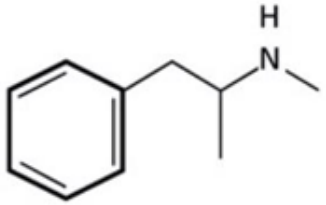
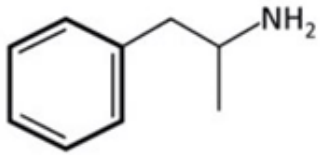
Stimulant-Related Psychosis

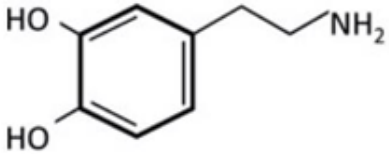
Olawale Ojo M.D MS



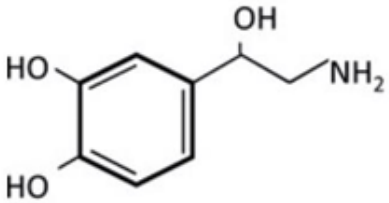
Methamphetamine



Amphetamine



Dopamine



Norepinephrine

Kevil, Art Thromb Vasc Bio, 2019

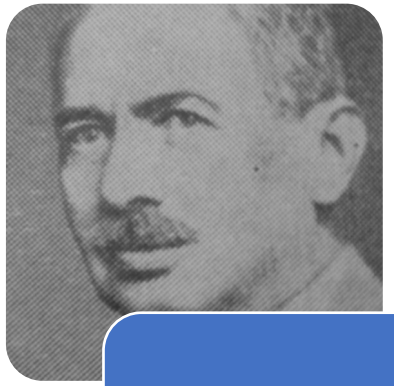
HISTORY

Ephedra sinica

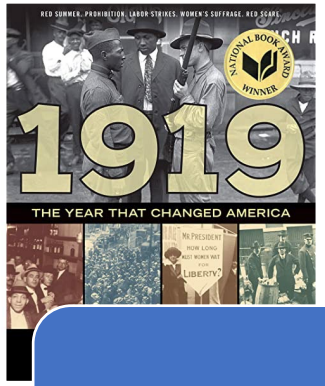
(Ma Huang)

Ephedrine isolated in 1887 by

Nagai Nagayoshi



Amphetamine synthesized by Lazar Edeleanu



- Methamphetamine synthesized by in 1919 by Akira Ogata

Benzedrine

Narcolepsy

Bronchodilator

Weight loss

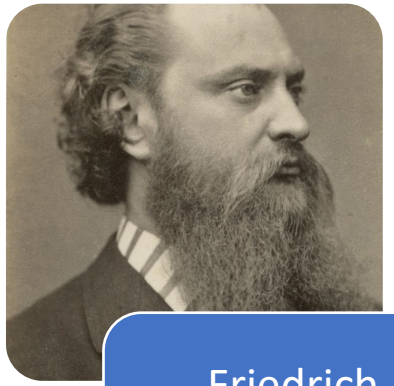
WW II

- Fatigue
- Courage and Endurance
- Performance enhancing
- Maintain wakefulness
- Kamikaze pilots
- Endemic use after WWII in Japan

- Use peaked in the 60s.
  - Beat generation (Beatnik culture), colleges, truck drivers, bikers (California gangs)
- Regulation of manufacture at the end of the decade- was classified as a Class II medication.
- Use increased dramatically in the 90s-
  - illicit manufacturing. (Farms = anhydrous ammonias)
  - Foreign production- smuggled by Mexican cartels

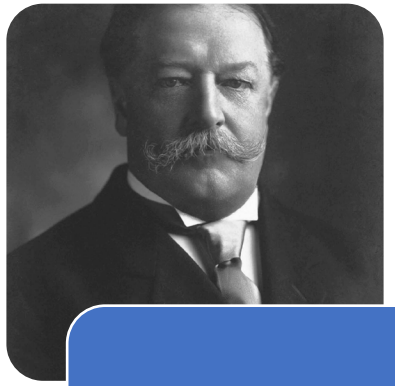
Erythroxylon Coca from the mountains of South America

Spanish Conquistadors in the 16th Century



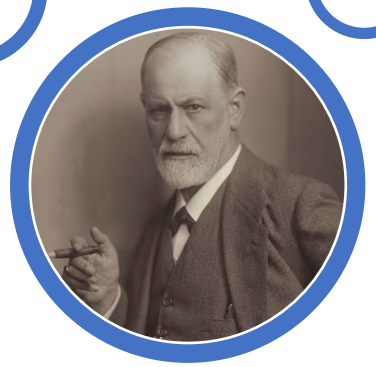
Friedrich Gaedecke extracted active component.

Albert Niemann



Harrison's Narcotic Act of 1914

Medicinal tonics

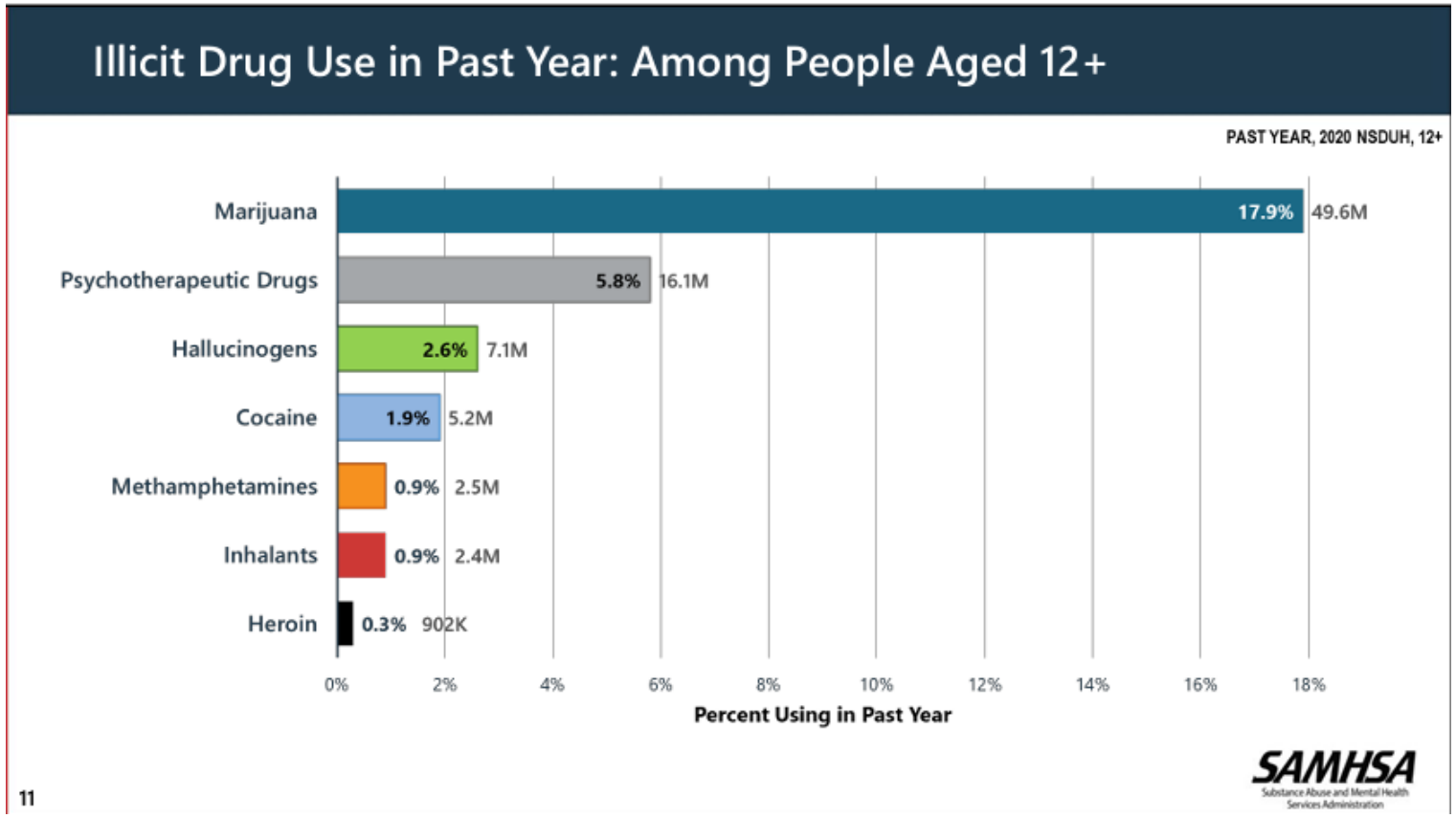


Local anesthetic

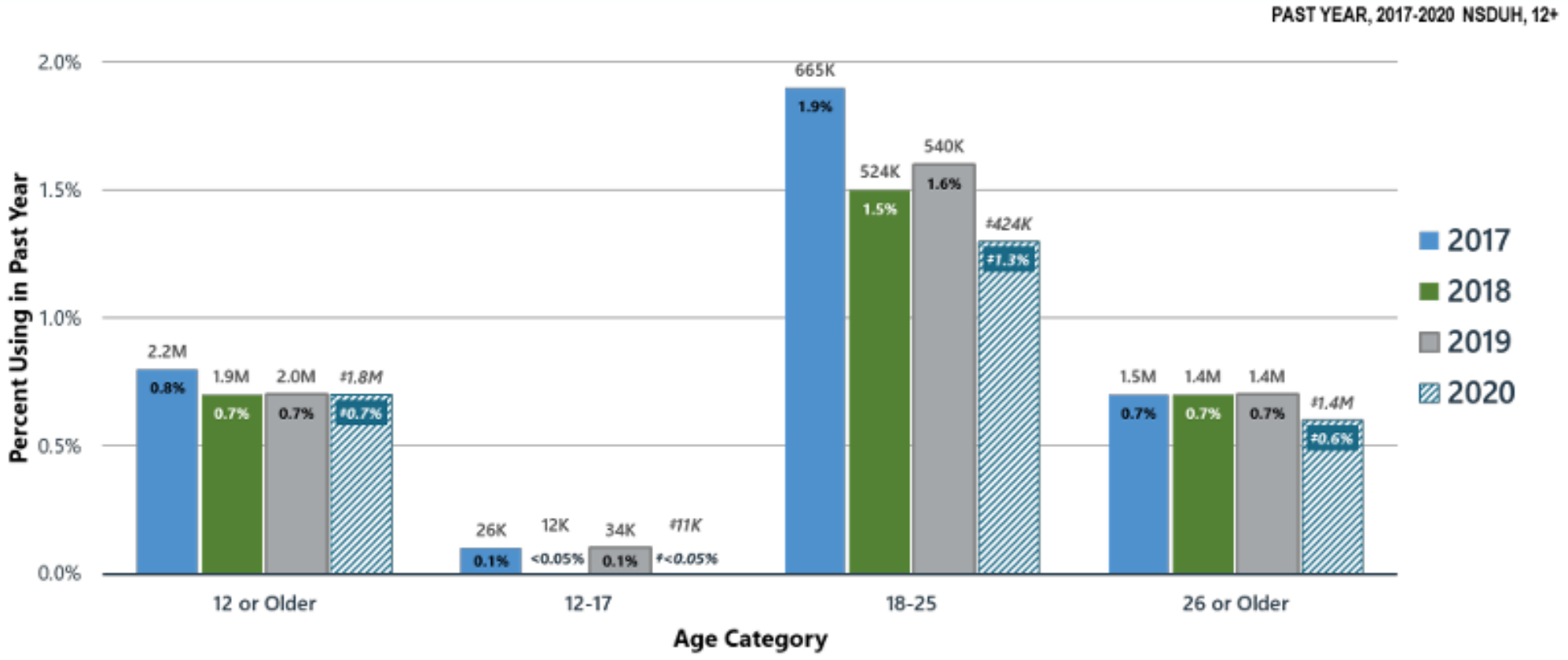
Soft drinks

- Limited use amongst Jazz musicians and the very wealthy until 1970s.
- Increased production in the 80s (estimated 3% of the population)
- Advent of “crack cocaine”
- Public awareness and celebrity deaths lead to rapid decline in use.
- Use also became increasingly criminalized.

Epidemiology



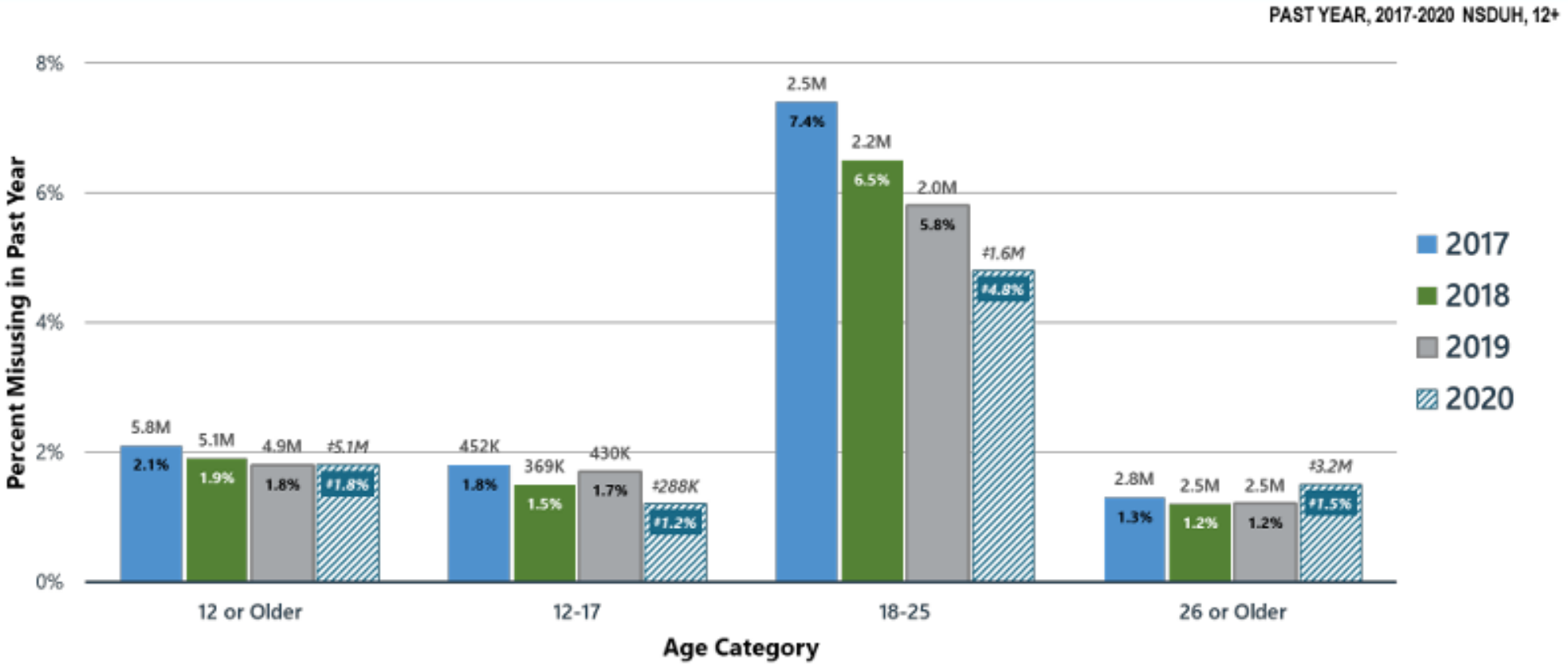
Cocaine Use in Past Year: Among People Aged 12+



‡ 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.

SAMHSA
Substance Abuse and Mental Health Services Administration

Misuse of Prescription Stimulants in Past Year: Among People Aged 12+



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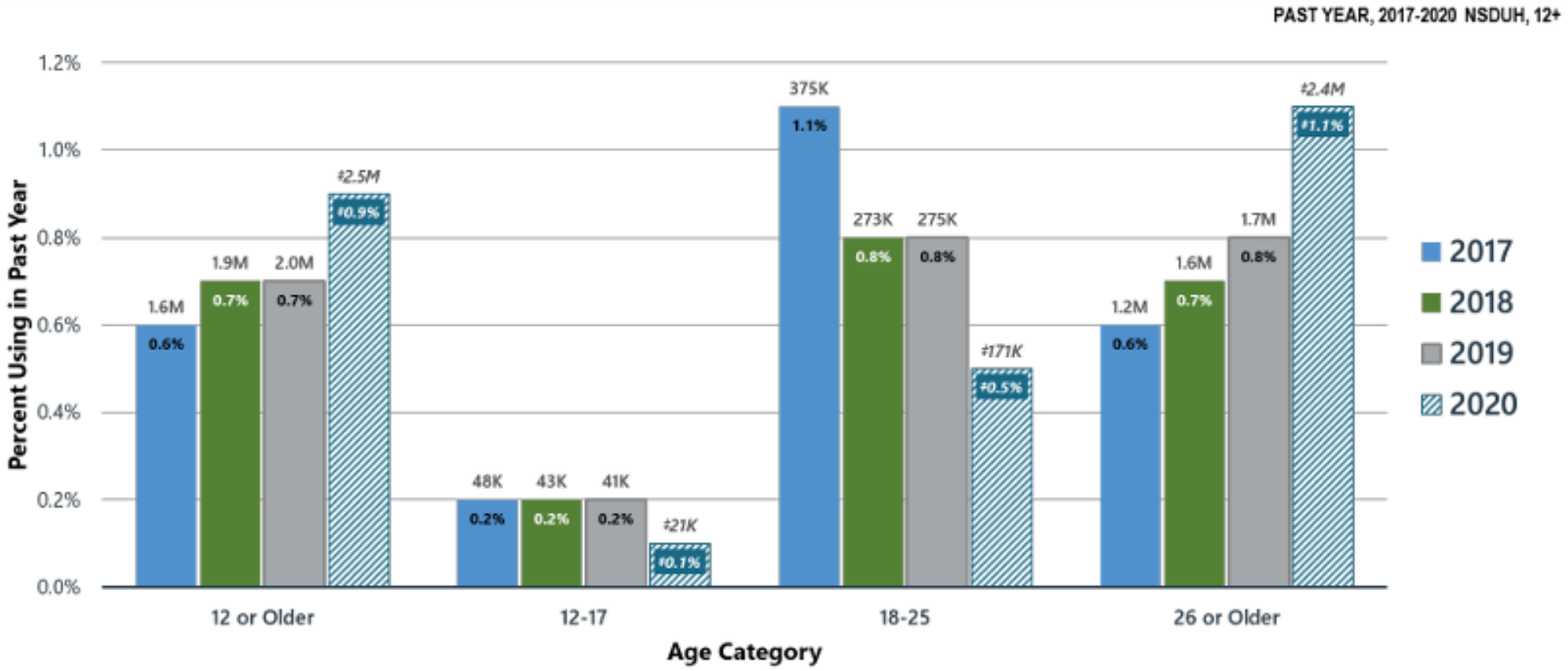
Substance Abuse and Mental Health Services Administration

Methamphetamine Use in Past Year: Among People Aged 12+



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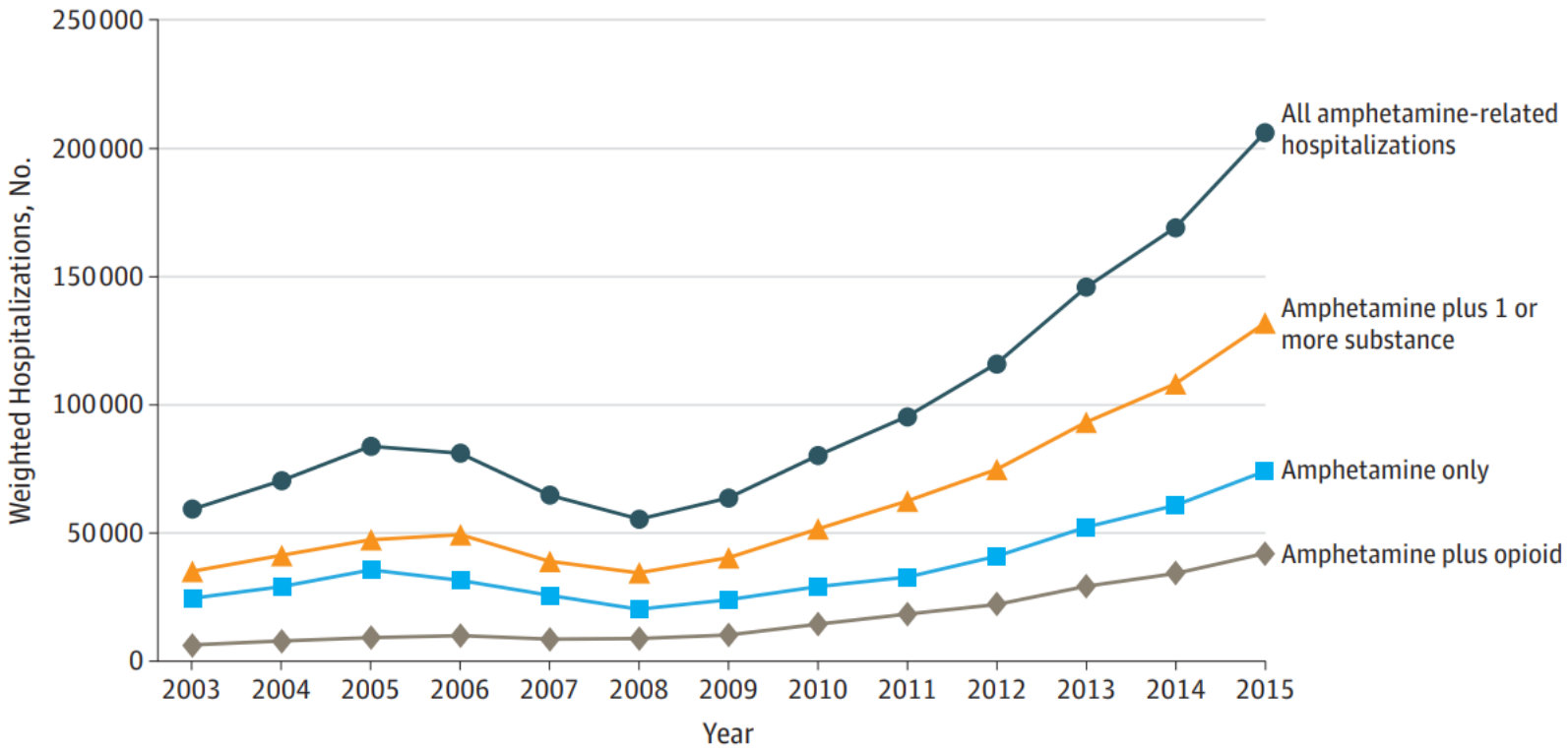
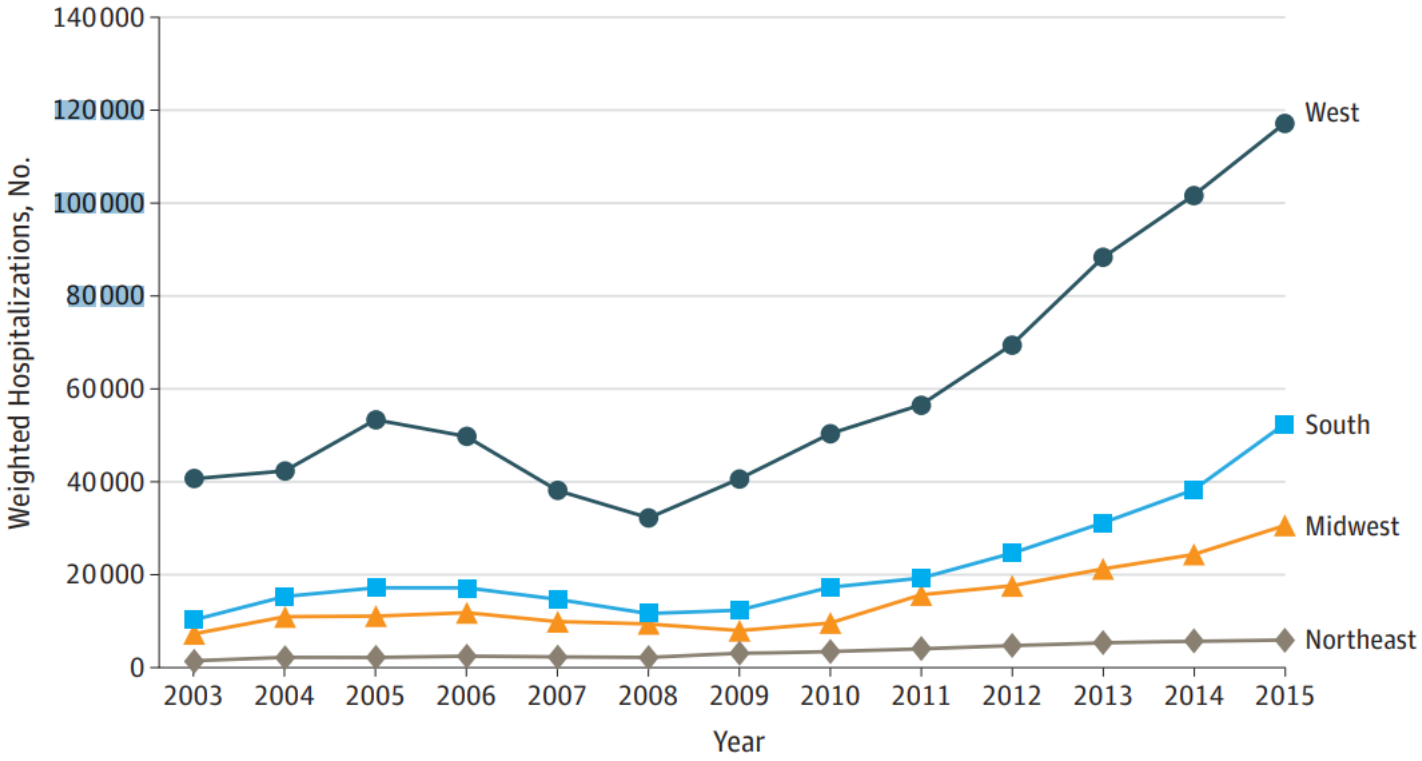
Substance Abuse and Mental Health Services Administration

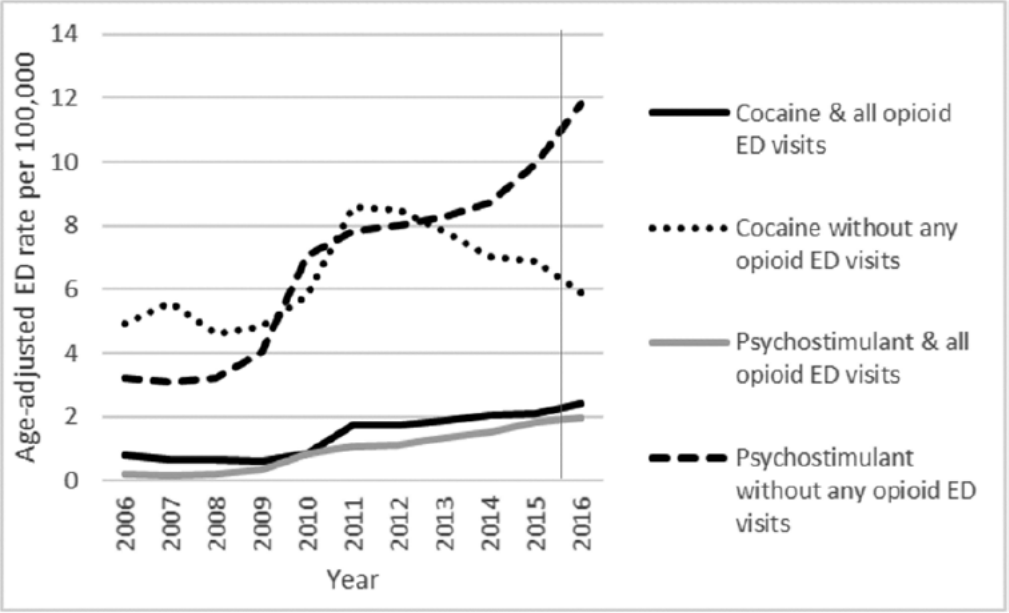
Amphetamine-Related Hospitalizations



By US Census Region



ED Visits and Mortality



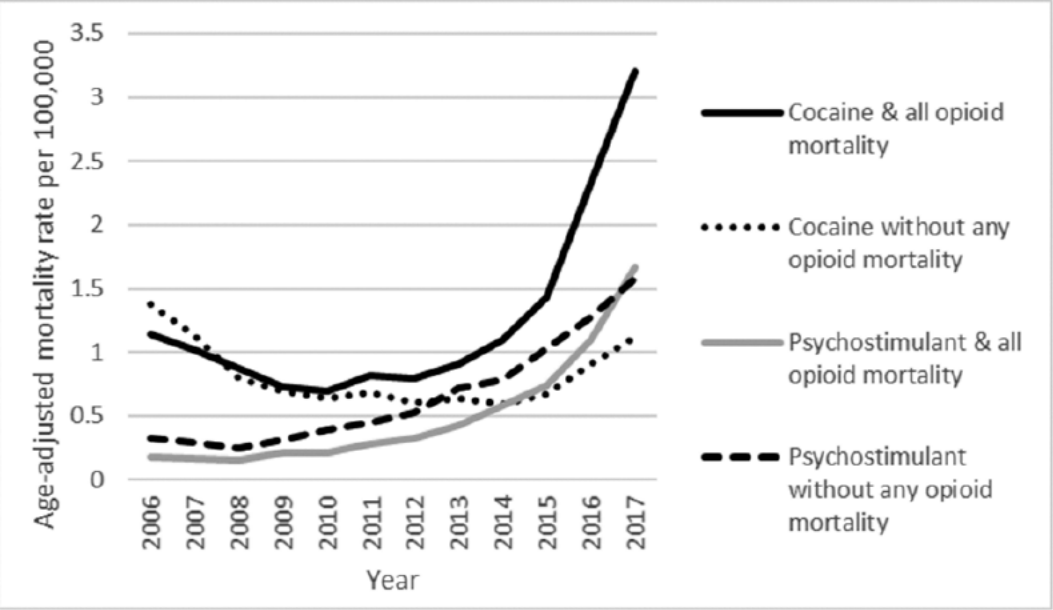
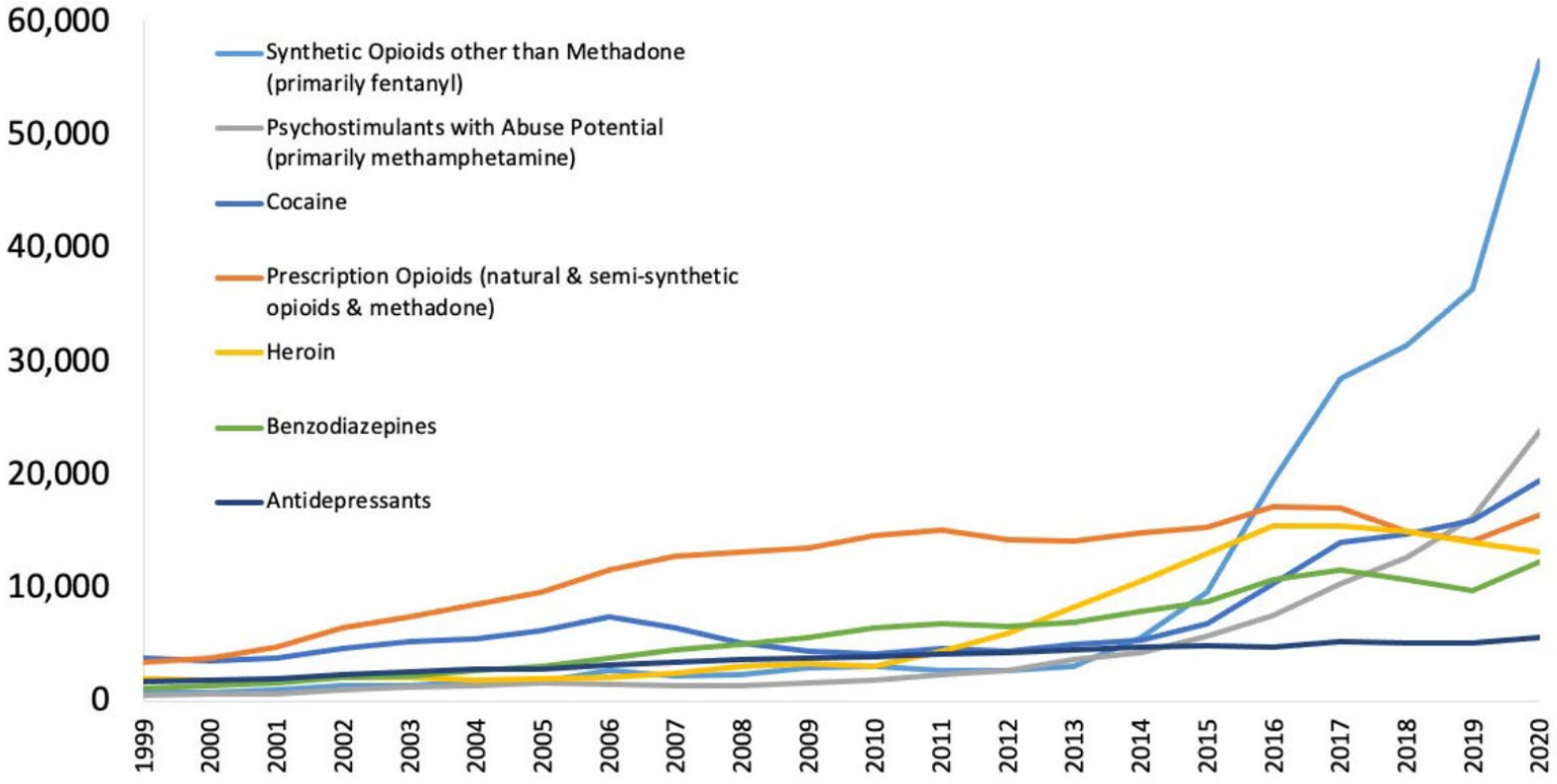
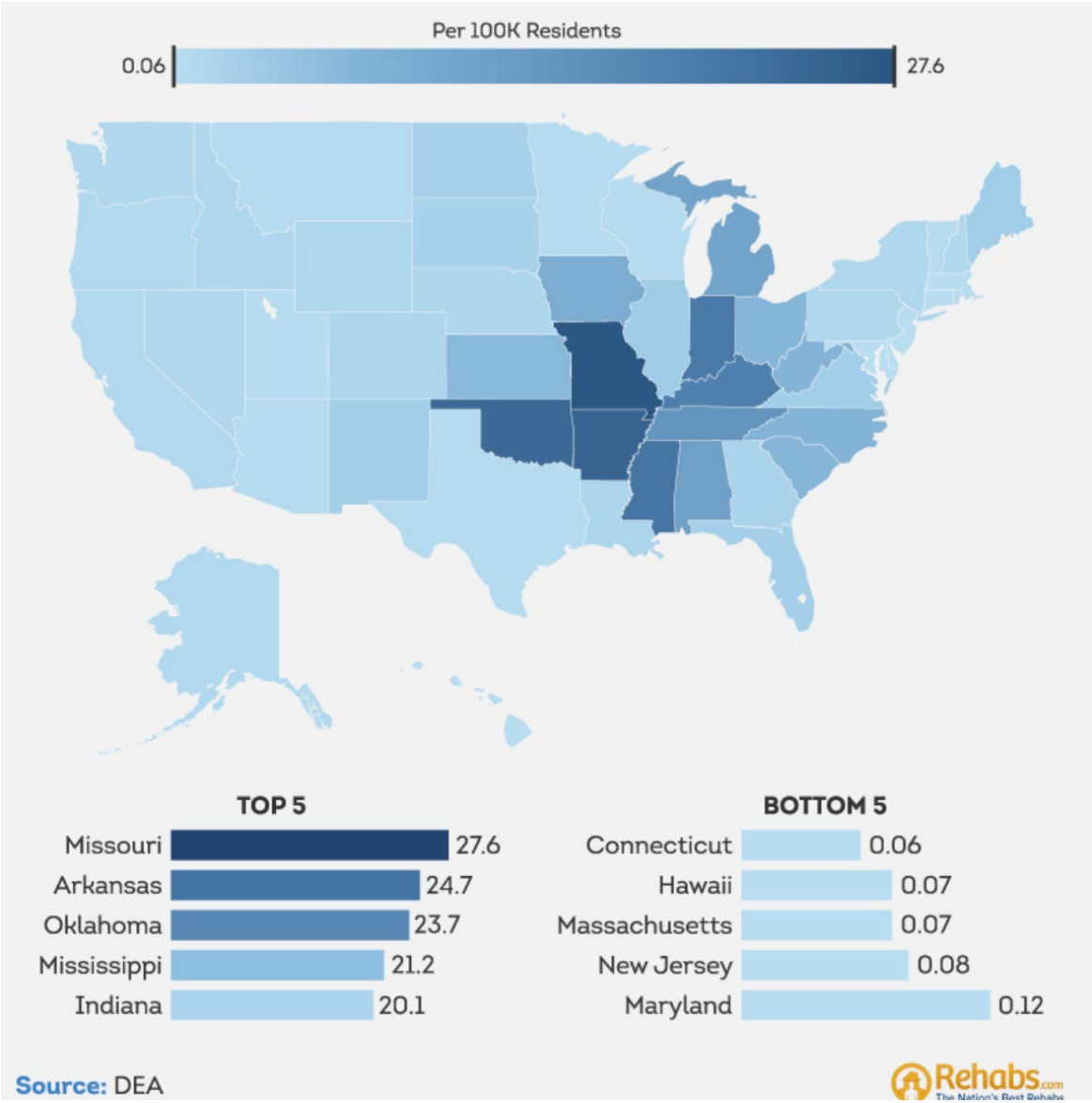


Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2020



*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.

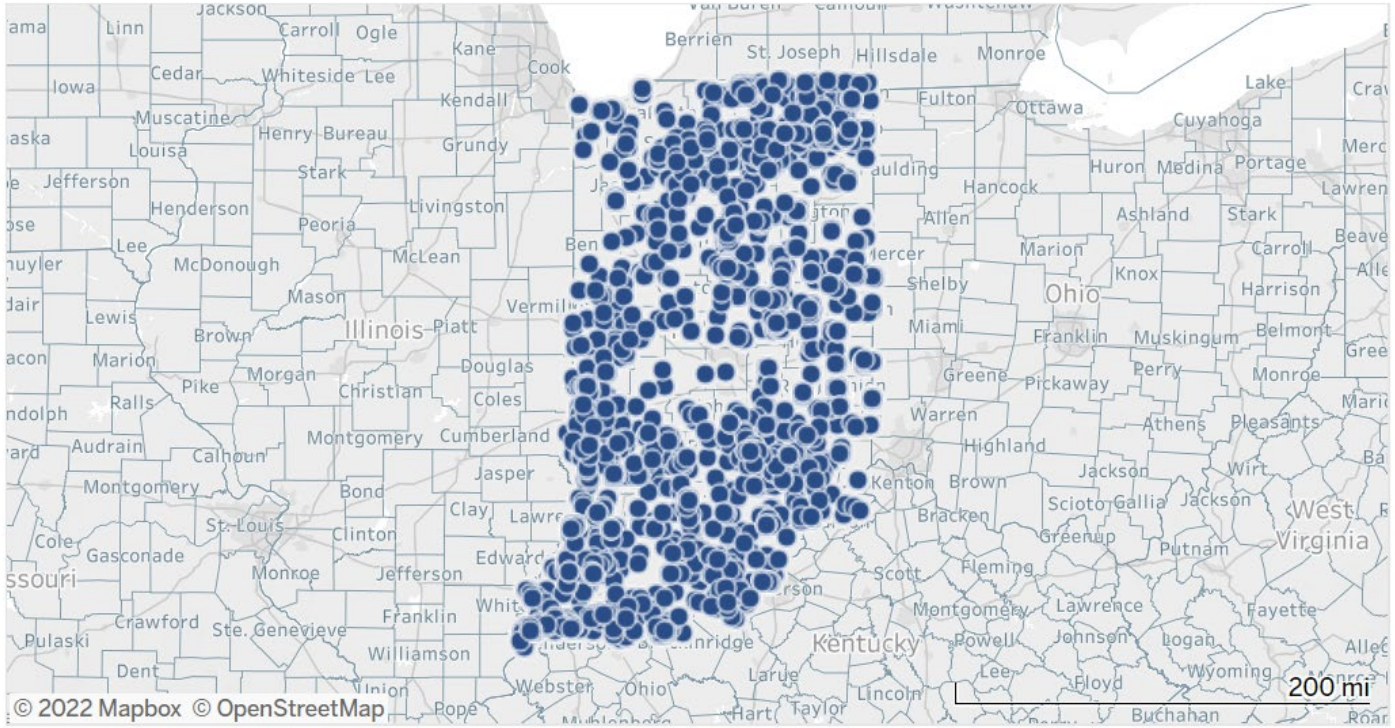

Per 100K Residents
0.06
27.6
TOP 5
Missouri 27.6
Arkansas 24.7
Oklahoma 23.7
Mississippi 21.2
Indiana 20.1
BOTTOM 5
Connecticut 0.06
Hawaii 0.07
Massachusetts 0.07
New Jersey 0.08
Maryland 0.12
Source: DEA
Rehabs.com

Clandestine drug labs (Meth Labs) 2007 to 2022

Total Statewide Distinct Lab Count: **2,520**

Last Updated: **November 1, 2022**

Selected Count(ies):	Map Type	Lab Address(es)
(All)	County Map	Highlight Lab Address(es)

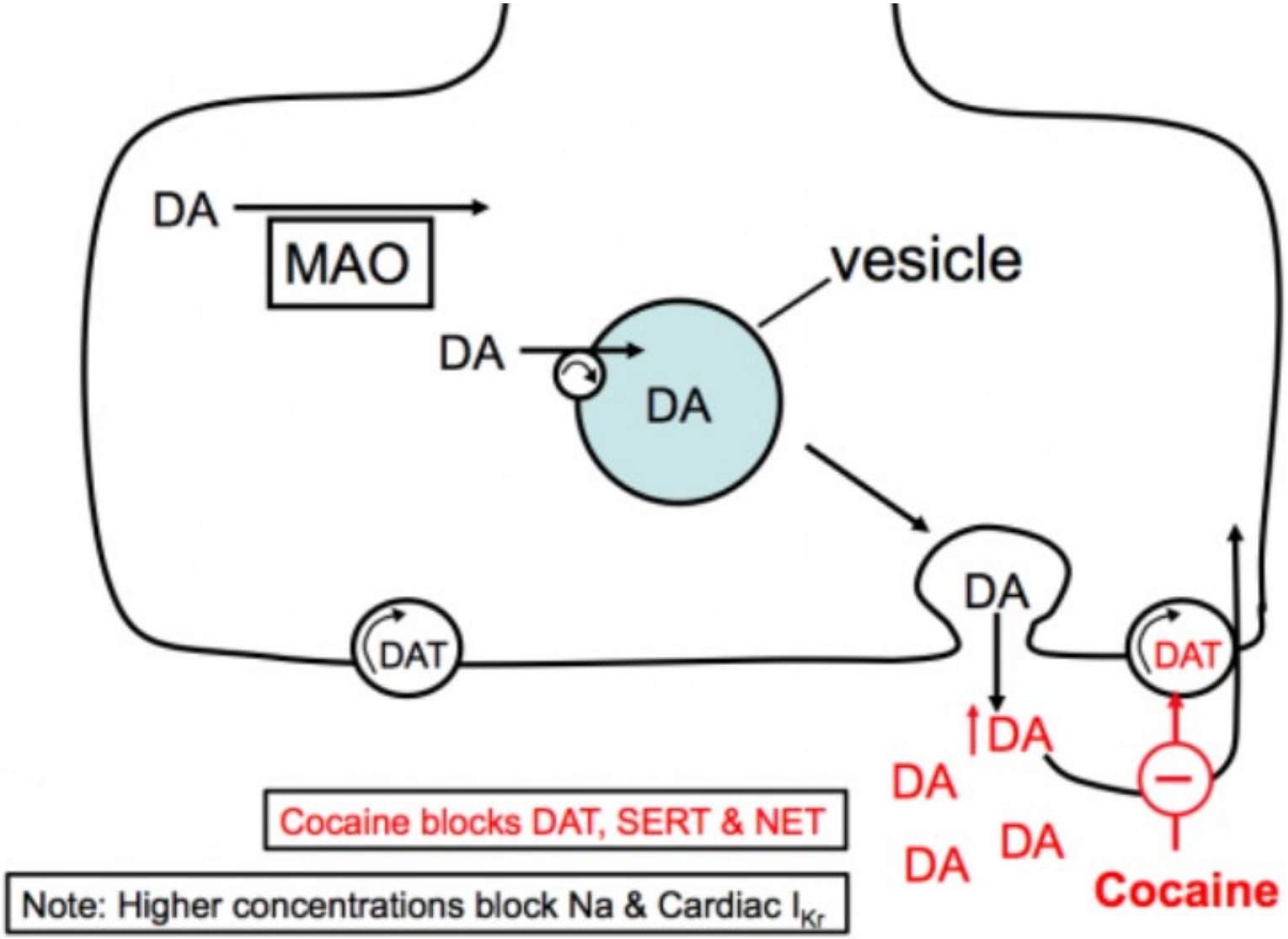


- Methamphetamine use - $2.17 billion in annual hospital costs by 2015 and higher in-hospital mortality rates.
- The U.S. economy took an estimated $23.4 billion hit from meth use in 2005, according to a RAND Corp. study.

Pharmacology

Cocaine

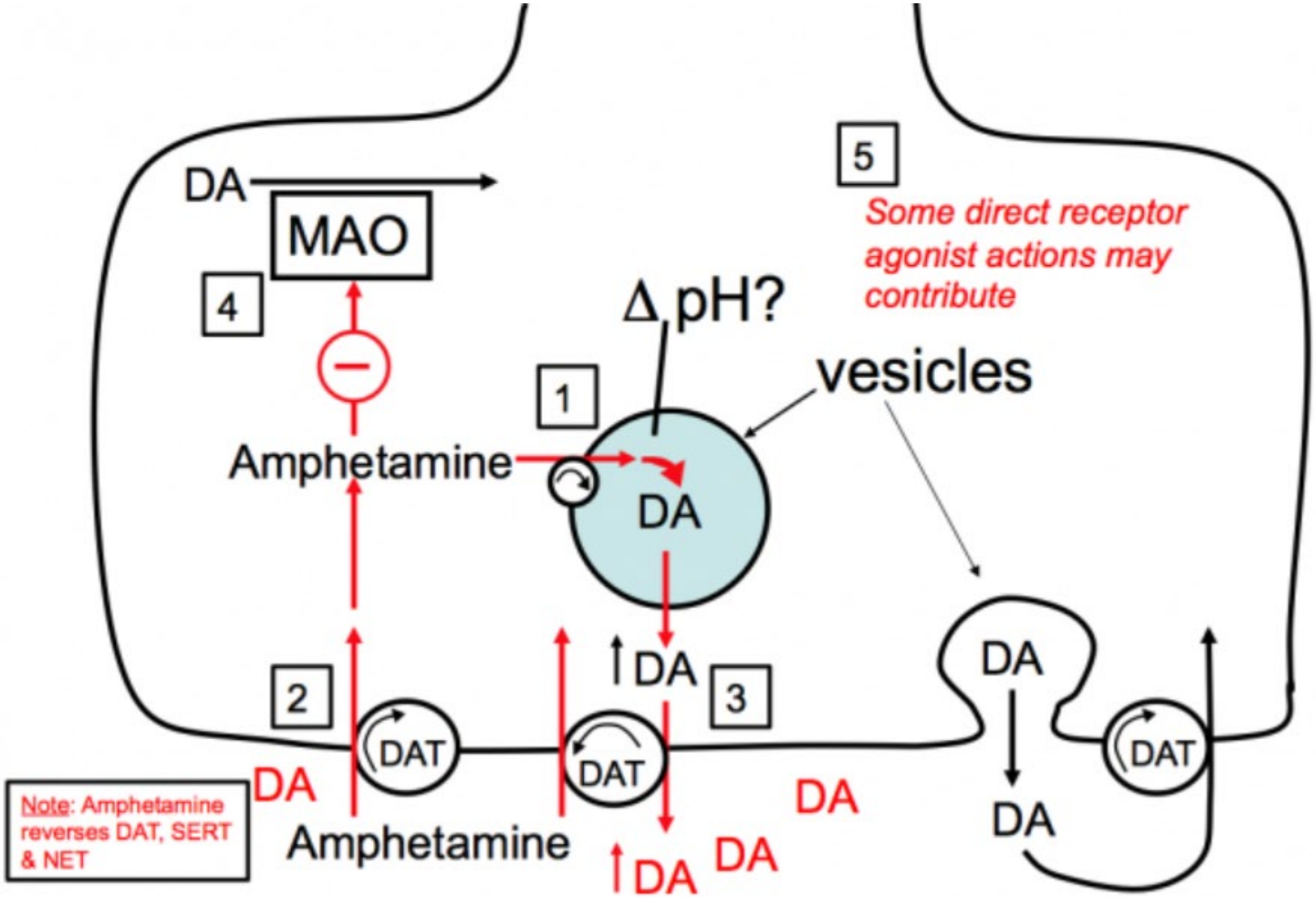
- Local anesthetic – Blocks membrane sodium channels.
- Stimulates CNS – Blocks presynaptic neurotransmitter reuptake pumps (transporters): dopamine (DAT), norepinephrine, serotonin.
- Stimulates sympathetic nervous system.
- Metabolized by esterases to benzoylecgonine (BE), excreted in urine.
- Euphoria last 20 to 30 min; Half-life of cocaine – 40-90 min
- With alcohol- cocaethylene (more toxic).


DA
MAO
vesicle
DA
DA
DA
DAT
DAT
DA
DA
DA
DA
DA
Cocaine
Cocaine blocks DAT, SERT & NET
Note: Higher concentrations block Na & Cardiac I_{Kr}

Pharmacology

Amphetamines

- Release of monoamines
- Reuptake inhibition of DA, NE & 5-HT
- Lesser MAOI effects
- Sensitization can also occur (e.g. to psychosis)
- Deplete catecholamines and 5-HT


DA
MAO
4
5
Some direct receptor agonist actions may contribute
Δ pH?
vesicles
1
Amphetamine
DA
↑DA
2
3
DA
DAT
DAT
DAT
DA
DA
DA
Amphetamine
↑DA
DA
Note: Amphetamine reverses DAT, SERT & NET

- https://www.youtube.com/watch?time_continue=50&v=TTMNXzL4O4s

- Route of administration matters- Bioavailability is 67% orally, 79% intranasal, 67 to 90% via inhalation, and 100% IV.
- Meth is designed to be lipophilic and cross the BBB fast.
- Intoxication- Amphetamine - 5-8 hours; Meth- 10-24 hours.
- Half life Methamphetamine 10–12 hours- metabolized to amphetamine.

Patterns of Use

- Patterns of use
- Binge pattern - binges 12-24 hrs to 2-3 days;
- Rapid tolerance
- Amount varies enormously from 10 mg to 1 gram or more/day
- Binges followed by “crash”

- Intoxication- Euphoria, hyperactivity (motoric & verbal), hypersexuality, Insomnia, increased alertness, decreased appetite, skin picking, teeth grinding, increased risk taking.

- Withdrawals- Dysphoria, anhedonia, fatigue, increased appetite, slowed psychomotor activity.

Neuropsychiatric Effects

- Acute: sustained sympathetic activation
  - Strokes, seizures, hyperthermia
  - **Psychosis** related to dopamine increase
- Chronic: sustained/repeated monoamine release
  - High dopamine + hyperthermia= neurotoxic nerve terminal damage
  - Fine motor movements deficit
  - Impairments in neuropsychological testing: most notably verbal learning, executive function, episodic memory

Dopamine Hypothesis for Psychosis

In the mesolimbic pathway-

- Excessive dopamine causes positive symptoms of schizophrenia
- Blocking dopamine with antipsychotics reverses psychosis

DSM V Criteria for Substance Induced Psychosis

- Presence of
  - Hallucinations
  - Delusions
- Symptoms develop during intoxication or withdrawal
- Substance can produce psychosis

Stimulant- Induced Psychosis

- Clear consciousness; rarely confused
- Minimal formal thought disorder
- Persecutory delusions
- Hallucinations- all forms
- Persistent Psychosis is possible

Clinical pearls

- Do not attempt to confirm psychiatric diagnosis while intoxicated or in withdrawals within 3-4 weeks of substance use.
- Verify drug free state with laboratory testing.
- Obtain careful longitudinal history tracking for both substance use and psychiatric symptoms.
- Utilize collateral sources of information.
- Review family history.
- For Substance induced psychosis
  - Within 30 days of intoxication or withdrawals.
  - Symptoms associated with substance involved.

Clinical course

- first group- Duration of symptoms are limited to a maximum period of 4 to 5 days after the intoxication, which can be seen in the withdrawal or intoxication periods. (64%)
- second group, psychotic symptoms can be resolved in less than a month (82%)
- In the third group, symptoms could be of much longer duration of up to several months, or of several years – 18%

Transition From Substance Induced Psychosis

- A total of 50 studies (including 25 studies of substance-induced psychosis) with 79 estimates of transition to schizophrenia among almost 41,000 people. The median follow-up period was 4 years. Mean study age was 28 and 61% of participants were male.
- Overall, 25% (95% CI 18-35%) of people with substance-induced psychosis had a follow-up diagnosis of schizophrenia
- The risk of transition to schizophrenia was highest for cannabis (34%), hallucinogens (26%), and **amphetamines (22%)** and lowest for alcohol (9%) and sedatives (10%).

Treatment of Stimulant induced psychosis

- A Systematic Review- Fluyau et al
  - 6 RCTs, 314 participants- aripiprazole, haloperidol, quetiapine, olanzapine, and risperidone.
  - Suggests most antipsychotics are effective
  - Although the side-effect profile of these agents varied, no drug was clinically superior to others.
- Minocycline- case reports and case series

Medications for Stimulant Use

No FDA approved medications.

- **Naltrexone**
- Topiramate
- **Bupropion (low intensity users)**
- **Mirtazapine**
- Riluzole
- Methylphenidate
- Topiramate (abstinent at start of treatment)
- Modafinil
- Studies on Combination of Bupropion and naltrexone
- Disulfiram for cocaine

Therapies

- Contingency management
- Cognitive behavioral therapy
- MATRIX model- 16 weeks of IOP with CM, 12-STEPS and CBT
- Community Reinforcement Approach (CRA)
- 12-step facilitation
- Motivational interviewing

Question

42-year-old woman presents to the ED with complaints of auditory hallucinations of the Freddie Krueger's voice. She looks arounds suspiciously. She tell you that the voices are not real and are a result of methamphetamine 6 hours ago. She has used methamphetamine since college to keep up with stress/work demands. Recently increased meth use to 2-3 days a week. She has no previous psychiatric history. What is the diagnosis?

A. Methamphetamine induced Psychotic disorder
B. Schizophrenia
C. Methamphetamine intoxication with hallucinations
D. Bipolar disorder

Clinical Pearl

- If patient has insight into symptoms of psychosis and symptoms occur within intoxication/withdrawal period, the right description is Stimulant intoxication with psychosis/hallucinations

Questions?

- https://www.nytimes.com/2009/02/05/us/05meth.html?_r=0
- Rippeth, J. D., et al. (2004). "Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons." J Int Neuropsychol Soc 10(1): 1-14.
- Rusyniak, D. E. (2011). "Neurologic manifestations of chronic methamphetamine abuse." Neurol Clin 29(3): 641-655
- Winkelman TNA, Admon LK, Jennings L, Shippee ND, Richardson CR, Bart G. Evaluation of Amphetamine-Related Hospitalizations and Associated Clinical Outcomes and Costs in the United States. JAMA Netw Open. 2018;1(6):e183758. doi:10.1001/jamanetworkopen.2018.3758
- Zarrabi H, Khalkhali M, Hamidi A, Ahmadi R, Zavarmousavi M. Clinical features, course and treatment of methamphetamine-induced psychosis in psychiatric inpatients. BMC Psychiatry. 2016 Feb 25;16:44. doi: 10.1186/s12888-016-0745-5. PMID: 26911516; PMCID: PMC4766712.

- Murrie, B.C., Lappin, J.M., Large, M., & Sara, G. (2019). Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-analysis. Schizophrenia Bulletin, 46, 505 - 516.
- https://pubmed.ncbi.nlm.nih.gov/20851278/
- Fluyau D, Mitra P and Lorthe K (2019) Antipsychotics for Amphetamine Psychosis. A Systematic Review. Front. Psychiatry 10:740. doi: 10.3389/fpsyt.2019.00740