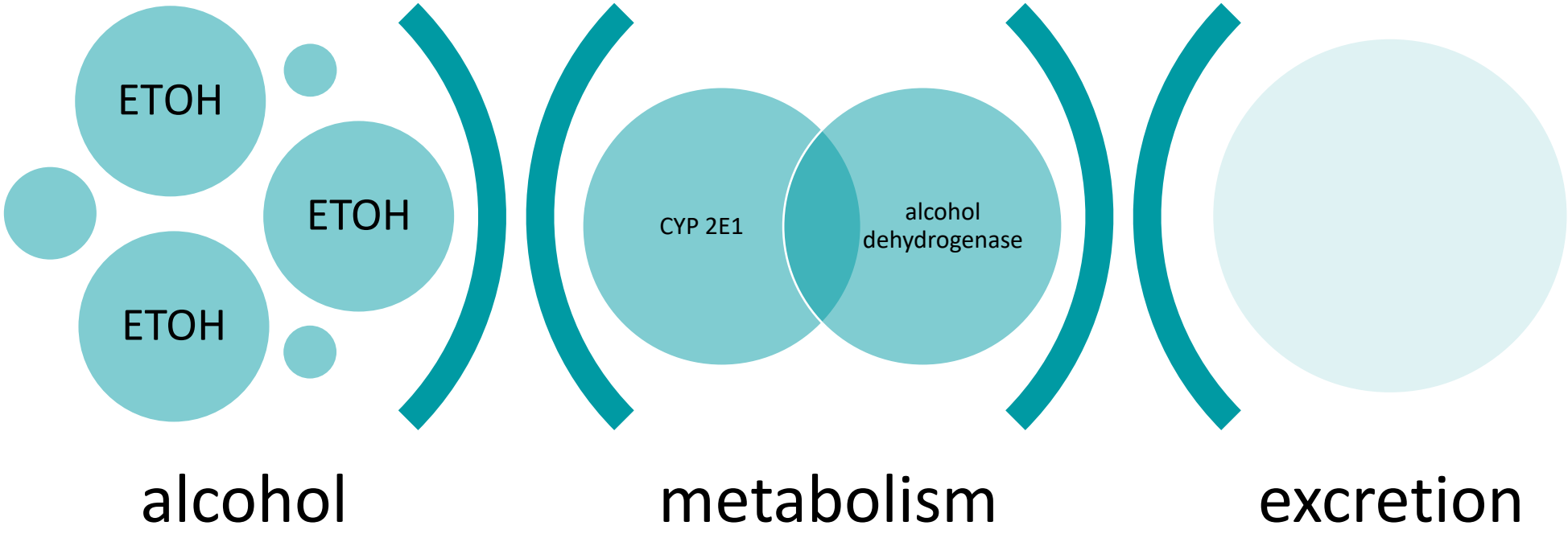
Effects of intoxication
A dose-response curve for alcohol



Kindling (sensitization): if at first you don't withdraw… what doesn't kill you may make you more vulnerable



Alcohol is generally metabolized at a fixed rate: ~ 20 mg/dL per hour (range 8-32)



https://pubmed.ncbi.nlm.nih.gov/1940231/
https://pubmed.ncbi.nlm.nih.gov/16912820/
https://pubmed.ncbi.nlm.nih.gov/23101976/

Box 1: Potential utility of combined biomarker testing in alcohol withdrawal risk

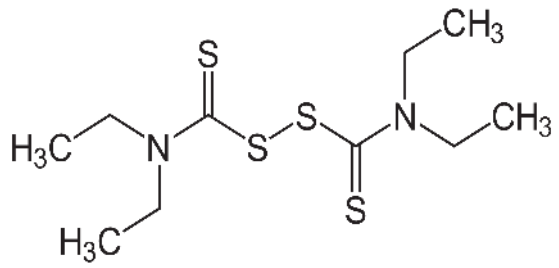
Combining phosphatidylethanol (PEth) and ethylglucuronide (EtG) testing for an individual patient could helpfully inform the management of patients in general hospitals with alcohol withdrawal syndromes. Elevated PEth and EtG values confirm recent alcohol consumption, while negative PEth and EtG values suggest very little or potentially no alcohol use in the past several weeks, a finding which could be particularly helpful in determining the need to monitor for and treat alcohol withdrawal syndromes where self-reporting is either unreliable or unavailable. Negative PEth and EtG values might remove the risk for alcohol withdrawal syndromes, although further study is needed to demonstrate this in clinical populations.

	Positive PEth	Negative PEth
Positive EtG	At risk for AWS, further risk stratification needed to provide appropriate monitoring and treatment.	Possible recent alcohol use or exposure with previous low/no alcohol use.
Negative EtG	Possible recent 3-5 day period of alcohol abstinence with previous alcohol use.	Likely low risk for AWS, might not require symptom monitoring or treatment.

"I got sober. I stopped killing myself with alcohol. I began to think: 'Wait a minute, if I can stop doing this, what are the possibilities?

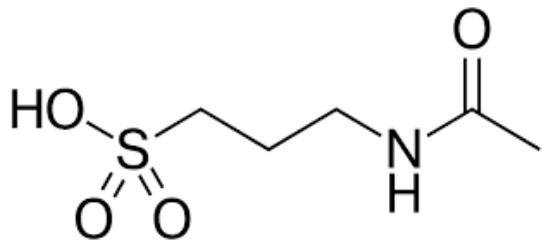
- Craig Ferguson

FDA-approved medications for the treatment of alcohol use disorder (mAUD)



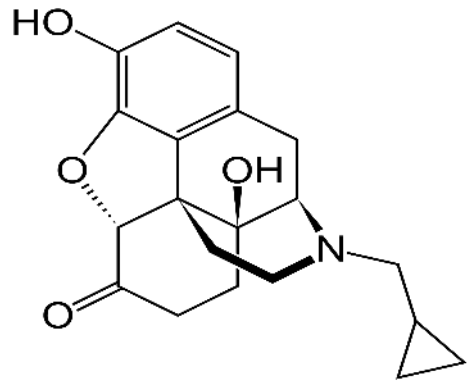
Disulfiram
[Antabuse]

1951



Acamprosate
[Campral]

2004



Naltrexone
[Revia/Vivitrol]

1994/2006

What is the goal of the treatment?

*To Drink **Less**?*

Naltrexone

[Gabapentin?]

[Semaglutide?]

*To Drink **Nothing**?*

Acamprosate

Disulfiram

[GLP-1s?]

Hospital admissions for alcohol withdrawal increased 1.8x early in the COVID-19 pandemic

JAMA Network | Open

Research Letter | Substance Use and Addiction

Alcohol Withdrawal Rates in Hospitalized Patients During the COVID-19 Pandemic

Ram A. Sharma, MD; Keshab Subedi, MS, MSc; Bayo M. Gbadebo, MBA; Beverly Wilson, MS; Claudine Jurkovitz, MD, MPH; Terry Horton, MD

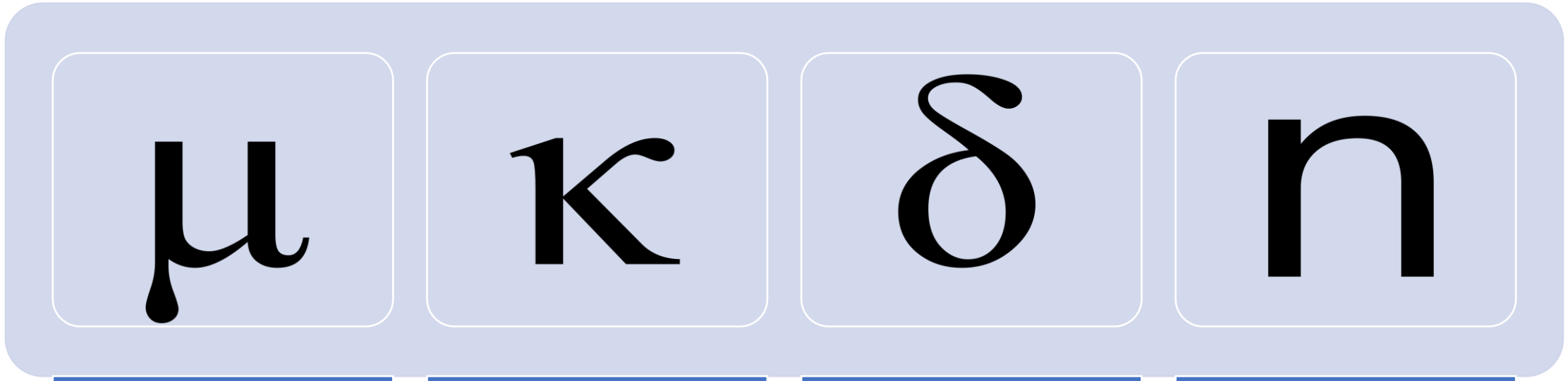
Introduction

Coronavirus disease 2019 (COVID-19) is disrupting communities across the globe, causing physical, mental, and financial distress.[1] Economic crises have been associated with increased alcohol consumption.[2] Necessary public health measures may exacerbate isolation and stress, negatively impacting those who are at risk for harmful alcohol use. Increased alcohol use has been documented in the US and other countries during the pandemic, and a recent study[3] has identified associated consequences. Alcohol withdrawal (AW) is a potentially dangerous complication of alcohol use disorder (AUD) in up to 8% of all hospitalized patients with AUD.[4] AW has been suspected to worsen after the COVID-19 stay-at-home orders,[5] but, to our knowledge, no objective data have been reported in the literature. We hypothesized that AW rates in hospitalized patients with AUD increased during the pandemic and conducted a cohort study at Christiana Care, a large, tertiary care hospital system in Newark, Delaware.

Author affiliations and article information are listed at the end of this article.

Learning Objective #2

Diagnose opioid use disorder and implement guideline-based **opioid agonist therapy**, and harm reduction strategies.



Mu opioid receptor

- Endorphins
- Enkephalins

Kappa opioid receptor

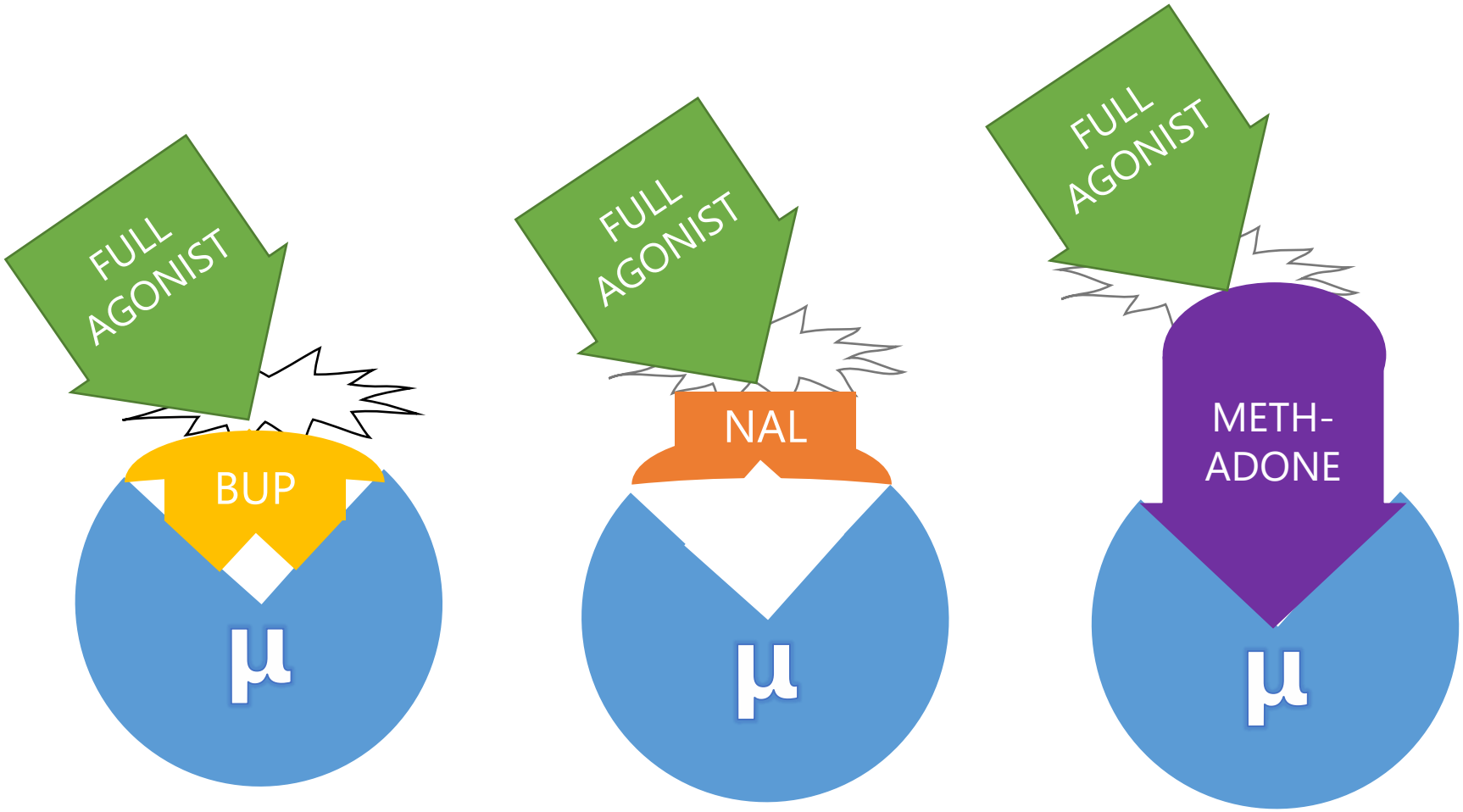
- Dynorphin

Delta opioid receptor

- Enkephalins

Nociceptin receptor

- Nociceptin



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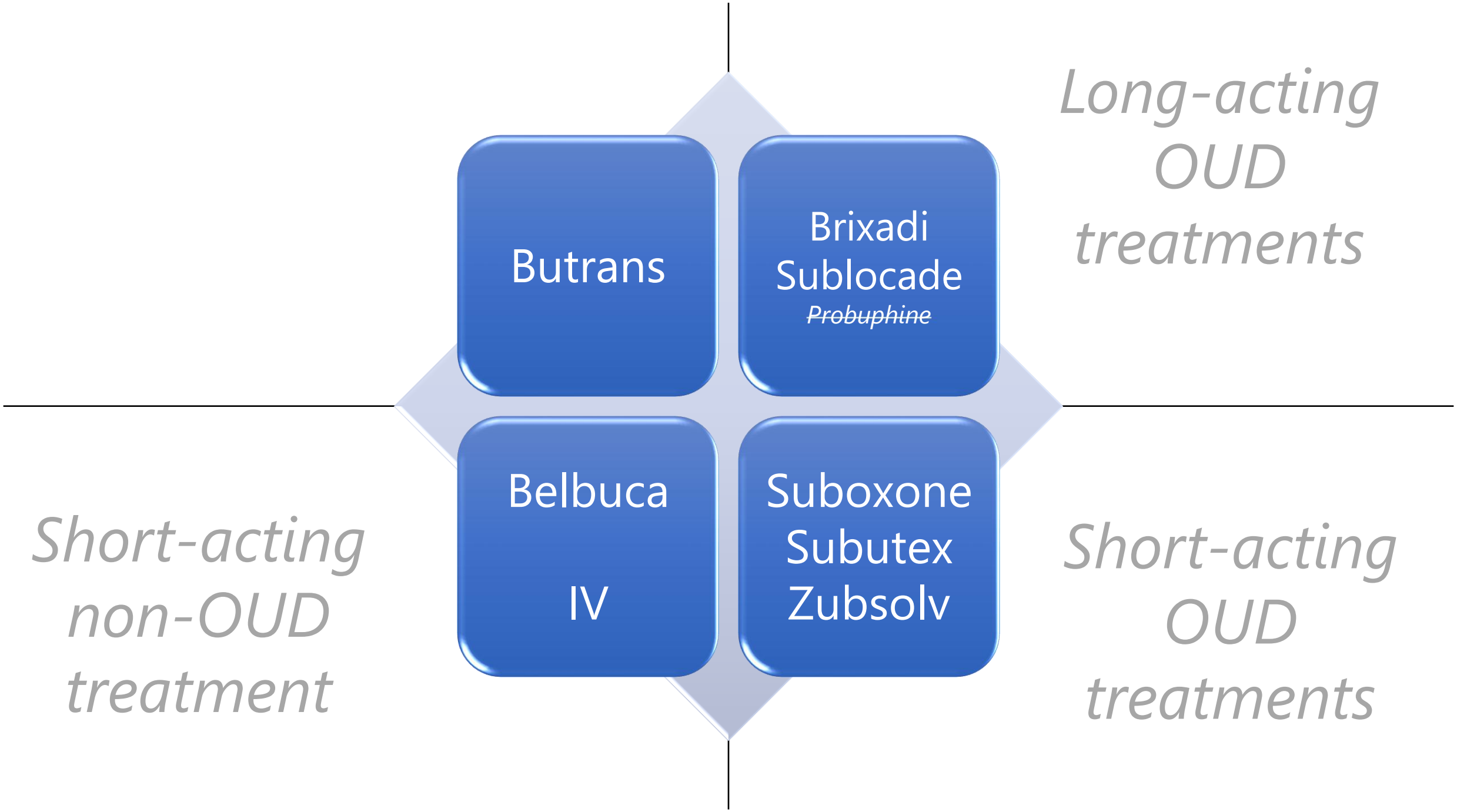

Butrans
Brixadi
Sublocade
~~Probuphine~~
Belbuca
IV
Suboxone
Subutex
Zubsolv
Long-acting OUD treatments
Short-acting non-OUD treatment
Short-acting OUD treatments

Buprenorphine plasma concentrations (ng/mL) & buprenorphine formulations

Buprenorphine

1.1 (8mg)

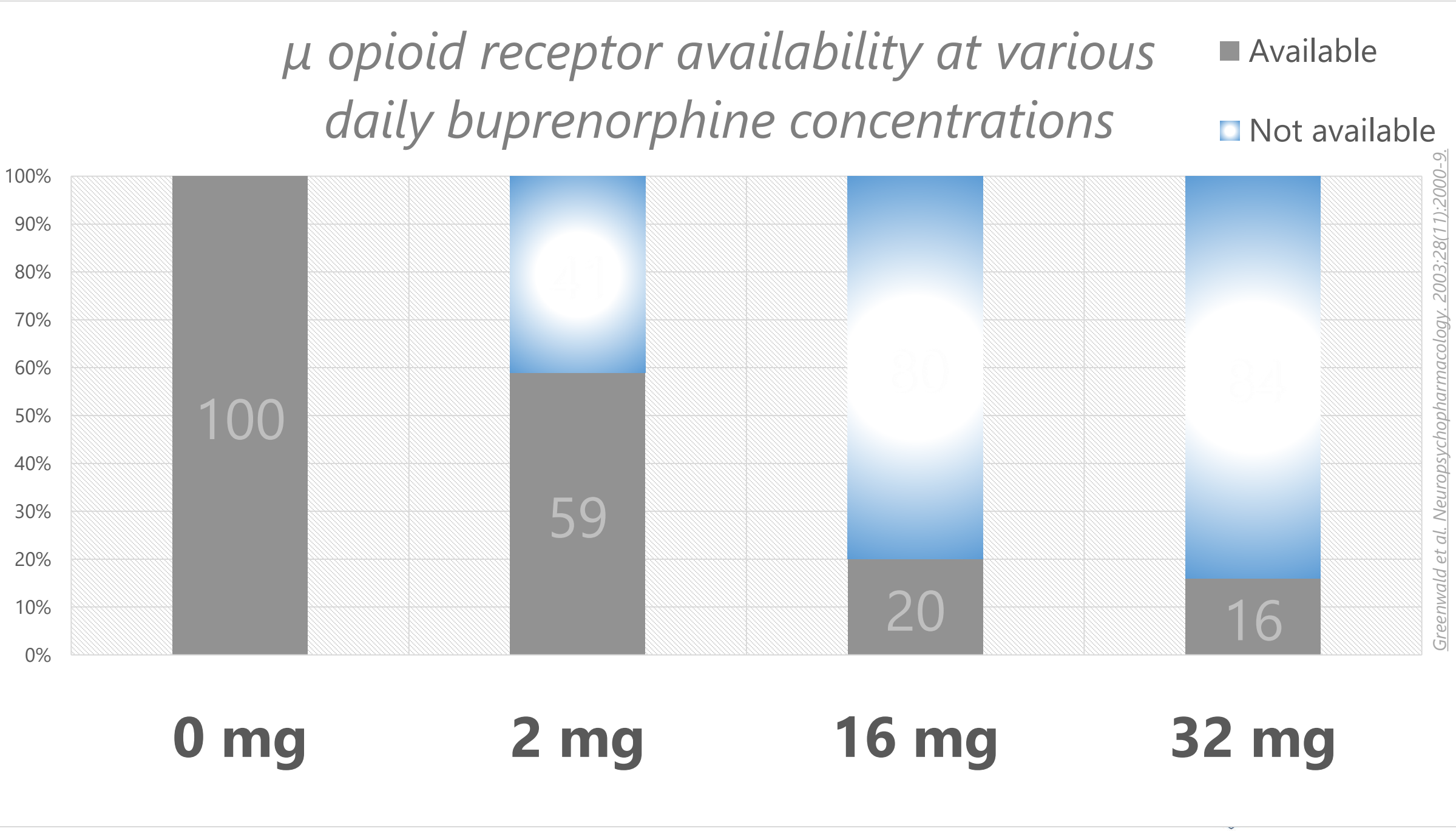
1.6 (16mg)

2.3 (24mg)

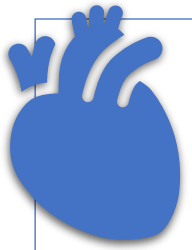
Sublocade

3.21 ± 0.82 (100mg)

6.54 ± 3.21 (300mg)


μ opioid receptor availability at various daily buprenorphine concentrations
Available
Not available
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
100
59
41
20
80
16
84
0 mg
2 mg
16 mg
32 mg
Greenwald et al. Neuropsychopharmacology. 2003;28(11):2000-9.

Symptomatic regimen



Hypertension/anxiety

- **Clonidine** 0.1mg PO TID
  - Hold if using methadone
  - Hold if hypotensive

Diarrhea

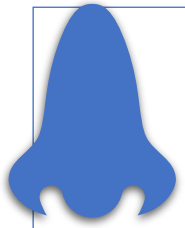
- **Loperamide** 4mg PO with first loose stool
- Then 2mg per loose stool
- Max 24 mg per day

Pain

- **Ibuprofen** 600mg *or*
- Acetaminophen 650 mg PO q4-6h

Abdominal cramping

- **Dicyclomine** 20mg po q4h



Nasal congestion

- **Diphenhydramine** 50mg PO q4h

Muscle cramps

- **Methocarbamol** 750mg PO q6h

Insomnia

- **Trazodone** 50-100mg PO qHS

Methadone dose

Typical good tx dose 80-120mg

5-10mg/day

Initial taper dose 30mg

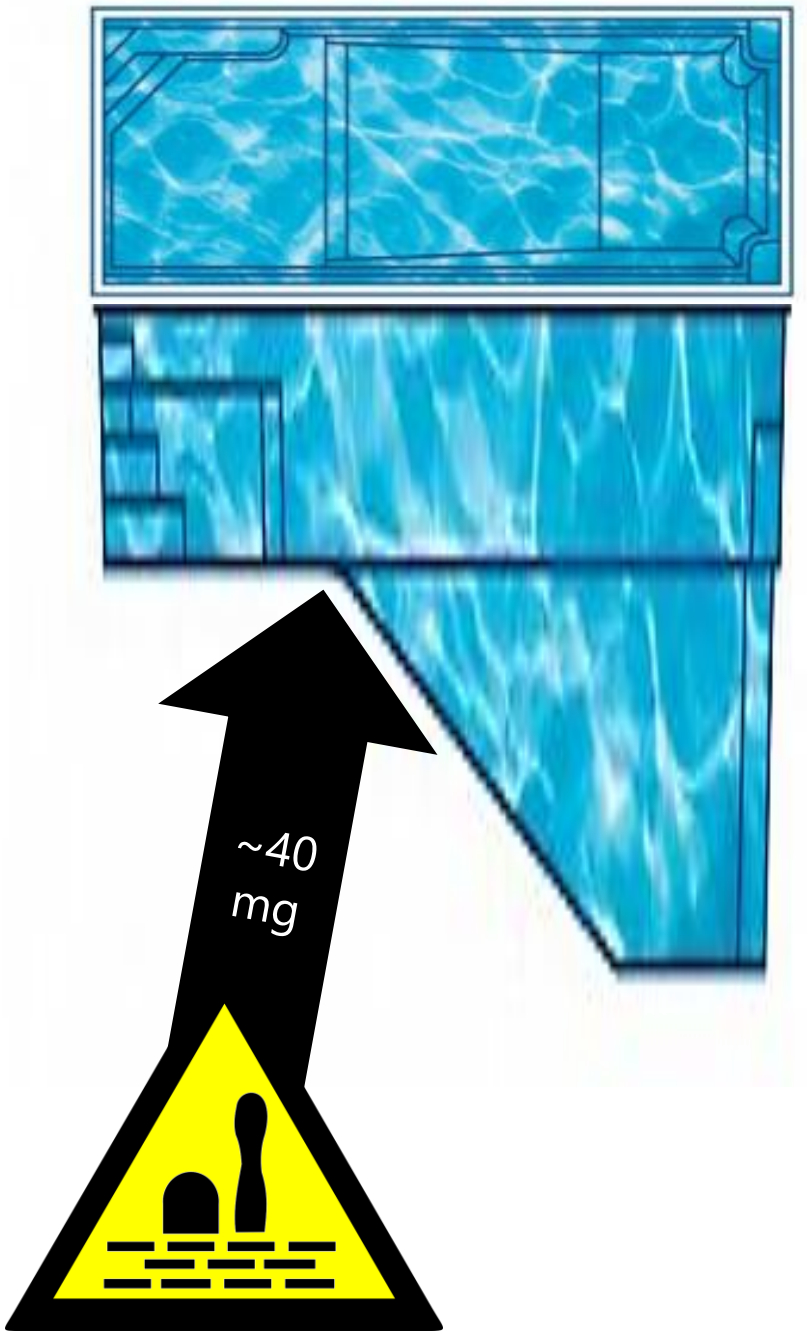
5-10mg/day

0mg

Beware of the deep end:
Methadone dosing is NON-LINEAR

:

Beyond 40mg, limit methadone dose increases to 10 mg per 5 days



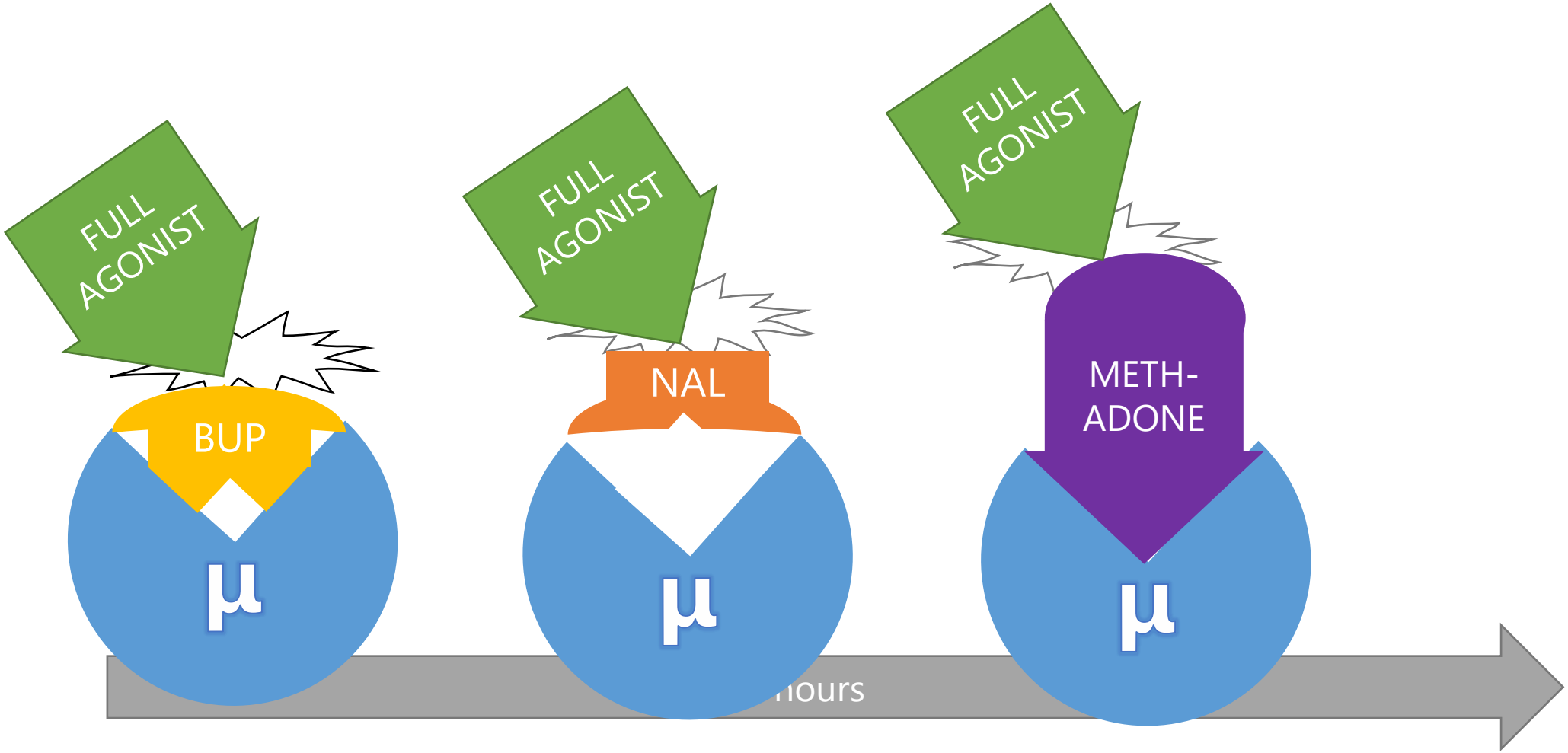


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Figure 1. Recommendations for the Perioperative Management of Home Buprenorphine-Naloxone

For all patients, continue buprenorphine-naloxone throughout the perioperative period, following these steps:

Step 1: Determine total 24-hour **home dose of buprenorphine** (regardless of any naloxone component)

- *If home dose is* **≤ 8 mg per day**: **Continue home dose**[1] throughout perioperative period[5] (do *not* discontinue prior to surgery); no need to proceed further in the algorithm.
- *If home dose is* **> 8 mg per day** (excludes obstetric patients[3]): *Proceed to Step 2.*

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Figure 1. Recommendations for the Perioperative Management of Home Buprenorphine-Naloxone

For all patients, continue buprenorphine-naloxone throughout the perioperative period, following these steps:

Step 2: Determine **anticipated opioid requirements/pain after surgery**[4]

Anticipated post-operative opioid requirements	*Before surgery*	*On day of surgery and throughout hospital stay*	*Preparing for discharge*[5]
LOW OPIOID REQUIREMENTS[4]	**Continue home regimen**[1] (do not discontinue prior to surgery and continue home dose throughout the perioperative period)[5]		

4. Low opioid requirements: i.e., low / mild post-operative pain or procedures where historically less than five-day courses of low-dose oxycodone or hydrocodone are prescribed.

Step 2: Determine anticipated opioid requirements/pain after surgery[4]

Anticipated post-operative opioid requirements	*Before surgery*	*On day of surgery and throughout hospital stay*	*Preparing for discharge[5]*
MODERATE TO HIGH OPIOID REQUIREMENTS	***IF HOME DOSE > 16 MG*** • **Consider titrating dose down**[1-2, 5] so that **on the day before surgery**, total buprenorphine dose is 16 mg daily (e.g., on day prior to procedure preferably drop to 8 mg BID vs. 16 mg as a single dose) • **May consider continuing home dose** if reliable continuous regional anesthesia techniques are available or based on patient and clinician preference	• Consider decreasing to **buprenorphine 8 mg per day *on day of surgery*** (preferably 4 mg BID vs. 8 mg daily) • **Anticipate need for higher opioid agonist dose requirement**, similar to opioid tolerant patients maintained on methadone • **Use additional opioid agonists as needed**; *Refer to Step 3*	• Provide a **post-discharge taper plan** for full agonist opioids • Ideally, **increase back to buprenorphine home dose** at time of discharge • Transition care back to **patient's outpatient buprenorphine prescriber** for ongoing care with plan to increase back to original home buprenorphine dose[5]
	IF HOME DOSE ≤ 16 MG **Consider continuing home dose** if reliable continuous regional anesthesia techniques are available and based on patient and clinician preference; *Refer to Step 3*		

Orders

Clear All Orders

Opioid Withdrawal Order Set

Manage User Versions

Starting medication treatment

The selection of medication to treat opioid withdrawal (e.g., methadone or buprenorphine) should be based on a shared decision-making process which integrates both the preferences and past experiences of patients and the clinical judgment of providers (see below).

Methadone	Buprenorphine
• Avoid in patients with *QT prolongation* • May be started immediately to treat opioid withdrawal, regardless of recent exposure to fentanyl or other opioids • Patients who receive a few doses of methadone to treat withdrawal *may still initiate buprenorphine later* in their hospitalization**	• May restart immediately if patient took their last dose of buprenorphine in the last 72 hours • Otherwise, wait for COWS score of 8 or higher before giving first dose** **Special circumstances which may necessitate low-dose buprenorphine initiation (microdosing) or consult to addiction / psychiatry (if available): • Transitioning from methadone to buprenorphine • Fentanyl exposure† in the last week • History of precipitated withdrawal • Severe pain requiring round-the-clock treatment with high-dose opioid medications

**Buprenorphine* here refers to both buprenorphine-naloxone and buprenorphine monoproduct

†Assume fentanyl exposure (unless proven otherwise by laboratory toxicology results) in any patient who has injected or insufflated non-prescription opioids within the last week

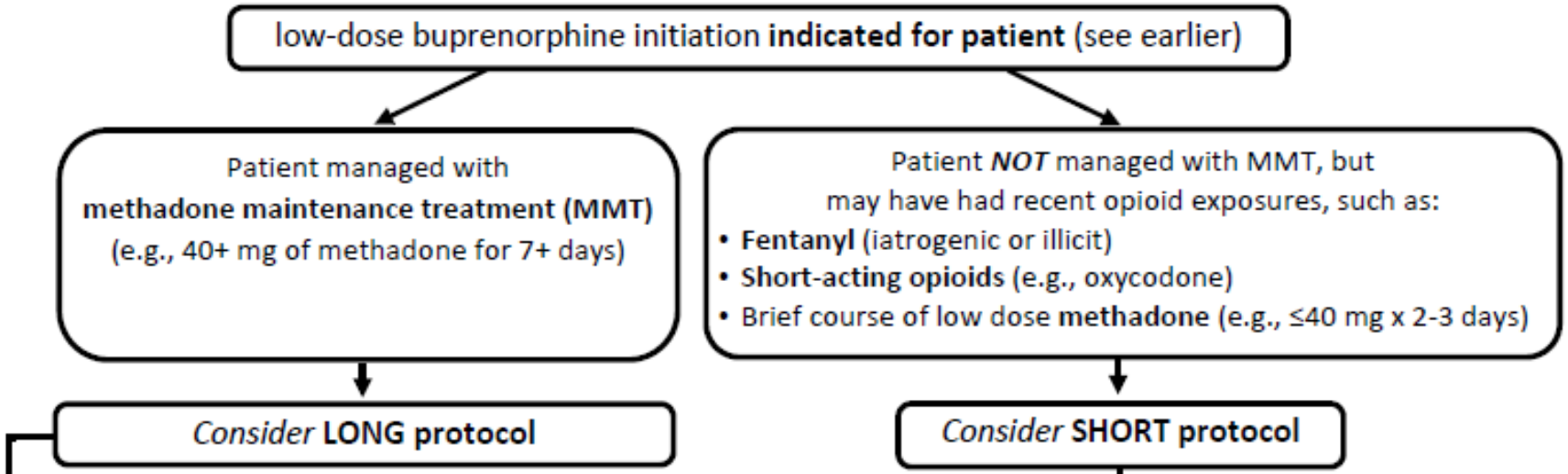
General

Notify Responding Clinician

☐ Notify responding clinician

Routine, Until discontinued

Low-Dose Buprenorphine Initiation ("Microdosing")

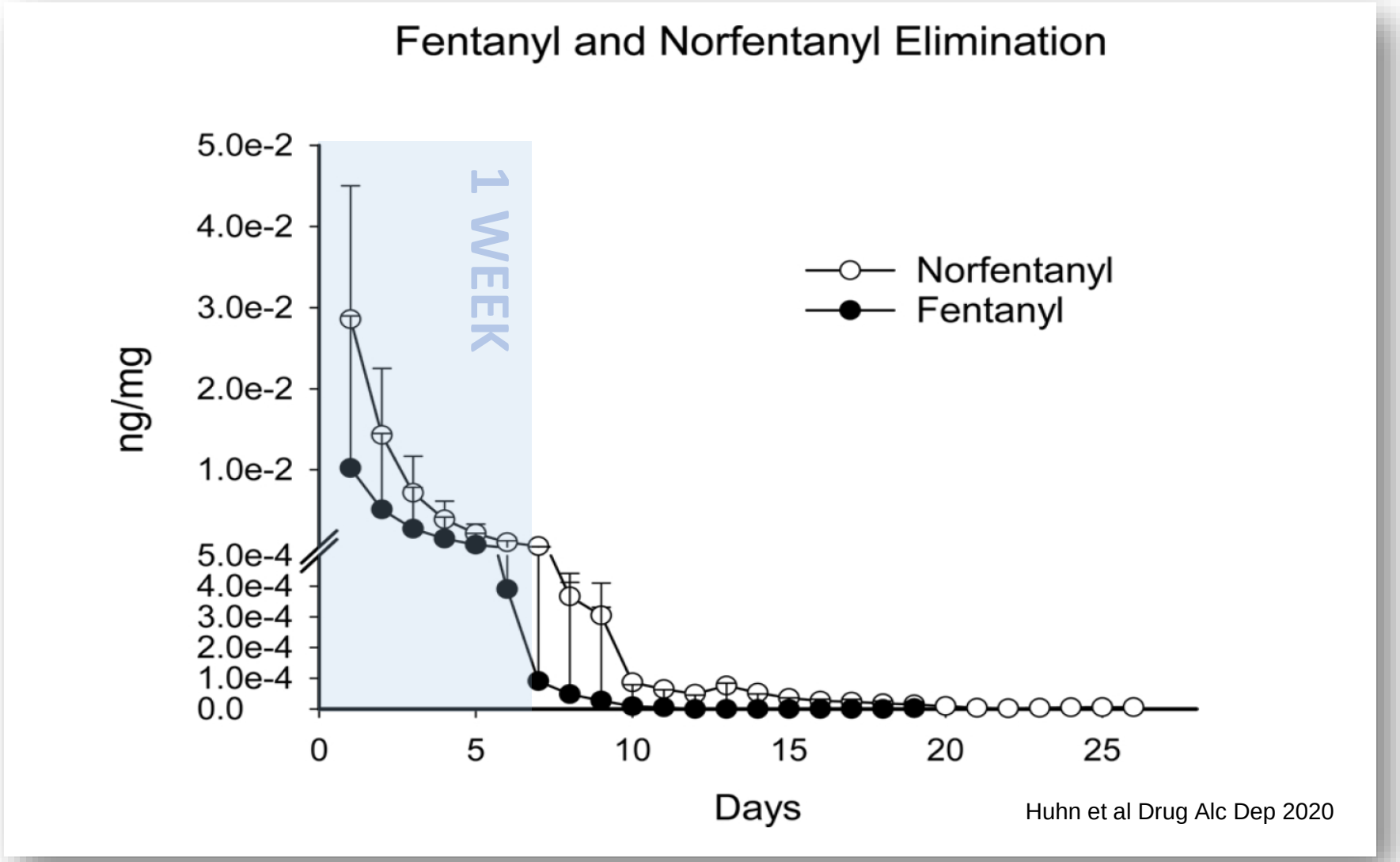


SHORT protocol for low-dose buprenorphine initiation

Day 1	Day 2	Day 3
• Consider starting taper of full-agonist opioids if patient's clinical condition allows (e.g., adequate pain control)* • Apply **buprenorphine patch** (20 mcg, or equivalent) at 8:00 AM (ideally)	• **Administer the first 2 mg dose** of a buprenorphine-containing product[8] around 10:00 AM** • As tolerated / if requested by patient, consider administering **additional doses** of buprenorphine in 2 - 4 mg increments every 2 to 4 hours,** up to a maximum total dose of 8 mg of buprenorphine on day 2† • **Remove buprenorphine patch** at 8:00 pm (approximately 36 hours after administration)	• Administer the AM dose of a buprenorphine-containing product equal to the cumulative dose administered on Day 2** • As tolerated / if requested by patient, consider administering additional doses of buprenorphine in 2-4 mg increments every 2 to 4 hours,** up to a maximum total dose of 12 mg of buprenorphine on day 3†

LONG protocol for low-dose buprenorphine initiation

Day 1	Day 2	Days 3 - 7	Day 8
•Continue methadone	• **Administer the first 2 mg dose**	•Continue methadone or	•Stop methadone



Huhn et al Drug Alc Dep 2020

Delayed clearance of fentanyl and norfentanyl

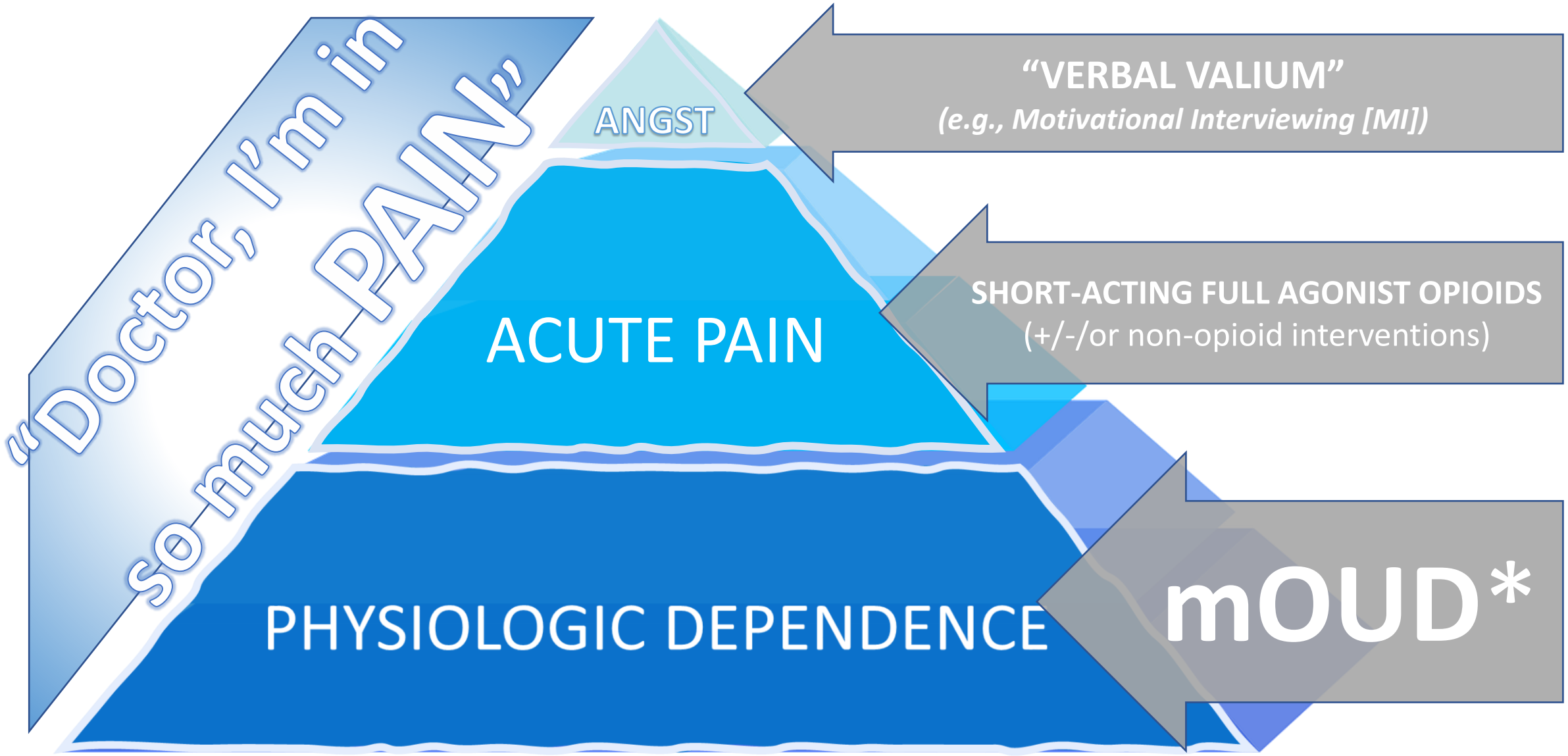
Slide credit: J. Suzuki

Table 2. μ-Opioid Receptor Binding Affinities (Ki) for Commonly Used Opioids and Antagonists

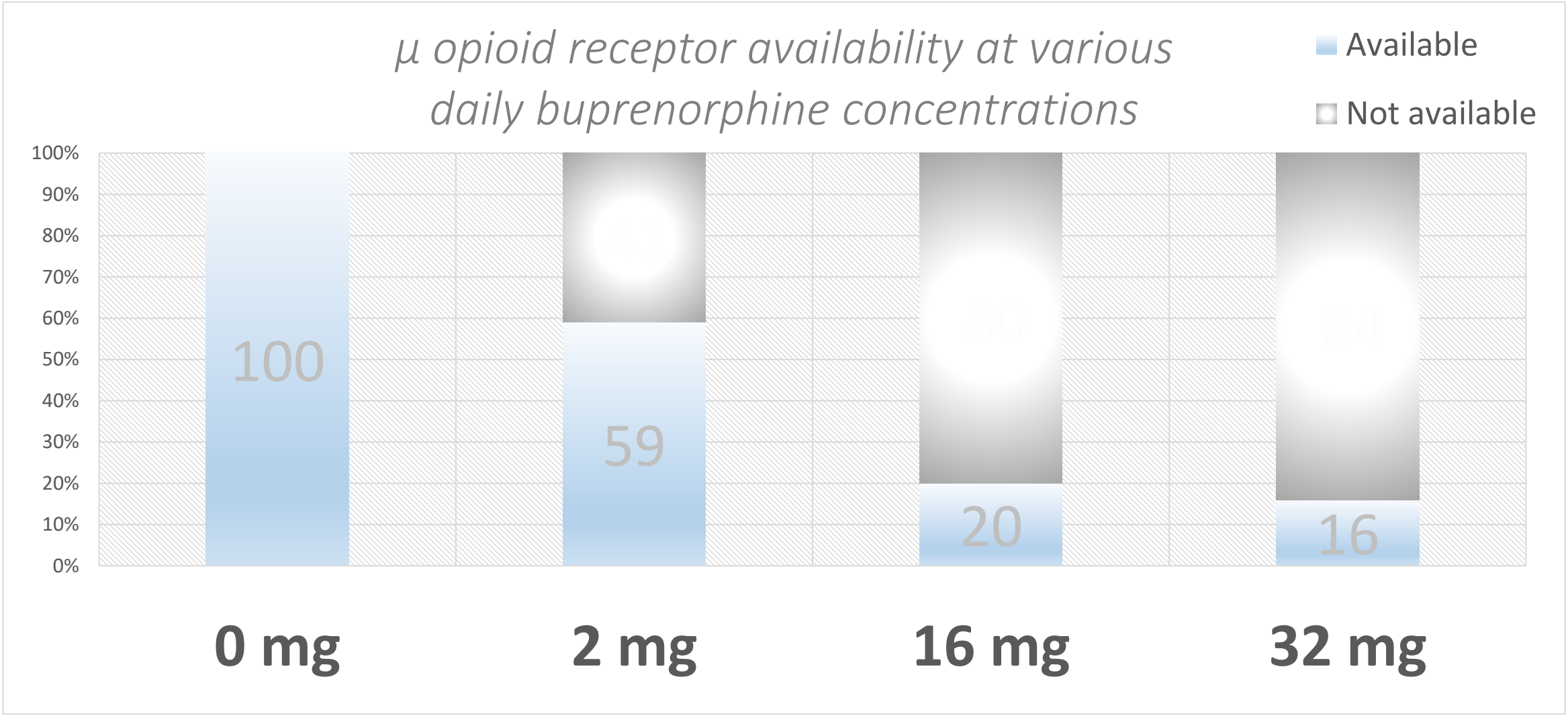
Opioid	Ki (nM)
Sufentanil	0.1380[3]
Buprenorphine	**0.2157**[3]
Hydromorphone	0.3654[3]
Morphine	1.168[3]
Fentanyl	1.346[3]
Naloxone	1.518[3]
Methadone	3.378[3]
Remifentanil	21.1[4]
Oxycodone	25.87[3]
Hydrocodone	41.58[3]
Codeine	734.2[3]
Tramadol	12,486[3]

Buprenorphine has extremely **high affinity** relative to other opioids

(Leighton et al 2017)



*mOUD = medication to treat opioid use disorder; e.g., methadone or buprenorphine-naloxone



Greenwald et al. Neuropsychopharmacology. 2003;28(11):2000-9.

What precipitated withdrawal feels like

When mu receptor activation drops precipitously (e.g., when you administer naloxone to a patient high on fentanyl)

Perhaps free-falling through an elevator shaft is a better analogy…

NEWS

Man Falls Down Empty Elevator Shaft In SoHo, Survives Urban Nightmare

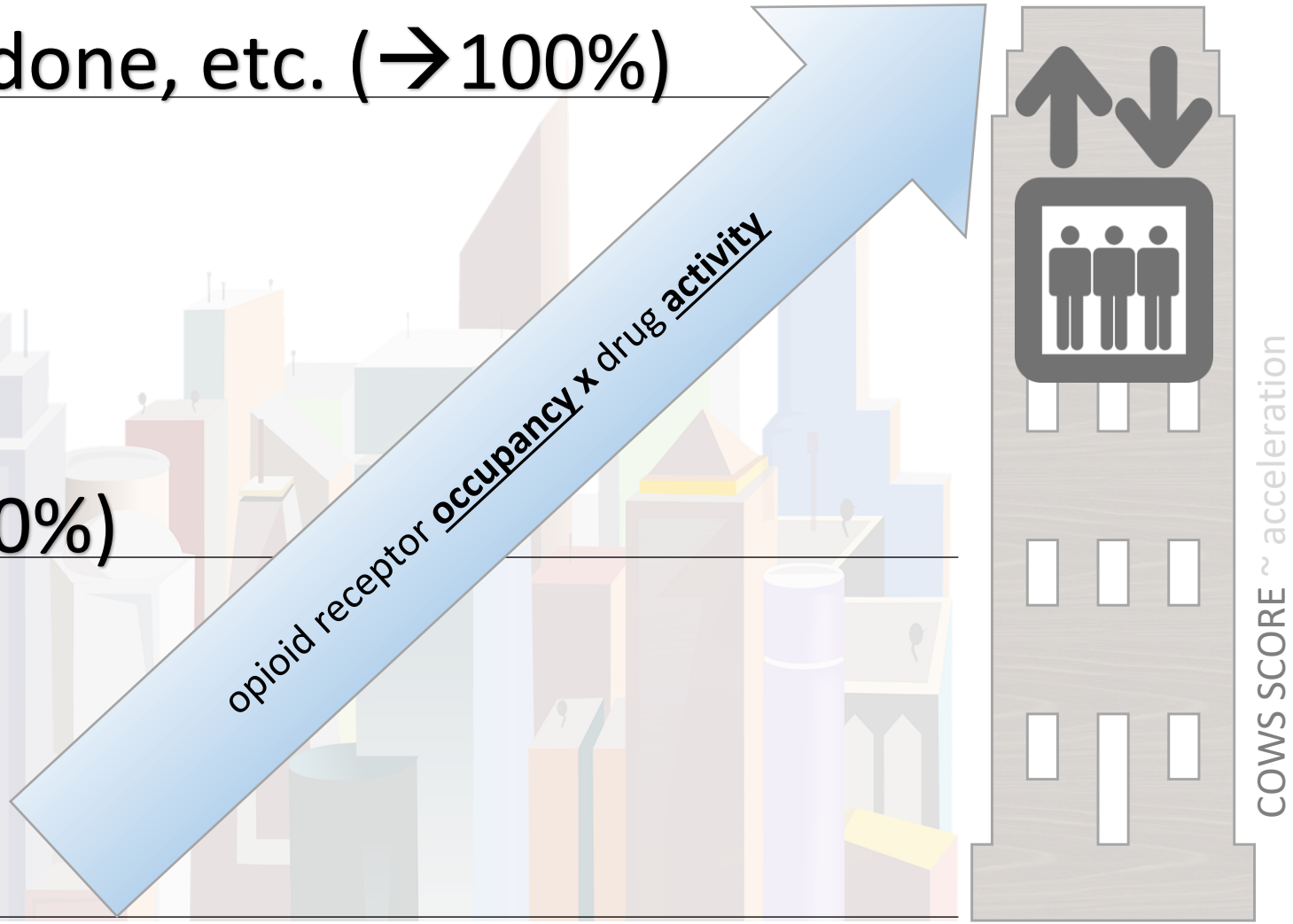
BY CLAIRE LAMPEN

FEB. 26, 2019 5:23 P.M. • 40 COMMENTS

Methadone, Oxycodone, etc. (→100%)

Buprenorphine (~40%)

Naloxone (~0%)



Opioid Withdrawal Order Set

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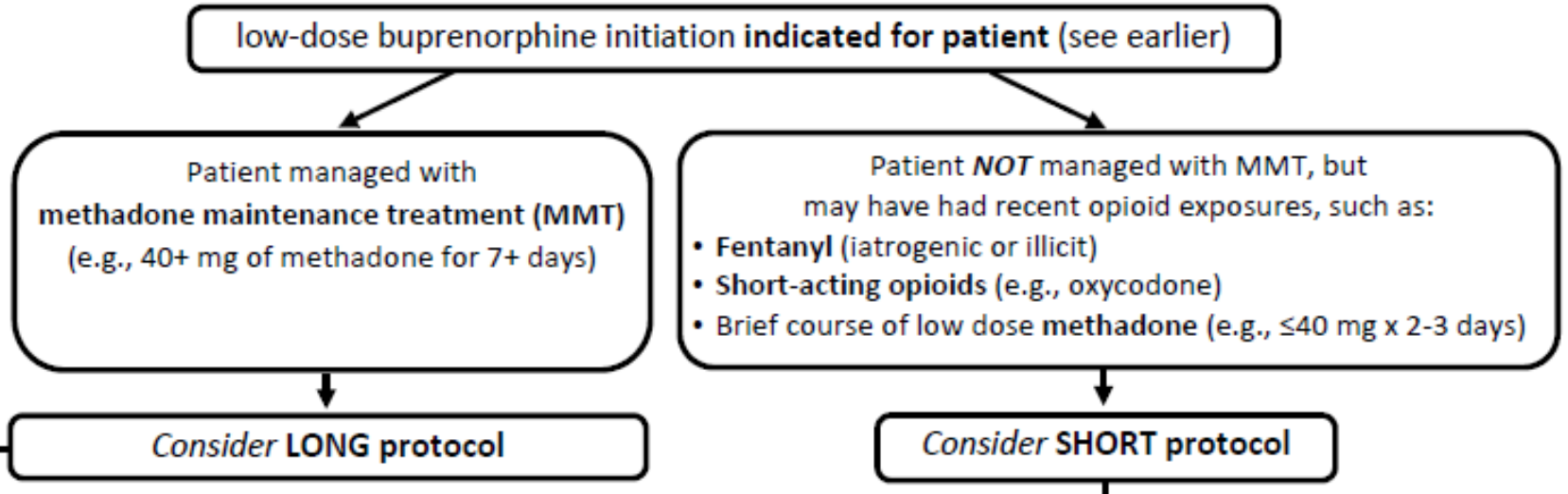
Low-Dose Buprenorphine Initiation ("Microdosing")



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Conclusion: SUD is treatable in medical settings

- Hospitalization is a clinical opportunity to identify and initiate treatment for alcohol and opioid use disorders.
- FDA-approved medications for alcohol use disorder (naltrexone, acamprosate, disulfiram) support recovery.
- Opioid use disorder treatment includes opioid agonist therapy (methadone, buprenorphine) and harm reduction strategies.

References

Kast KA, Sidelnik SA, Nejad SH, Suzuki J. Management of alcohol withdrawal syndromes in general hospital settings. *BMJ*. 2025;388:e080461. Published 2025 Jan 8. doi:10.1136/bmj-2024-080461

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Winder GS, Clifton EG, Denysenko L, et al. "But I didn't drink!": What to do with discordant phosphatidylethanol results. *Liver Transpl*. 2024;30(2):213-222. doi:10.1097/LVT.0000000000000223


Mass General Brigham