Hope for Treating Methamphetamine Use Disorder

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Methamphetamine on the Front Lines

California Hospital Association

December 6, 2022

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Quiz

In September 2017 1 person died and 7 were hospitalized after exposure to methamphetamine in:

a. Marijuana
b. 7 Up
c. Burritos
d. Beer

Mexicali Valley,
120 miles east of San Diego
Pepsi Co plant
70,000 bottles removed
2017

What is Meth?

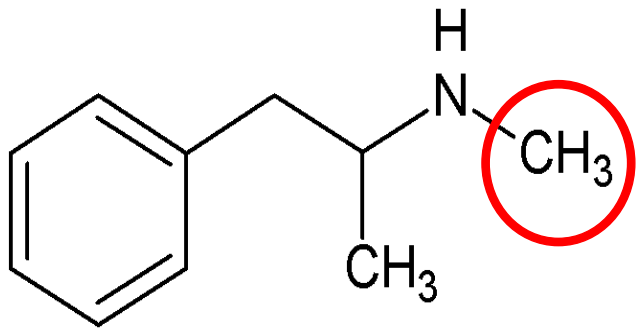
Central Nervous System Stimulant, Neurotoxin, Psychostimulant, Recreational drug

History

- 1887: Amphetamine – Germany
- 1893: Methamphetamine – Japan
- WWII: Pervitin – "tank chocolates" for pilots
- 1950-60s: Obetrol – diet pill
- 1970s: Scheduled II controlled drug
- Desoxyn – prescribed methamphetamine sold by Italian company

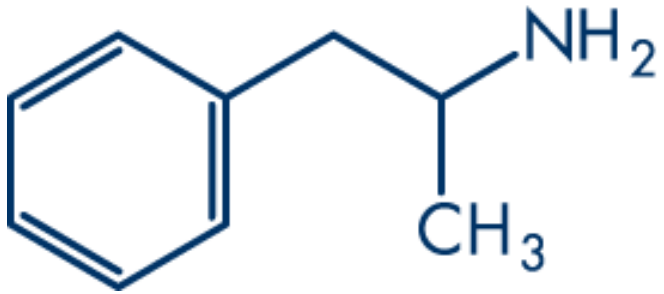
Chemistry

Methamphetamine

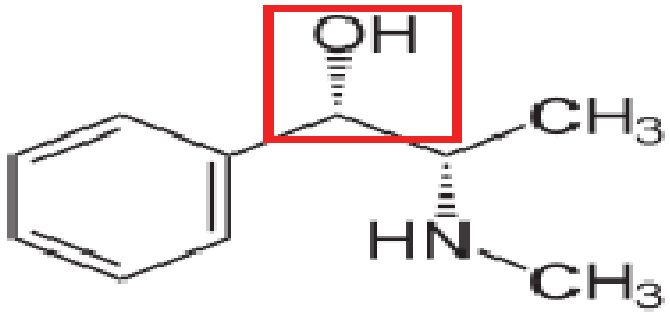


Methyl Group

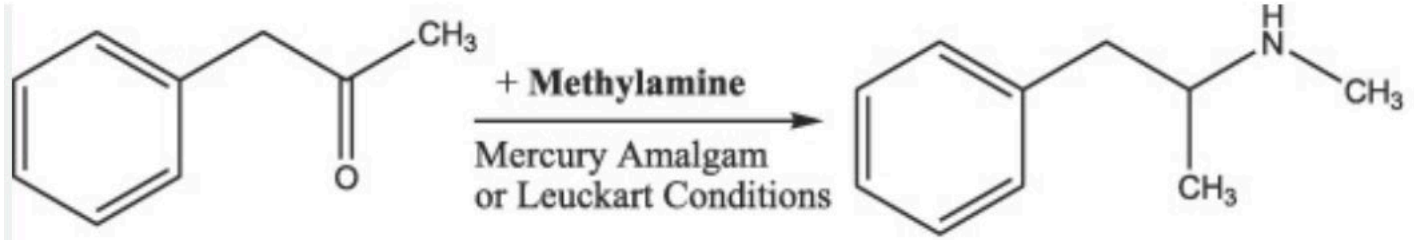
Amphetamine



Pseudoephedrine (Sudafed)



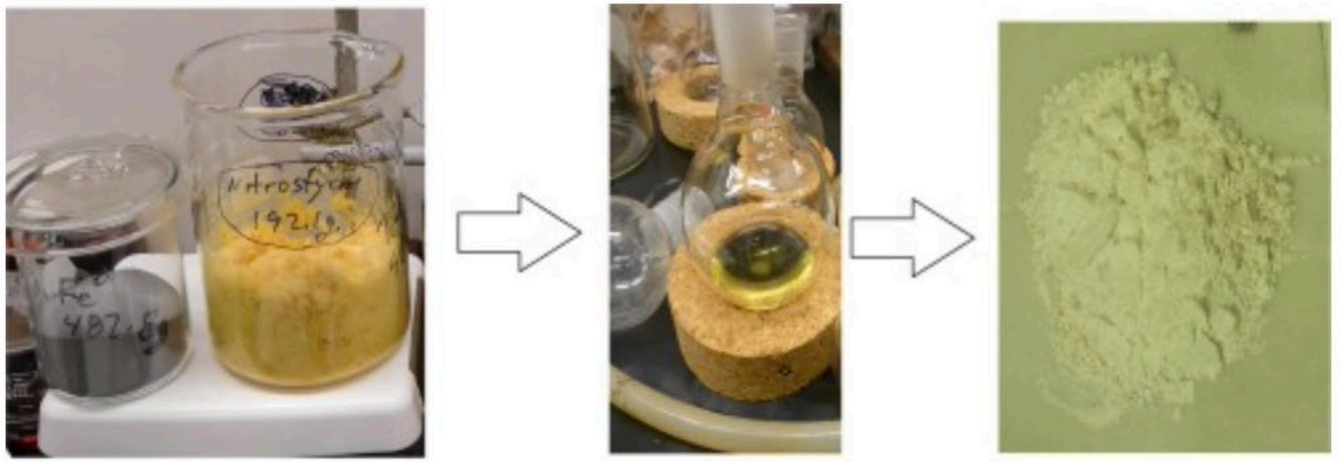
Illicit Production



P2P

Phenyl-2-Propanone

Methamphetamine



Nitrostyrene **P2P** **Methamphetamine HCl**

Medicinal vs. Illicit Meth

PRESCRIPTION

Desoxyn = Methamphetamine

Adderall, Dexedrine, Dexostat, Vyvanse = Amphetamine

2.5 – 10 mg per day

Max = 60 mg

ILLICIT

100 – 1000 mg

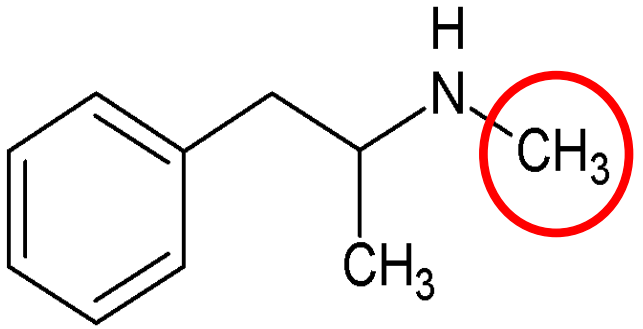
10 – 100 X

Illicit methamphetamine is 10 - 100 times stronger than prescription strength

Drug Testing

Methamphetamine

- Illicit
- Desoxyn

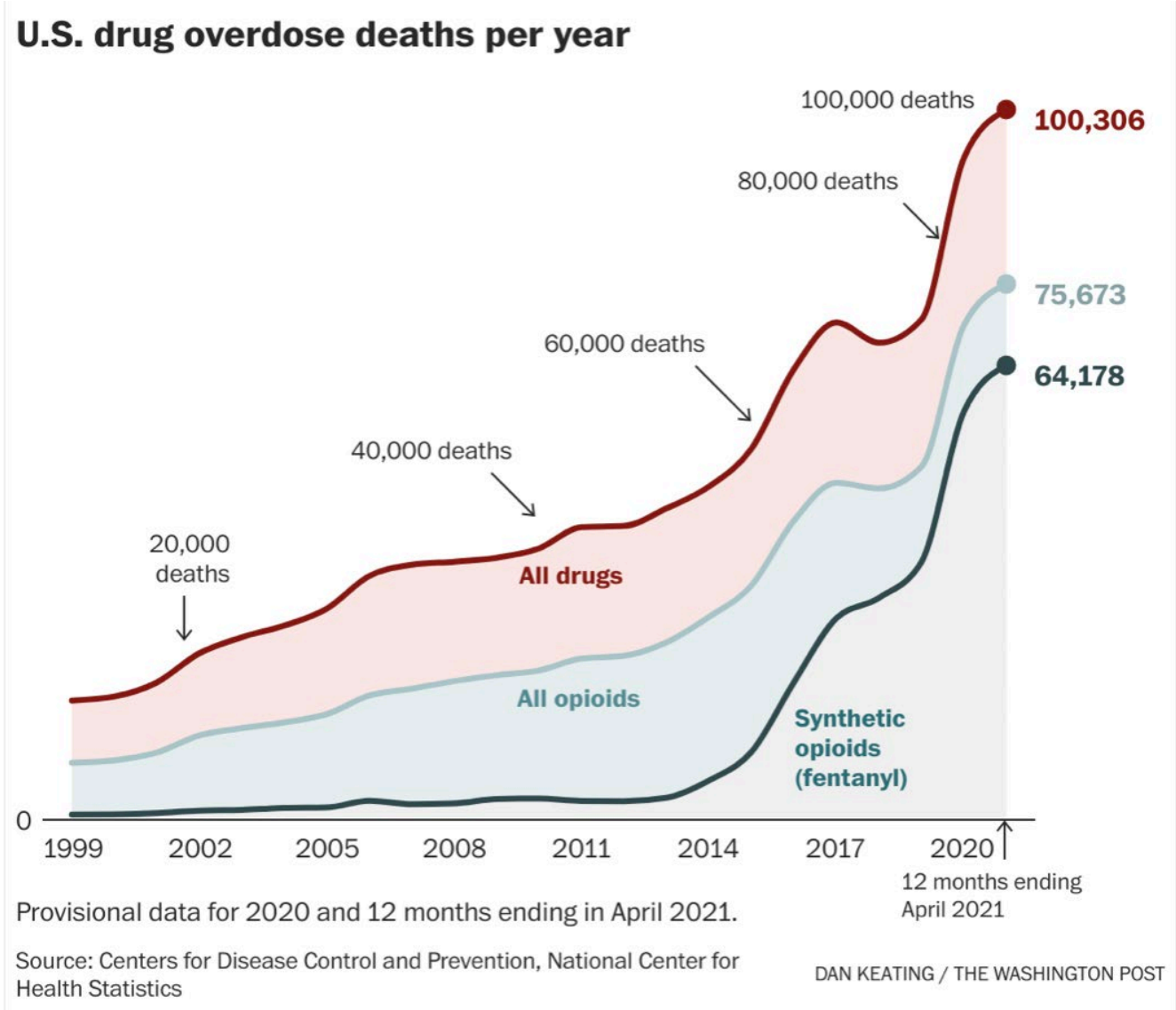


Methyl Group

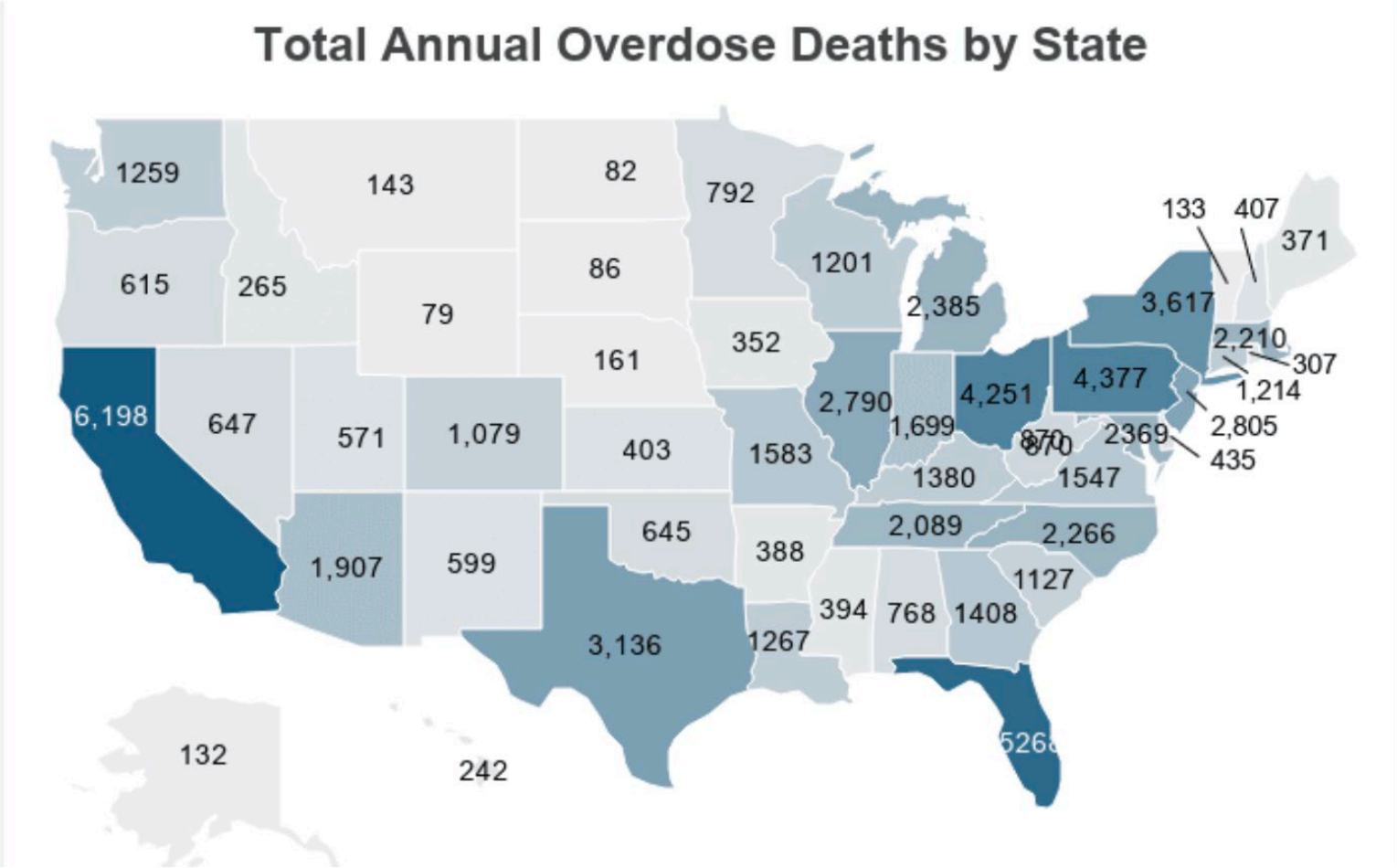
Amphetamine

- Metabolite of Methamphetamine
- Prescription stimulant
- Vicks inhaler – 50 mg of L-Meth
- D isomer is illicit

National Overdose Deaths



California is Leading the Nation in Drug Deaths

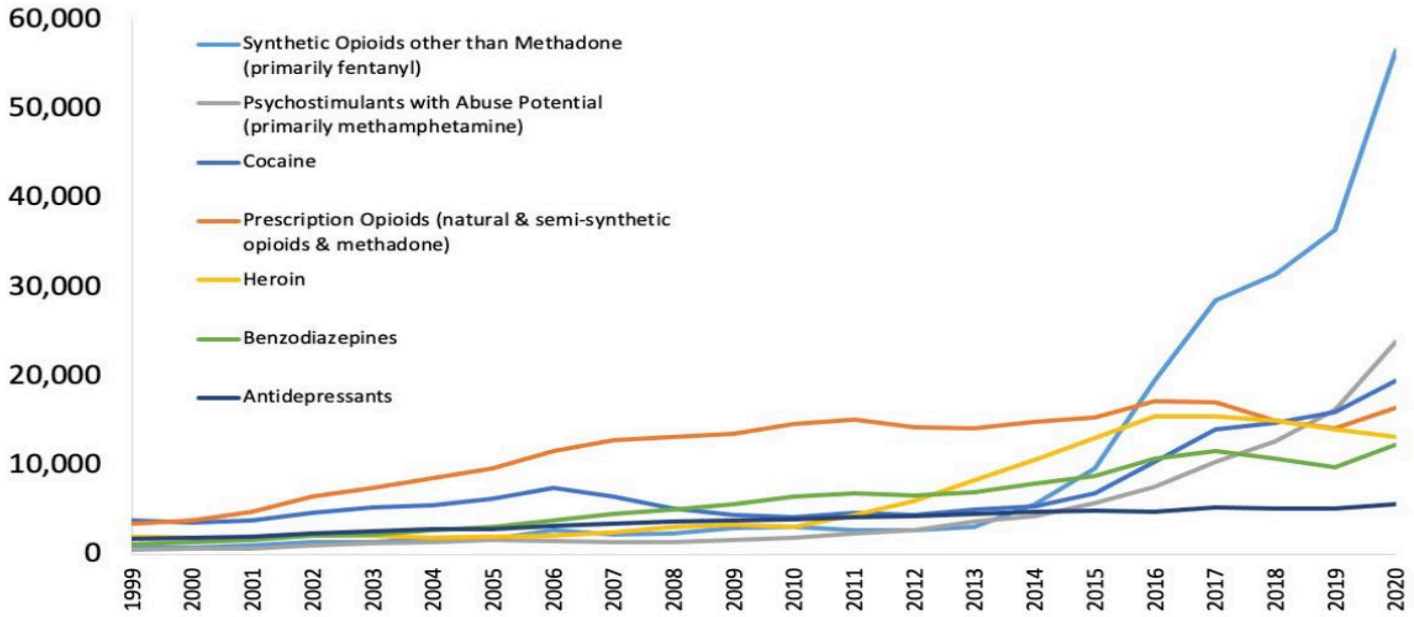


National Center for Drug Abuse Statistics 2022

Psychostimulant Deaths

- Psychostimulant deaths Increased
- Fentanyl included in methamphetamine and cocaine deaths

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2020



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021.

San Diego Meth Strike Force Report Card

SAN DIEGO COUNTY MSF Meth Strike Force
PREVENT · TREAT · ENFORCE

The Status of Methamphetamine Use in San Diego County

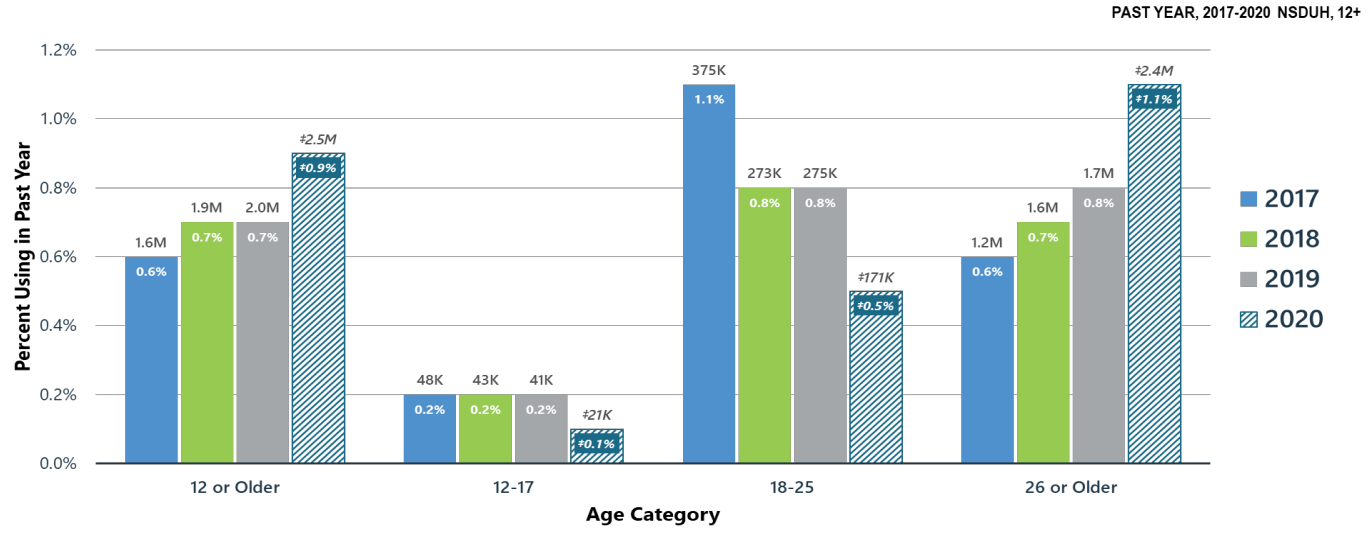
The Methamphetamine Strike Force (MSF) was established by the San Diego County Board of Supervisors in 1996. Today the MSF is a collaboration at federal, state and local levels, with contributions from more than 70 participating agencies. The annual MSF Report Card provides data from 2021 on leading indicators of methamphetamine problems. All data sources are identified on page 2.

	Indicator	2017	2018	2019	2020	2021
1.	Unintentional Methamphetamine-Caused Deaths [a]	271	328	379	553	756
	• Rate per 100,000 residents	8.2	9.8	11.3	16.5	22.8
2.	Amphetamine- Related Emergency Department (ED) Visits [b]	12,951	13,151	16,204	16,536	Available in 2023
	• Rate per 100,000 Residents	391	395	483	495	
3.	Amphetamine-Related Hospitalizations [b]	11,871	12,599	12,131	12,454	
	• Rate per 100,000 Residents	359	378	362	373	
4.	Methamphetamine Primary Substance Used	4,911	6,906 [c]	6,591	4,740	4,909
	• Percent of all Public Drug Treatment Program Admissions	37%	30%	33%	31%	32%
5.	Positive Methamphetamine Tests					
	• Adult Arrestees	56%	57%	59%	56%	54%
	• Juvenile Arrestees	11%	10%	11%	8%	3%
6.	Number of Arrests for Methamphetamine Sales and Possession [d]	9,293	10,156	11,313	7,211	10,948
7.	Availability Measures					
	• "Easy to Get" [e]	89%	89%	88%	84%	89%
	• Price per Ounce	$120-250	$150 -300	$150-325	$150-300	$90-250
	• Methamphetamine Seizures at Border Points of Entry	13,831 kg.	19,171 kg.	34,182 kg.	42,087 kg.	60,508 kg.

No2meth.org

Methamphetamine Use Disorder

- 2.5 million Americans age > 12 use meth in past year
- 53% met criteria for methamphetamine use disorder
- 3% injected methamphetamine



‡ Estimates on the 2020 bars are italicized to indicate caution should be used when comparing estimates between 2020 and prior years because of methodological changes for 2020. Due to these changes, significance testing between 2020 and prior years was not performed. See the *2020 National Survey on Drug Use and Health: Methodological Summary and Definitions* for details.

NSDUH 2020

Emergency Department Drug Surveillance

- 76% + Amphetamine in Drug Surveillance

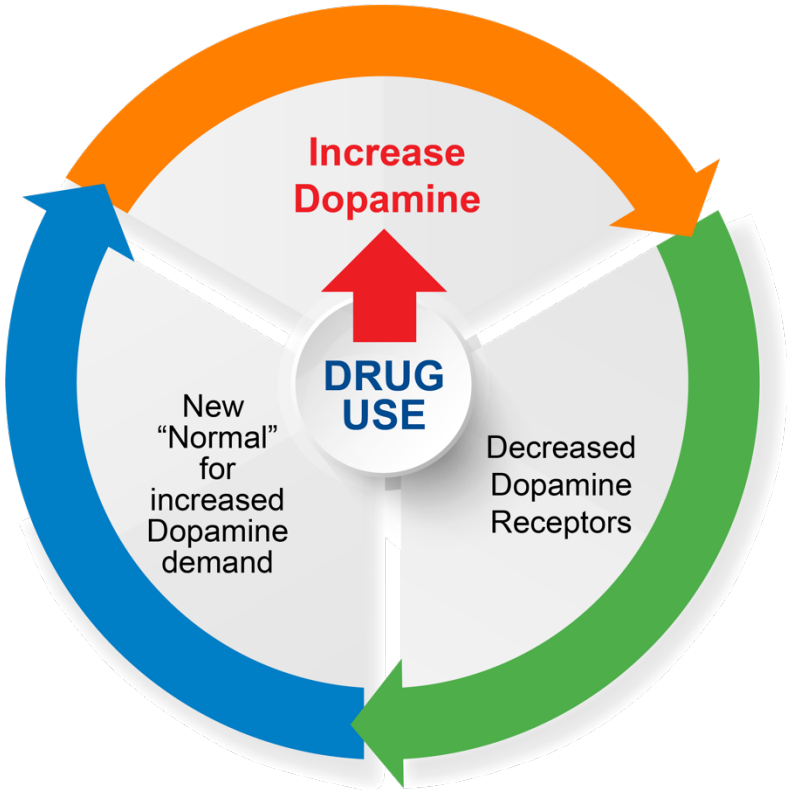
Table 1: EDDS Re-Test Results, by Hospital's Drug Screen Result

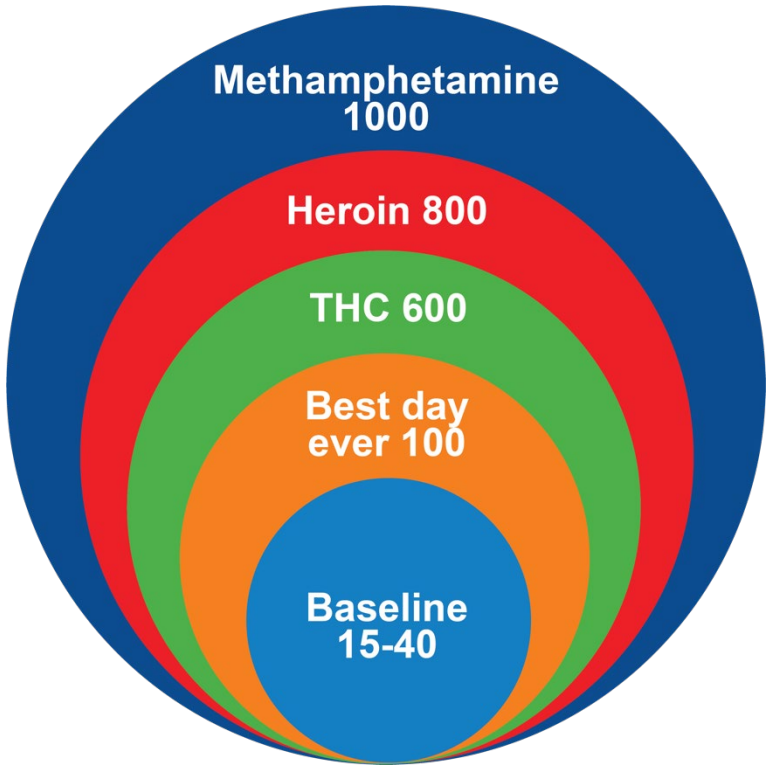
EDDS Found Positive for:	Hospital Found Positive for any drug (N=100) %	Hospital Found Negative for all drugs (N=50) %
Marijuana	48	12
Cocaine	5	4
Any Amphetamine	76	50
Methamphetamine	67	50
Amphetamine	46	2

https://cesar.umd.edu/sites/cesar.umd.edu/files/pubs/EDDS-CA-SanDiego-Bulletin-Dec2021.pdf

Understanding Addiction

- Drugs hijack Dopamine set point

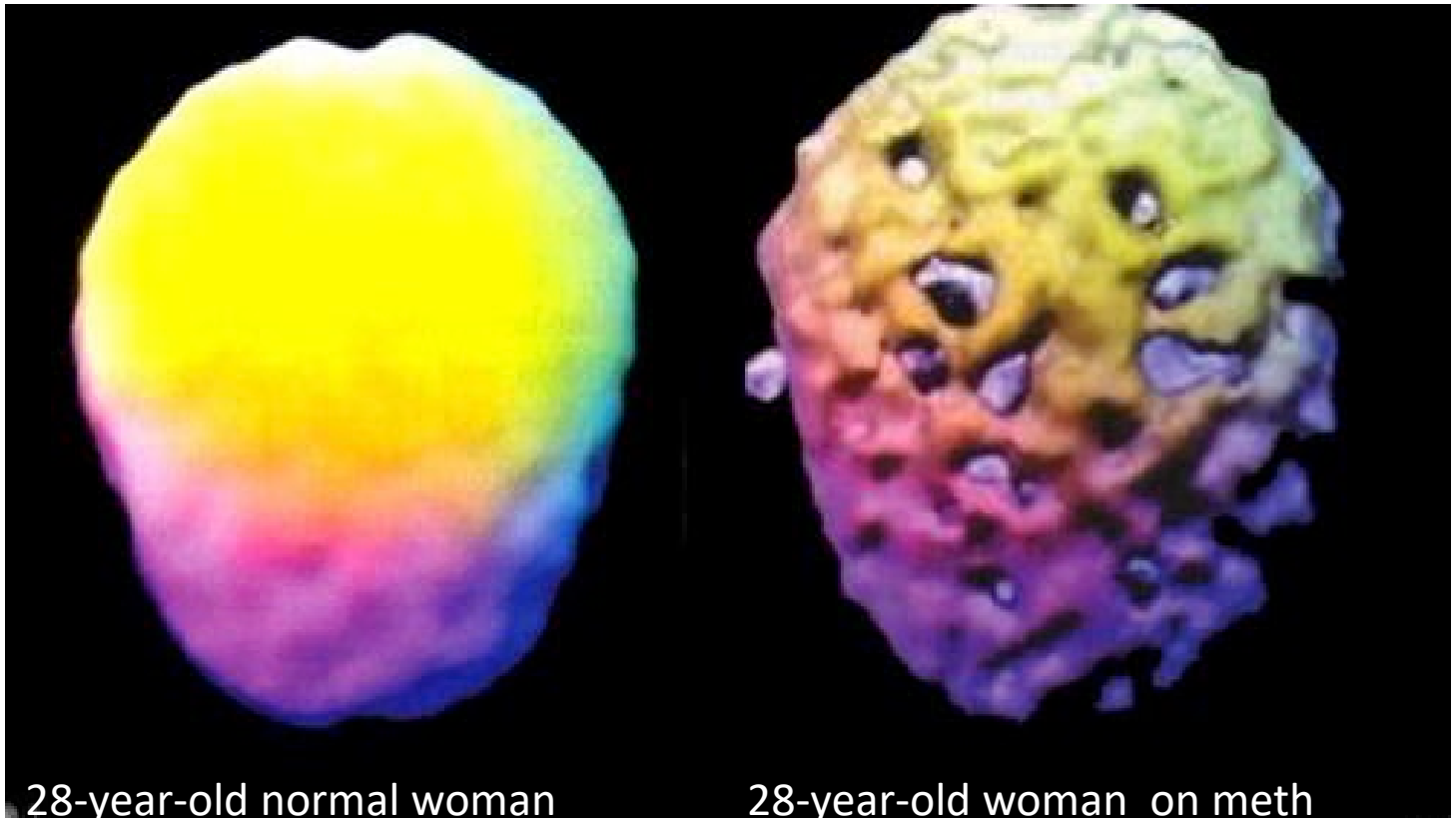




Source: Adapted from Dr. Corey Waller, Dr. George Knoob, Nester Neuroscience, 2005

The Brain on Methamphetamine

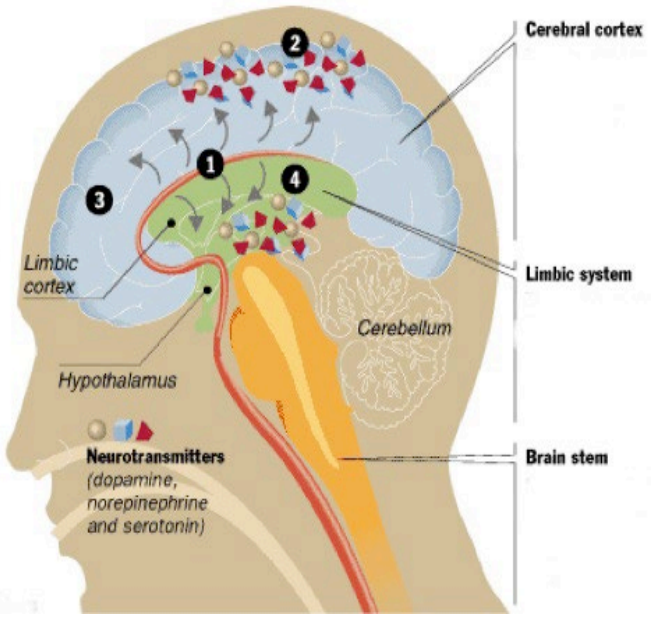
- Methamphetamine creates "holes" in the brain



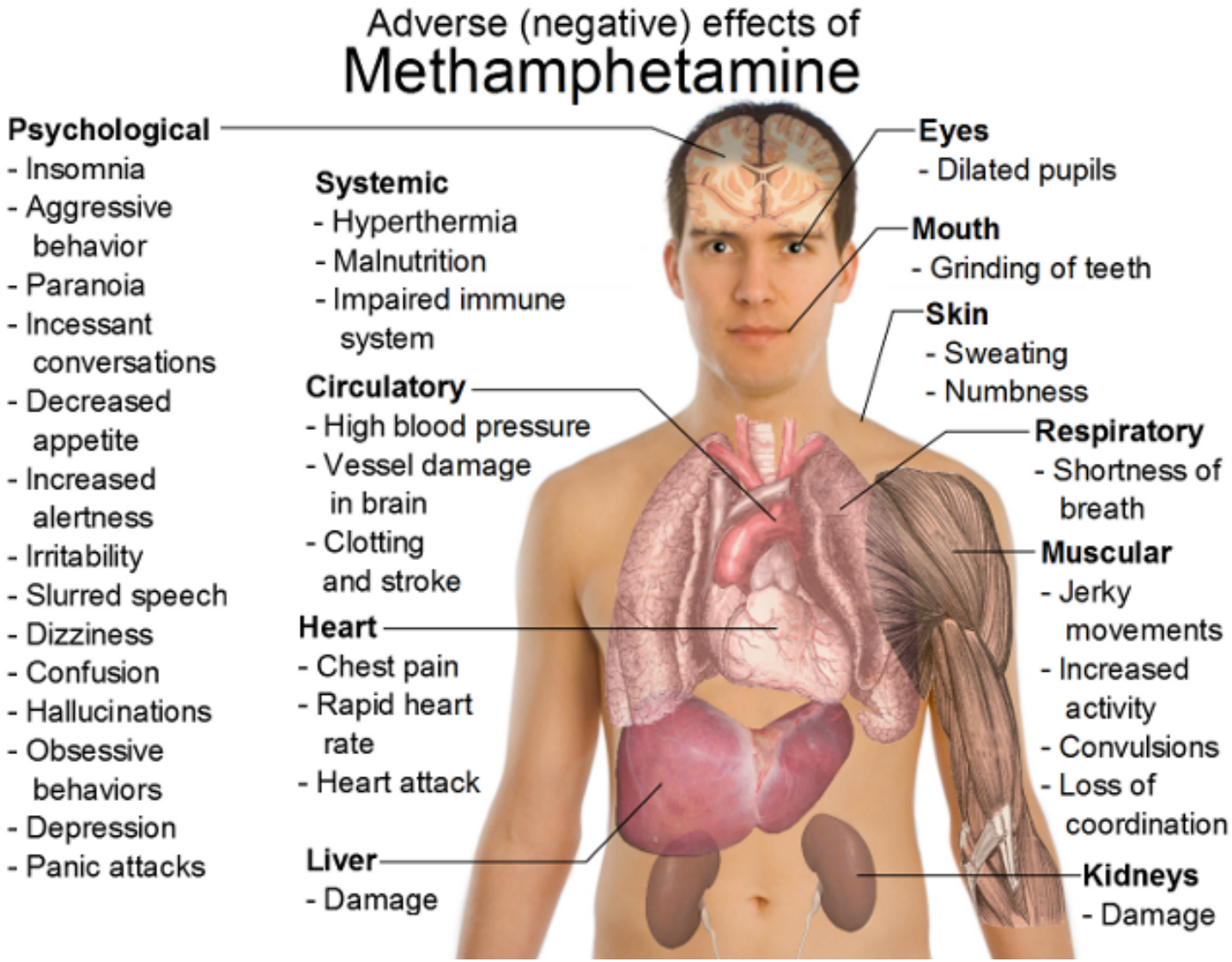
SPECTscan measures amount of blood flow to tissue

Stages of Methamphetamine Poisoning

Rush	5 minutes
Shoulder	1 hour
Tweaking	4-24 hours
Crash	1-3 days
Baseline	2-7 days



Methamphetamine Effects on Body



Excited Delirium

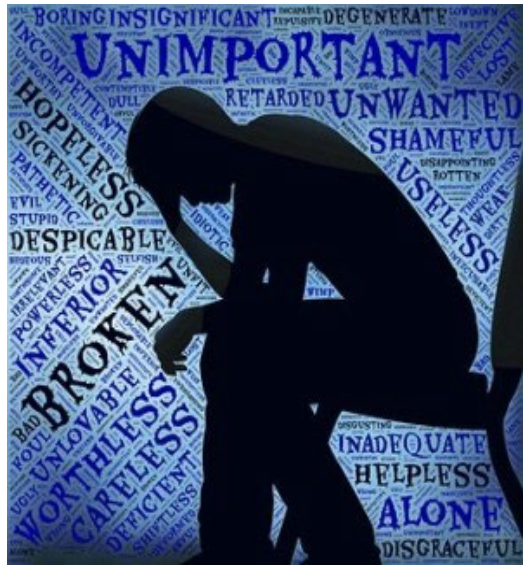
Code Green

- Methamphetamine
- THC
- PCP - phencyclidine
- TCP – tenocyclidine
- Fentanyl

What is the mystery drug?

Psychiatric Conditions

- Methicidal vs Drunkicidal
- Formication
- Hallucinations
- Depression
- Medication Non-Compliance



Mental Health Crisis

6 am Snapshot

Sea of Red

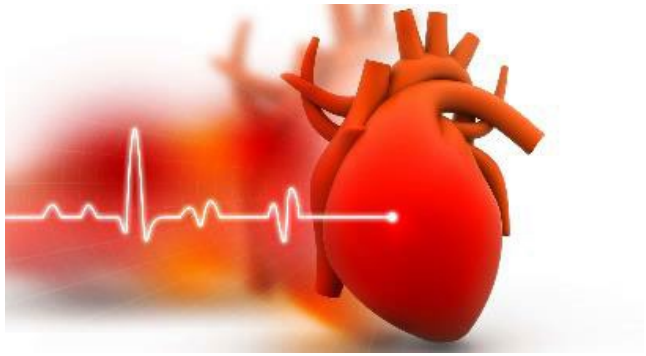
22 patients

16 held for psychiatric

189 hours = 8 days

Cardiac Toxicity

- Methamphetamine attacks heart muscle causing myocarditis, cardiomyopathy, and heart failure



- 6-year study
- 4 x increase in % Meth patients with CHF
- CHF improved in stop meth
- CHF worse if continue
- Average age if Meth = 51

Cardiac Toxic

- Methamphetamine
- Alcohol
- Cocaine

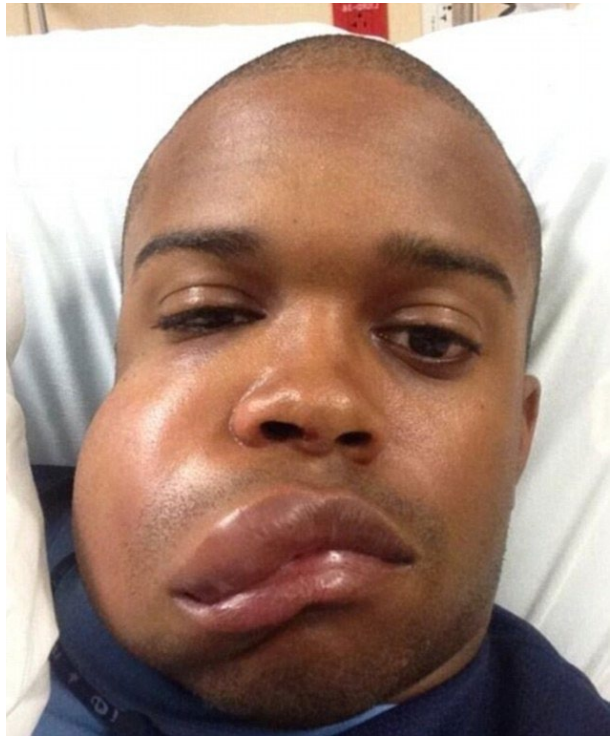
Non-Cardiac Toxic

- Heroin
- Opioids

Silman S, Waalen J, Shaw D. Methamphetamine Associated Congestive Health Failure: Increasing Prevalence and Relationship of Clinical Outcomes to Continued Use or Astinence. Cardiovasc Toxicol. 2015

Rashes, Abscesses, Cellulitis, Necrotizing Fasciitis

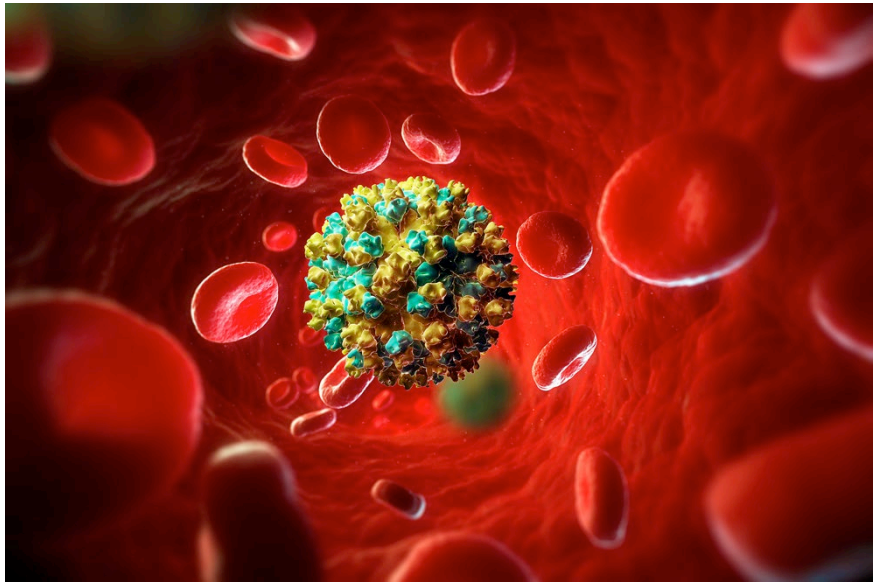
Meth Mouth



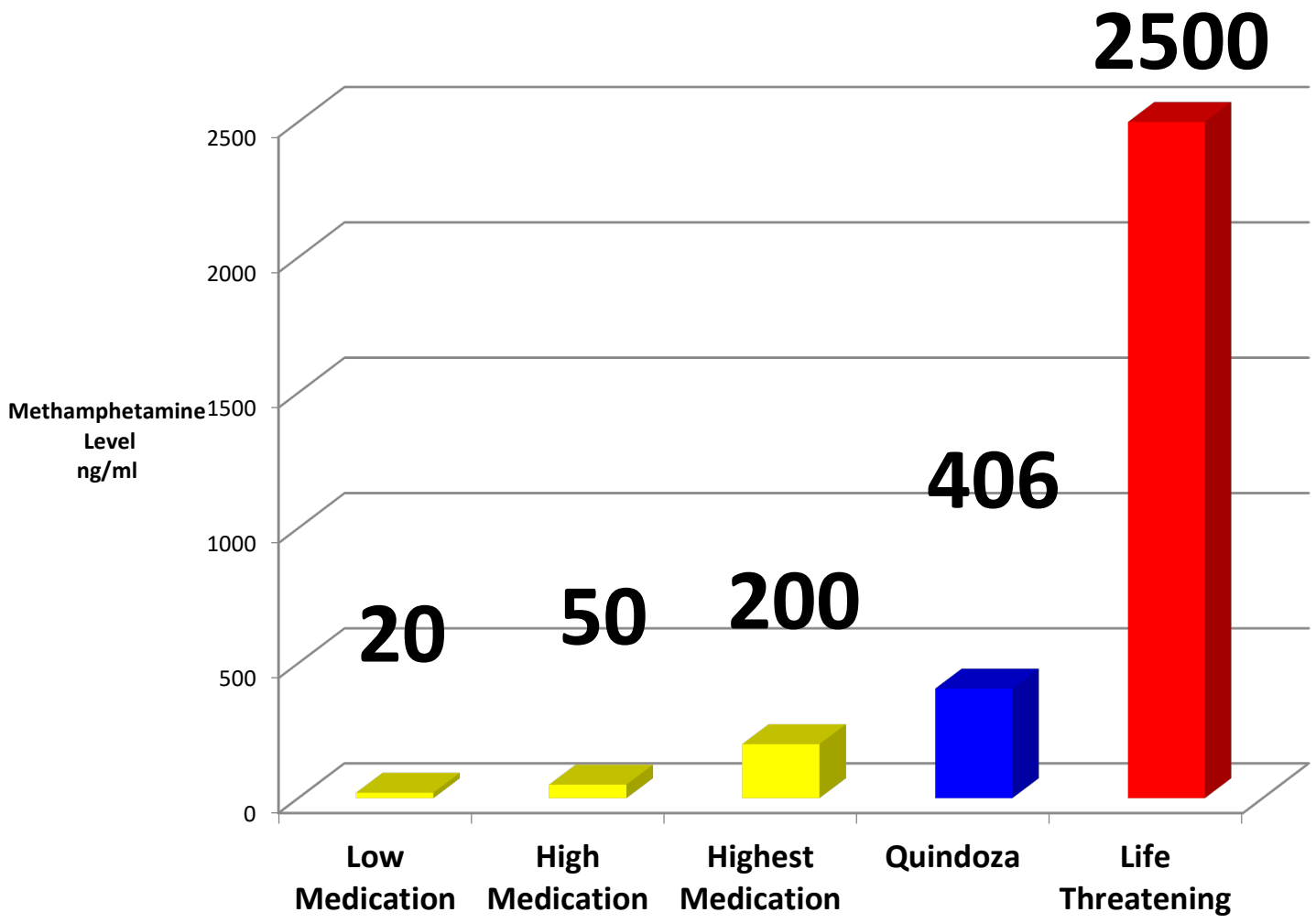
Infectious Disease

- Hepatitis C
- HIV/AIDS
- Wound Botulism

Methamphetamine travels by blood stream to any organ…



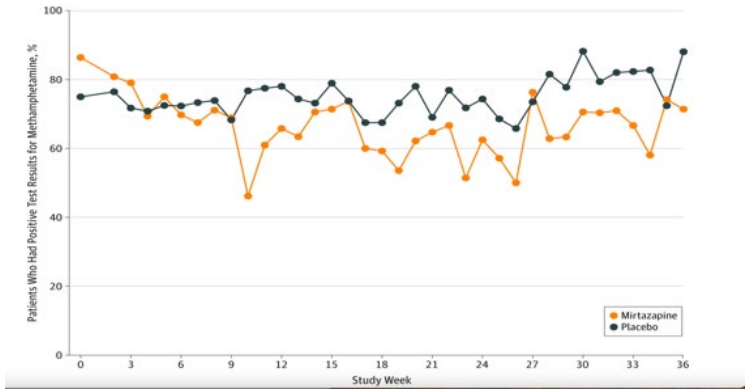
Drugged Driving



Methamphetamine Use Disorder Treatment

- No FDA approved medication to treat Methamphetamine Use Disorder
- Bupropion (Wellbutrin) + Naltrexone - Poor results
  - NEJM 2021 400 adults with meth use disorder, 6-week study
  - 3% success with Bupropion 450 mg qd + placebo
  - 14% success with bupropion + naltrexone ER 380 mg IM q 3 weeks
  - NNT number needed to treat = 9
- Mirtazapine (Remeron) Trial
  - 120 persons MSM in San Francisco
  - Mirtazapine 30 mg vs placebo for 24 weeks with counseling
  - Mirtazapine resulted in 15% decrease in positive urine drug screens at weeks 24 to 36.

Amphetamine/Methamphetamine MAT is **NOT** recommended



Coffin PO, Santos G, Hern J, et al. Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex With Men: A Placebo-Controlled Randomized Clinical Trial. *JAMA Psychiatry.* 2020;77(3):246–255. doi:10.1001/jamapsychiatry.2019.3655

Trivedi MH, et al. Bupropion and Naltrxone in Methamphetamine Use Disorder NEJM 2021

Contingency Management Implementation Resources

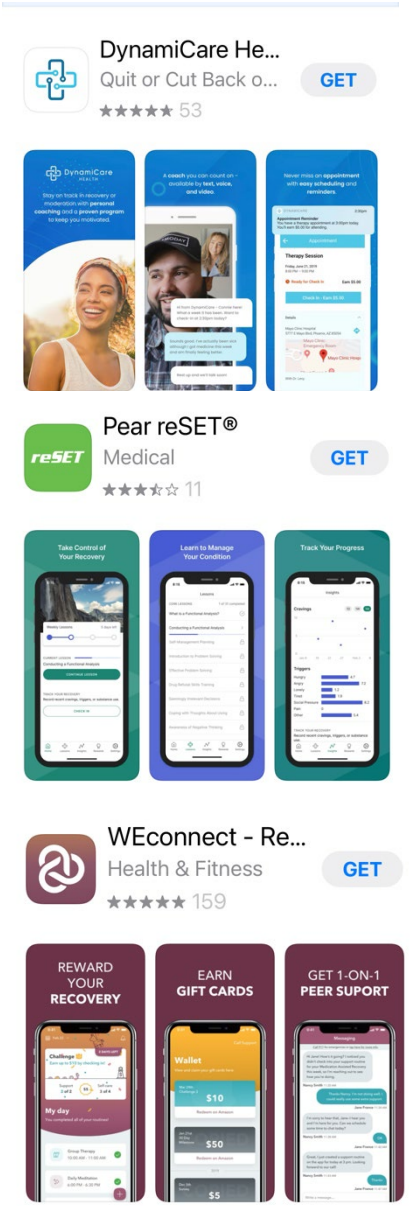
- Contingency Management (CM)
  - 50% Veterans - 14 sessions in 12 weeks
  - 42% - 2 sessions in 1 year
  - 92% of 28,000 tox screens in 2 VA studies

Learn more about the major components of CM and how to implement it by reviewing:

- The Substance Abuse and Mental Health Services Administration's (SAMHSA) Addiction Technology Transfer Center (ATTC) Network online course Contingency Management for Healthcare Settings (https://attcnetwork.org/centers/northwest-attc/news/new-online-course-contingency-management-healthcare-settings).
- The Motivational Incentives Suite—a collection of tools and other resources to help organizations understand and implement CM (http://www.bettertxoutcomes.org/bettertxoutcomes/).
- The ATTC Network's guidance on the founding principles of CM (https://attcnetwork.org/centers/network-coordinating-office/contingency-management-part-2-founding-principles).

Contingency Management Mobile Applications

- DynamiCare CM
  - Stimulant-free saliva tests
- ReSet (Pear Therapeutics)
  - Prescription Digital Therapeutics
  - CBT for SUD - Complete treatment modules
- WeConnect CM
  - Treatment plan activities



M & M

- Meth & Methadone
- Meth & Marijuana
- Meth & Mental Health
- Meth & Missing a Home

Methamphetamine and Fentanyl

San Diego Medical Examiner
2021 mid-year overdose deaths:

- 757 Methamphetamine deaths
- 198 had both fentanyl and methamphetamine
- 296% increase in that combination compared to mid-year 2020
- 662% increase compared to mid-year 2019

Where is Fentanyl Found

- Heroin
- Cocaine
- Methamphetamine
- Fake hydrocodone pills
- Fake oxycodone 30 pills (M30)
- Fake hydrocodone pills (yellow)
- Fake Xanax pills
- Fake Adderral
- Vaping products

Tyler's Law

January 1, 2023
All California hospitals must include fentanyl whenever a urine drug screen is ordered.

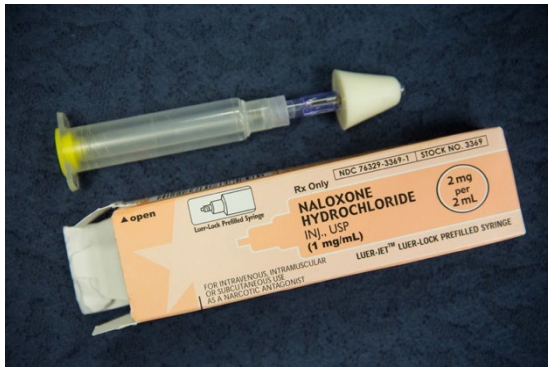
Fentanyl Testing Tool Kit
https://www.sdpdatf.org/fentanyl-testing-toolkit-hospital-settings

Naloxone

Naloxone for drugs is like Epi-Pen for Allergies

- It's not just for opioids, because fentanyl is everywhere

- Naloxone = generic
- Narcan = brand, 4 mg
- Kloxxado = brand, 8 mg



High Truths on Drugs and Addiction Podcast Hosted by Dr. Lev

Spike Steffenhagen – Lived Experience

Recovery for 36 years

Author, *San Diego Reader* and various comic book companies

Recovery Incentives Program: California's Contingency Management Benefit

Ivan Bhardwaj

Chief, Medi-Cal Behavioral Health Division

DHCS

DHCS Goals for the Contingency Management Pilot Program

Mission: To expand access to evidence-based treatment for stimulant use disorders, DHCS intends to pilot Medi-Cal coverage of CM services as the Recovery Incentives program from Quarter 1 2023 through March 31, 2024. While Contingency Management (CM) has been tested using other sources of funding, California is the first state in the country to receive federal approval of CM services as a benefit in the Medicaid program through the CalAIM 1115 Demonstration.

Vision: DHCS intends to use the pilot as a basis for informing the design and implementation of a statewide CM services benefit through the Drug Medi-Cal Organized Delivery System (DMC-ODS), pending budgetary and statutory authority.

Pilot Program Overview

DHCS intends to pilot Medi-Cal coverage of CM services in DMC-ODS counties that elect and are selected to participate from Quarter 1 2023 through March 2024. Eligible Medi-Cal beneficiaries will:

Participate in a structured **24-week CM Program--**12 weeks with twice weekly testing/incentives and a 12-week continuation with once weekly testing/incentives

Receive incentives for testing **negative for stimulants only** even if they test positive for other drugs

Earn a **maximum of $599** over the 24-week period in the form of gift cards

Generate incentives and track progress using **Incentive Manager** software

Recovery Incentives Program Counties

24 DMC-ODS counties plan to participate in the Recovery Incentives Program:	
Alameda	San Diego
Contra Costa	San Francisco
Fresno	San Joaquin
Imperial	San Luis Obispo
Kern	San Mateo
Los Angeles	Santa Barbara
Marin	Santa Clara
Nevada	Santa Cruz
Orange	Shasta
Riverside	Tulare
Sacramento	Ventura
San Bernardino	Yolo

Role of the CM Coordinator

Providers will have a designated CM coordinator to lead the tracking and delivery of all CM services, including urine drug screen tests and incentive distribution.

- The CM coordinator will be expected to:
  - Enter beneficiary information in the electronic health record for reimbursement and reporting purposes
  - Collect urine drug test (UDT) samples and recognize sample tampering efforts
  - Enter UDT results into the Incentive Manager software program, understanding the incentive amount and being able to explain it to the beneficiary
  - Provide praise for stimulant-negative UDT; provide encouragement in the case of stimulant-positive UDT
  - Ensure delivery of the incentive to the beneficiary for a stimulant-negative UDT
- The CM coordinator role can be filled by licensed professionals, paraprofessionals, and/or peer support workers.

Basic Treatment Approach

The CM treatment framework will be a 24-week outpatient treatment experience followed by a six month or longer period of aftercare and recovery support services.

Escalation/Reset/Recovery Period (Weeks 1-12)

- During the initial 12 weeks of the CM protocol, beneficiaries will be asked to visit the treatment setting in person for a minimum of two treatment visits per week.
- Sessions will be separated by at least 72 hours (e.g., Monday and Thursday, or Tuesday and Friday) to help ensure that drug metabolites from the same drug use episode will not be detected in more than one UDT.
- Beneficiaries will be able to earn incentives during each visit.
- A "reset" will occur when an individual submits a stimulant-positive sample or has an unexcused absence. The next time they submit a stimulant-negative sample, their incentive amount will return to the initial value (i.e., $10).
- A "recovery" of the pre-reset value will occur after two consecutive stimulant-negative urine samples. At that time, the beneficiary will recover their previously earned incentive level without having to restart the process.

Basic Treatment Approach (cont.)

The CM treatment framework will be a 24-week outpatient treatment experience followed by a six month or longer period of aftercare and recovery support services.

Stabilizing Period (Weeks 13 – 24)

- During weeks 13–24, beneficiaries will be asked to visit the treatment setting for testing once a week.
- During weeks 13–18, beneficiaries will be eligible to receive $15 per stimulant-negative UDT.
- During weeks 19–23, beneficiaries will be eligible to earn $10 per stimulant-negative UDT.
- The total possible earnings during weeks 1–24 for all stimulant-negative tests is $599.
- Following the stabilizing period, beneficiaries may participate in an additional 6 month or longer period of aftercare and recovery support services.

Sample Incentive Delivery Schedule – Part 1

Week	Reward for Stimulant-Free Test
Week 1	$10 + $10 = $20
Week 2	$11.50 + $11.50 = $23
Week 3	$13 + $13 = $26
Week 4	$14.50 + $14.50 = $29
Week 5	$16 + $16 = $32
Week 6	$17.50 + $17.50 = $35
Week 7	$19 + $19 = $38
Week 8	$20.50 + $20.50 = $41
Week 9	$22 + $22 = $44
Week 10	$23.50 + $23.50 = $47

Sample Incentive Delivery Schedule – Part 2

Week	Reward for Stimulant-Free Test
Week 11	$25 + $25 = $50
Week 12	$26.50 + $26.50 = $53
Weeks 13-18	$15 per week/test
Weeks 19-23	$10 per week/test
Week 24	$21 per week/test
Total	**$599**

Incentive Delivery

DHCS will procure and work with an external vendor(s) to design, implement and support the distribution of incentives to beneficiaries participating in the Recovery Incentives program.

- **Incentive Calculation**
  - The CM coordinator will enter the results of the beneficiary's UDT into a secure Incentive Manager program that will calculate and report the amount of any incentive the beneficiary should receive during that visit.
  - The Incentive Manager program will notify the CM Coordinator when to distribute an incentive.
- **Incentive Distribution**
  - Upon entry of stimulant-negative UDT results, the incentive amount shall be delivered immediately to participating beneficiaries in a format approved by DHCS.

Incentive Delivery (cont.)

DHCS will procure and work with an external vendor to design, implement and support the distribution of incentives to beneficiaries participating in the Recovery Incentives program.

- **Incentive Types**
  - Participating beneficiaries shall receive incentives in the format of an e-mail, hard copy, refillable gift card, or other mechanism as approved by DHCS, which the vendor will disburse upon entry of stimulant-negative UDT results.
  - Restrictions shall be placed on the incentives so they cannot be used to purchase cannabis, tobacco, alcohol or lottery tickets.

Other Program Elements

The Recovery Incentives program will be complemented with ongoing training and technical assistance and a robust evaluation process, while protecting against fraud, waste, and abuse.

Training	Evaluation	Oversight
• Participating counties and SUD providers will be required to participate in start-up training and ongoing technical assistance. • Synchronous, live trainings will be offered beginning in January 2023.	• The impact of the pilot program will be measured through a robust evaluation process. • DHCS will release an interim and a final evaluation report, along with quarterly reports to inform future budget decisions.	• Each treatment program will have a policies and procedures manual. • All providers will be required to complete readiness reviews. • DHCS and counties will conduct robust monitoring and oversight of CM providers.

How to Help Beneficiaries Gain Access to CM Services

- Providers should contact local DMC-ODS county administrator for more details about the provider network in the 24 participating counties.
- SUD Non-Emergency Treatment Referral Line for Beneficiaries
  - To reach the referral line, please call the following telephone numbers:
    (800) 879-2772 – Statewide Toll Free, or
    (916) 327-3728 – Outside California

For additional details, please visit:

- https://www.dhcs.ca.gov/Pages/DMC-ODS-Contingency-Management.aspx

- E-mail: RecoveryIncentives@dhcs.ca.gov

Hope for Treating Methamphetamine Use Disorder

Xinhua Li, Mitch Zakin

Shekar Shetty and Winston Henderson

Clear Scientific, Inc., Cambridge, MA

CHA Conference
Riverside CA December 2022

Disclosure Information

- **Financial interests**
  - The authors work for Clear Scientific, Inc. Cambridge, MA. We own stock and receive salary and benefits

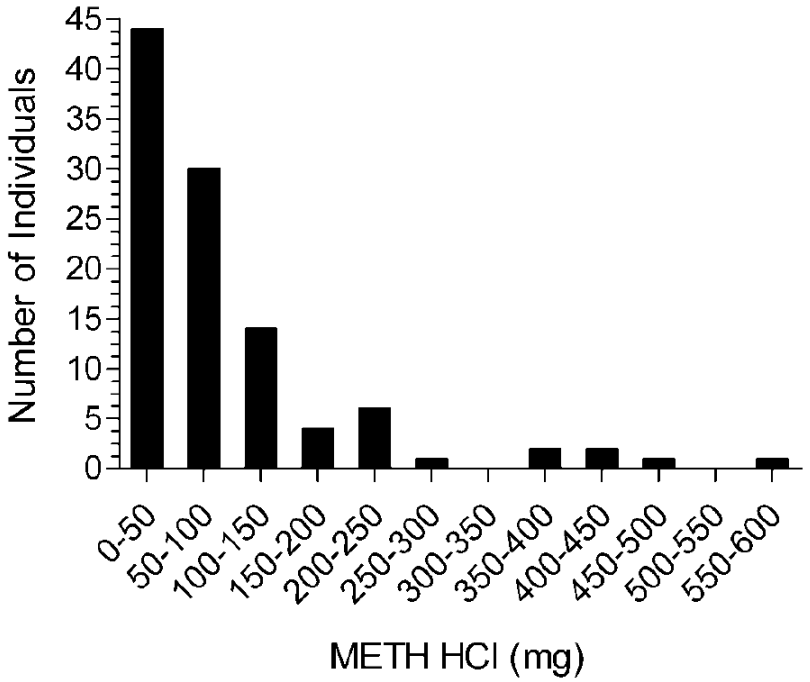
- **Acknowledgments**
  - NIH/NIDA for funding to further advance our therapeutic programs
    - 1U01DA053054-01
    - 1R43 DA052957-01, 2R44DA052957-02 and 1R43DA057782-01
  - Early work on our therapeutic candidates performed by
    - Prof. Lyle Isaacs at the University of Maryland
    - Dr. Matthias Eikermann and Dr. Joe Cotten at Massachusetts General Hospital

Methamphetamine Use, An Urgent Public Health Crisis

- Powerful, highly addictive stimulant that affects the central nervous system
- Fastest growing drug of abuse in the U.S.
- Overdose often leads to a stroke, heart attack, or organ problems
- 325,300 Emergency department visits per year, 36% of ED visits result in hospitalization,-> 32,000 deaths per year, costs the healthcare system more than $8 billion annually
- Co-use with synthetic opioids make things much worse
- No FDA-approved therapies available for treating Meth intoxication
- Current standard of care is to treat symptoms only – “sedate and wait”

The Challenge: Too Much and Too Long

- Large amount of Meth in the body for a long time
  - Meth: **lethal dose: 200 mg, half-life: 10-14 hrs**
  - Fentanyl: lethal dose: 3 mg, half-life: 2-6 hrs
- Estimated initial body burden of Meth
  - **60% of people have more than 50 mg of Meth in the body**
    - 40%: < 50 mg
    - 43%: 50-150 mg
    - 10%: 151-300 mg
    - 7%: 350-600 mg
  - Blood samples were obtained from 105 individuals detained by police for possible criminal activity and testing positive for stimulants by EMIT assay
  - Estimates of initial Meth body burdens were calculated for all individuals: Body weight (kg) × 3.4 L/kg (Meth volume of distribution) × Meth concentration in blood.

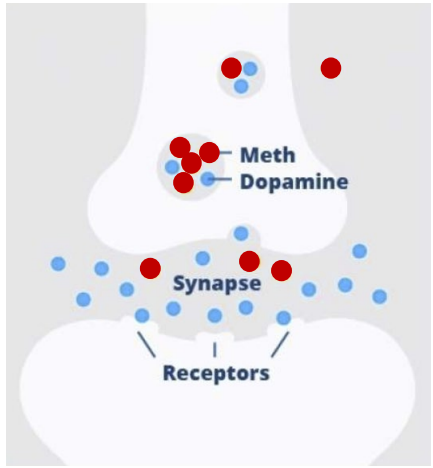


Frequency distribution of estimate of initial body burden of Meth.HCl. The data set was obtained through the Kern County District Attorney's Office: Forensic Science Division, Bakersfield, CA.

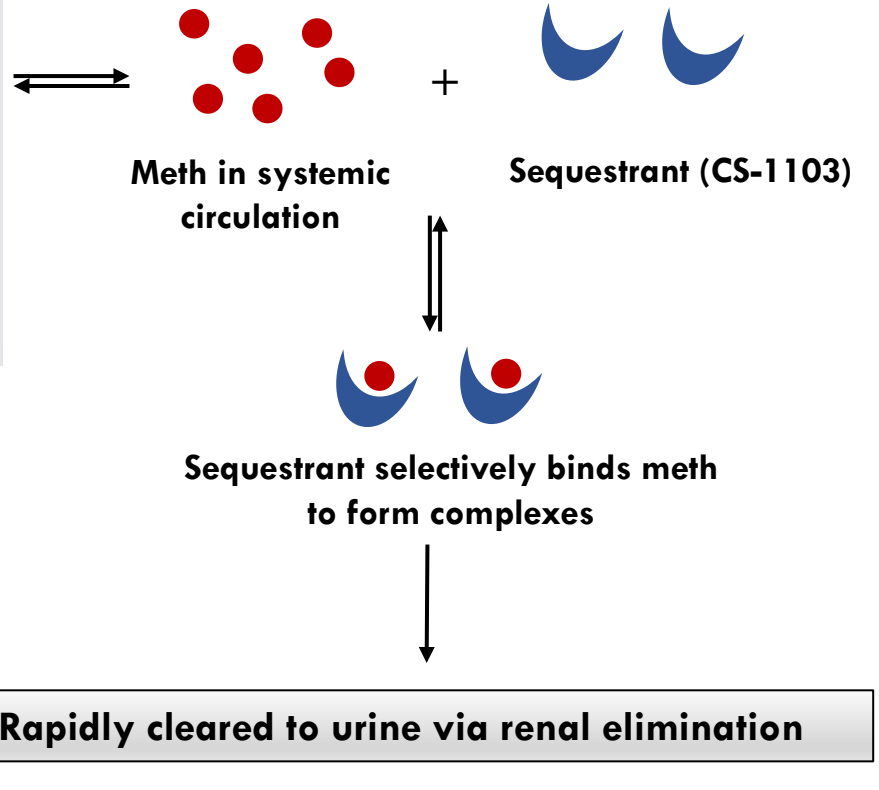
Melega WP, Cho AK, Harvey DC, Lacan G , Synapse, 2007; 61: 216-220.

Our Approach: Remove the Cause, Remove the Effect

- Our small-molecule sequestrant therapeutic agents **bind**, **inactivate**, **and clear harmful substances** from the body with high specificity (mechanism similar to Merck's Sugammadex Bridion®, a reversal agent for neuromuscular blocking agents)
- Removal of Meth from the circulating blood creates a **negative concentration gradient** between brain and circulation so that Meth partitions into the circulation
- Our sequestrant **lowers the level of Meth in the human body**, reversing acute intoxication, preventing damage to blood vessels of heart and brain, thus reducing long-term toxic effects

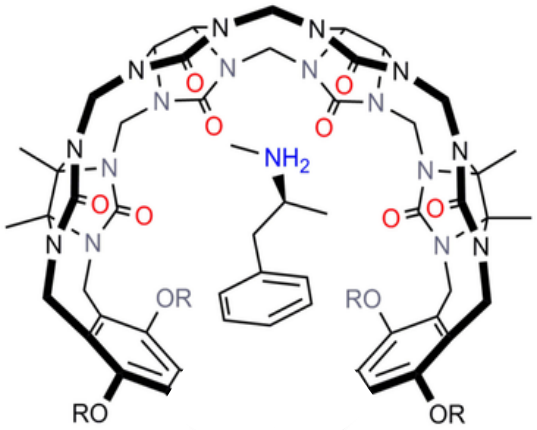


Meth in the brain



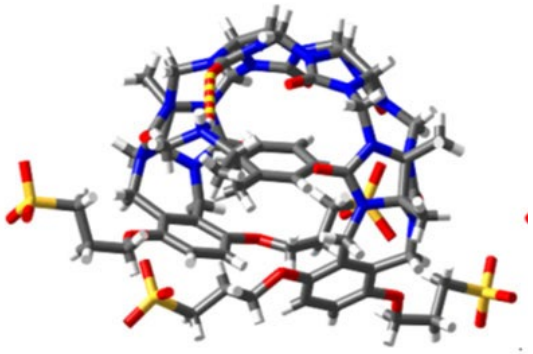
Our Drug Candidate, CS-1103, A Small Molecule Sequestrant

- ***In vitro*:**
  - CS-1103 forms 1:1 complex with Meth with binding constant $K_a = 7.5 \times 10^6$ M^{-1}
  - CS-1103 forms 1:1 complex with Fentanyl with binding constant $K_a = 1.1 \times 10^7$ M^{-1}
  - CS-1103 *has lower binding* affinity to catecholamines ($K_a \sim 10^4$ M^{-1})
  - The selective binding to Meth and Fentanyl is due to:
    - Size of the molecules
    - Hydrophobic, aromatic interaction
    - Charge-charge interaction
- ***In vivo*:**
  - CS-1103 binds and sequesters Meth in blood. The complex is rapidly eliminated via the kidney in ~2h in NHP



R = $-(CH_2)_3SO_3Na$

A 1:1 Complex of CS-1103 and Meth



Crystal Structure of a 1:1 Complex of CS-1103 and Meth

CS-1103 is Well-Tolerated and Non-Toxic - *IND-Enabling Studies*

- CS-1103 does not inhibit hERG at up to 900 μM, is non-mutagenic up to 5000 μg/plate and non-genotoxic up to 500 μg/mL.
- CS-1103 produced no neurobehavioral effects and no increase in respiratory rate in rats at doses of ≤1500 mg/kg.
- Cardiovascular (CV) assessment in canine indicated no significant changes in CV parameters
- Pharmacokinetics: The plasma half-life of CS-1103 in rat and canine is 37 and 70 min, respectively
- Metabolism, Biodistribution, and Elimination: Using 14C-labeled CS-1103 in rat, we observed that CS-1103 is eliminated unmetabolized in the urine with 89.4% of recovered radioactivity detected in urine at 24 hrs
- In rat, no statistical significance in catecholamine level (epinephrine, norepinephrine, dopamine) was observed when performing t-test between the CS-1103 treated group (at 500mg/kg and 1000mg/kg dose) and the vehicle treated control group
- In a GLP Single-Dose Tox with 14-day Recovery Study, CS-1103 was well-tolerated in rat and canine
  - NOAEL 1500 mg/kg for rat, 500 mg/kg in canine.
  - With a 10-fold safety margin, we estimate the corresponding human equivalent dose to be 28 mg/kg; this approximates the proposed clinical dose range.

Pharmacokinetics (PK) of CS-1103

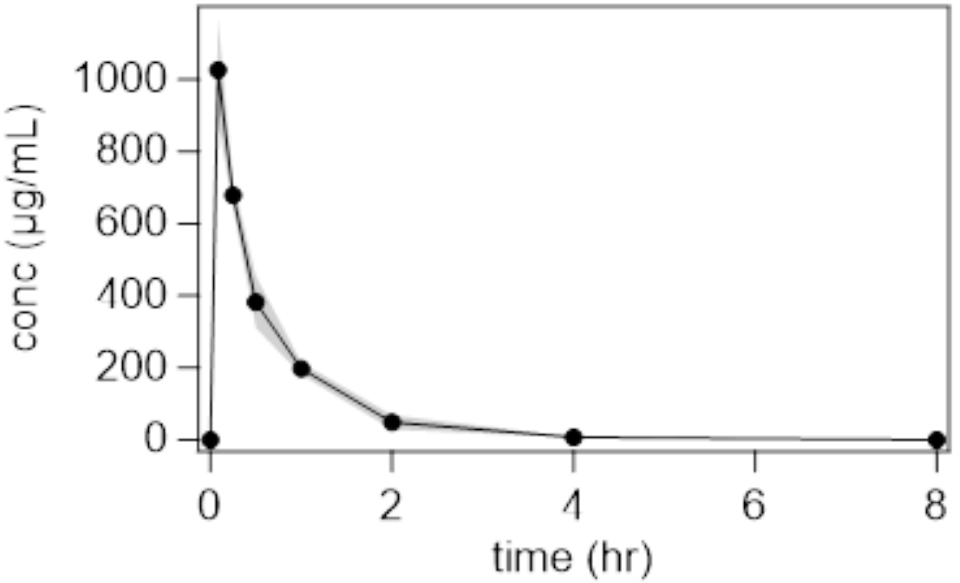
In rats:

- CS-1103, is not metabolized. >80% of dose recovered in the urine within ~1h after single IV administration
- $T_{1/2}$ for IV administration: ~37 min
- CS-1103 was rapidly available via IM injection, reaching maximum concentration (C_{max}) in plasma in 5 min

In large animals:

- $T_{1/2}$ for IV administration in canine: ~72 min
- Similar PK properties observed after IV and IM injection
- CS-1103 was rapidly available via IM injection

Plasma concentration of CS-1103 after a single IV dose at 500 mg/kg in rats



IV PK profile like Sugammadex (Bridion®)

Efficacy: Dose-Response Using [^{14}C]Meth in Rats

CS-1103 increased clearance of meth from blood and tissues and increased excretion of meth in urine

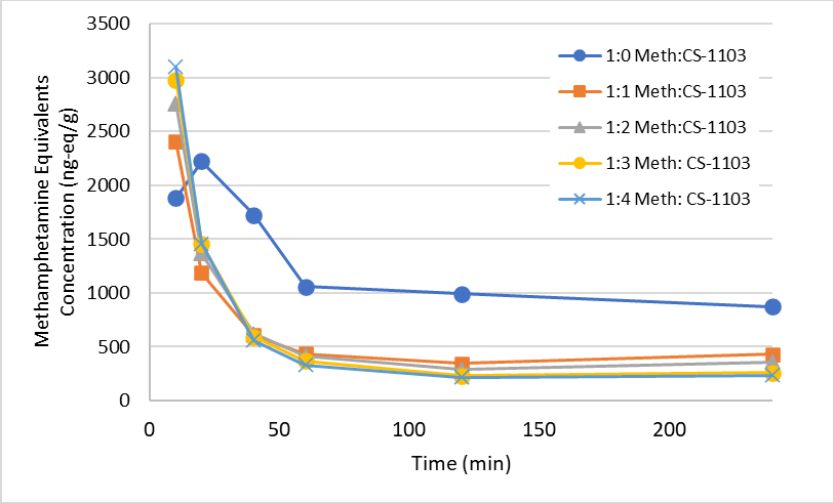


Figure 1. Concentration of meth equivalents in blood following IV administration of [^{14}C]Meth and CS-1103 to rats

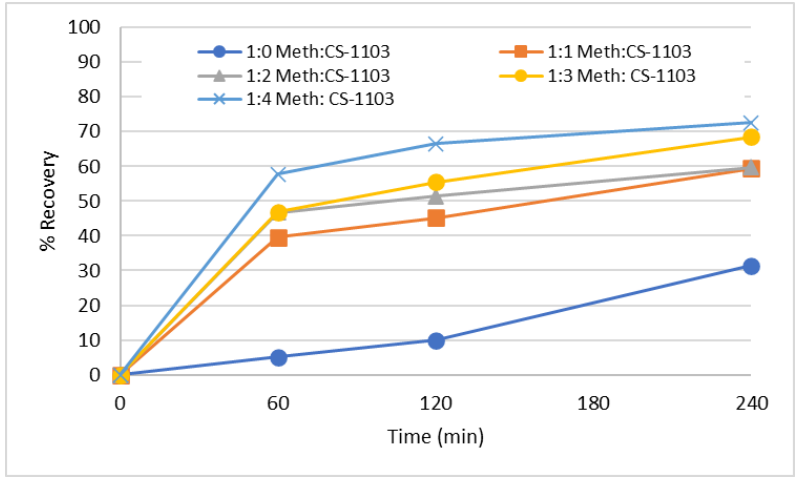


Figure 2. Cumulative recovery of radioactivity in urine following IV administration of [^{14}C]Meth and CS-1103 to rats

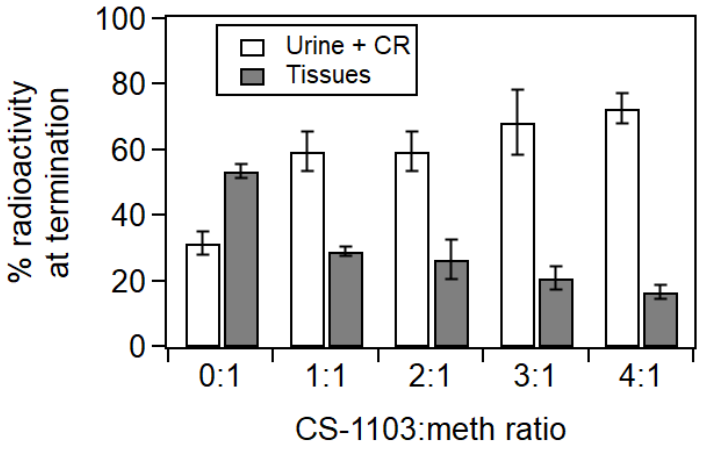
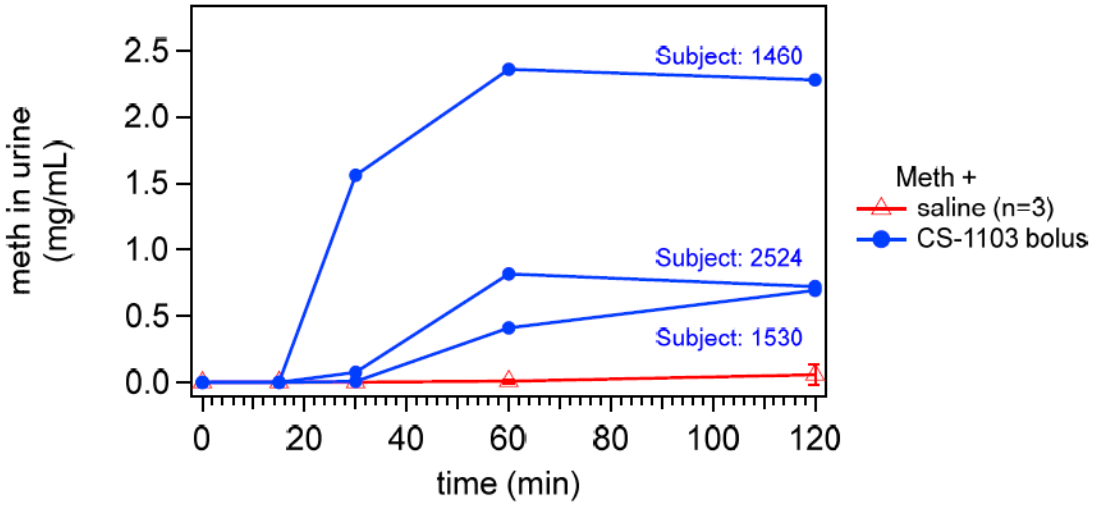
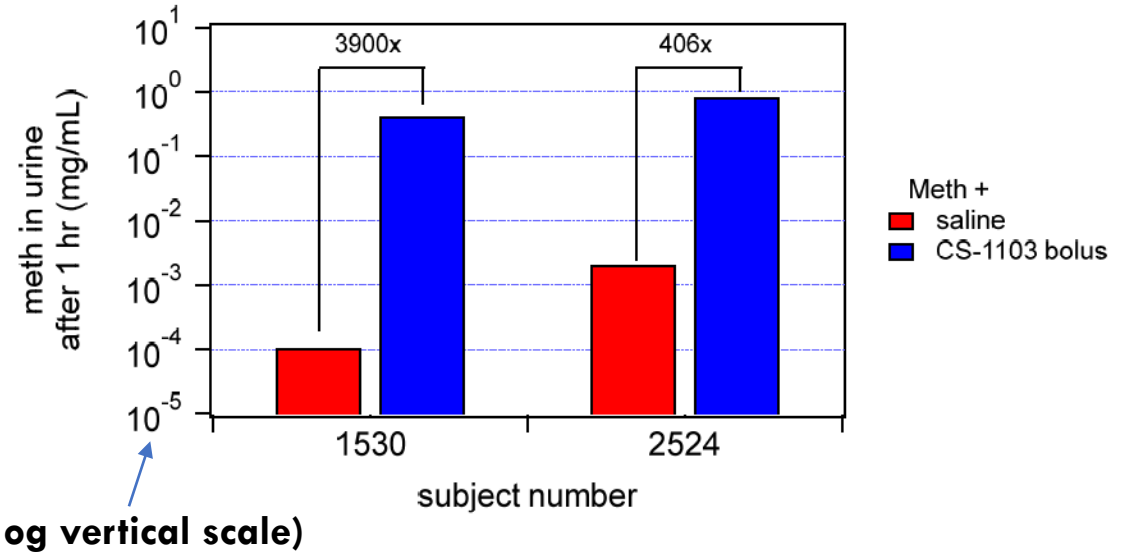


Figure 3. Dose recovered at termination (4h post-dose) following IV administration of [^{14}C]Meth and CS-1103 to rats

Remove the Cause: CS-1103 Dramatically Accelerates Meth Clearance into the Urine in NHP

- 4 mg/kg Meth was administered by IV bolus injection, followed within 5 min by IV bolus injection of:
  - saline as control, or
  - 200 mg/kg CS-1103 for treatment
- Used a crossover design with a 7-day washout period between each experimental set
- **Meth clearance increased 400 – 4000x.** C_{max} in urine at ~1h.
- When CS-1103 was administered (n=3) as an infusion over 20 min, similar clearance of Meth was found to bolus administration (data not shown)





(Note the log vertical scale)

CS-1103 rapidly removes Meth from the body

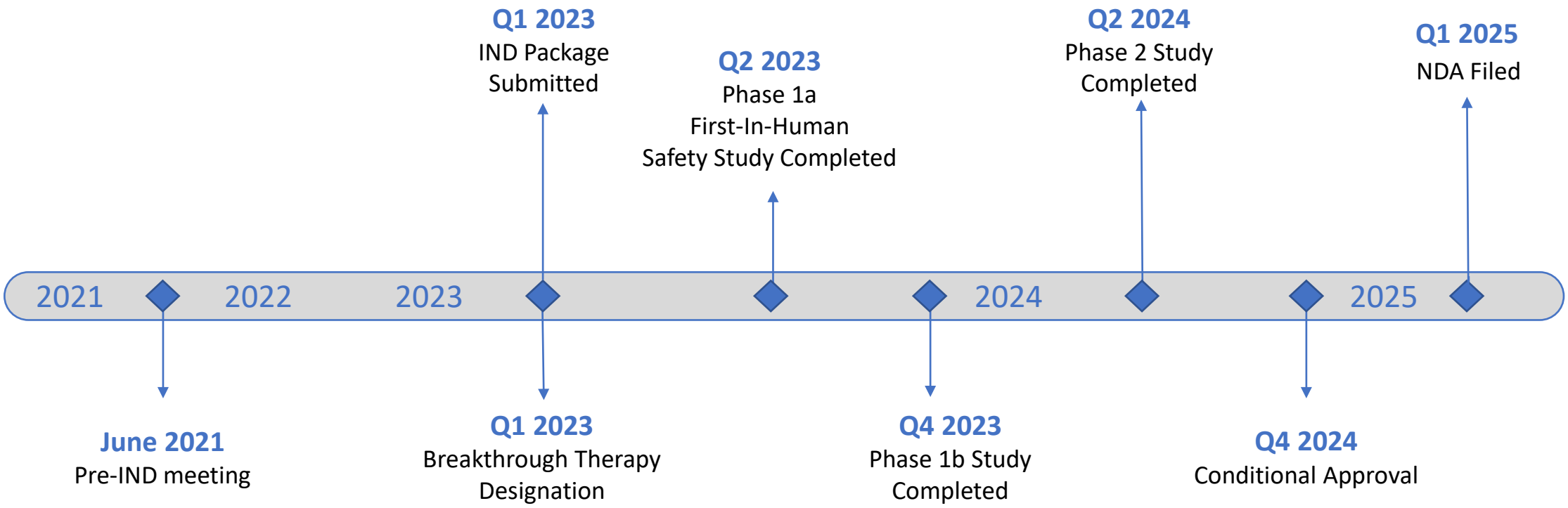
Remove the Effects: CS-1103 Reverses Acute Meth Intoxication in NHP

Remove the effects in NHP (4 mg/kg Meth dose):

- CS-1103 reverses acute intoxication effects including behavior and vital signs within 2-3 minutes
  - Reversed Meth-induced restlessness and pacing (surrogates for dysphoria)
  - Reversed Meth-induced lip-smacking and grooming (stereotypy)
  - Reversed Meth-induced hypertension and tachycardia
- The toxic effects lasted over 24h in saline control group
- CS-1103 restored normal behavior including sleeping/eating [observations over 24h]
  - Control group received saline– didn't sleep/eat, paced all night, repetitive motions
  - Treatment group received CS-1103 (200 mg/kg)- eat and sleep as usual

Summary

- Demonstrated a new approach for treating acute intoxication caused by Meth
- Identified a drug candidate CS-1103 for treating Meth intoxication
- Demonstrated safety and efficacy of CS-1103 in non-clinical studies



Questions

California Hospital Association

Thank you

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