ASAM REVIEW COURSE 2025

Stimulant Use Disorders: From Neurobiology to Public Health

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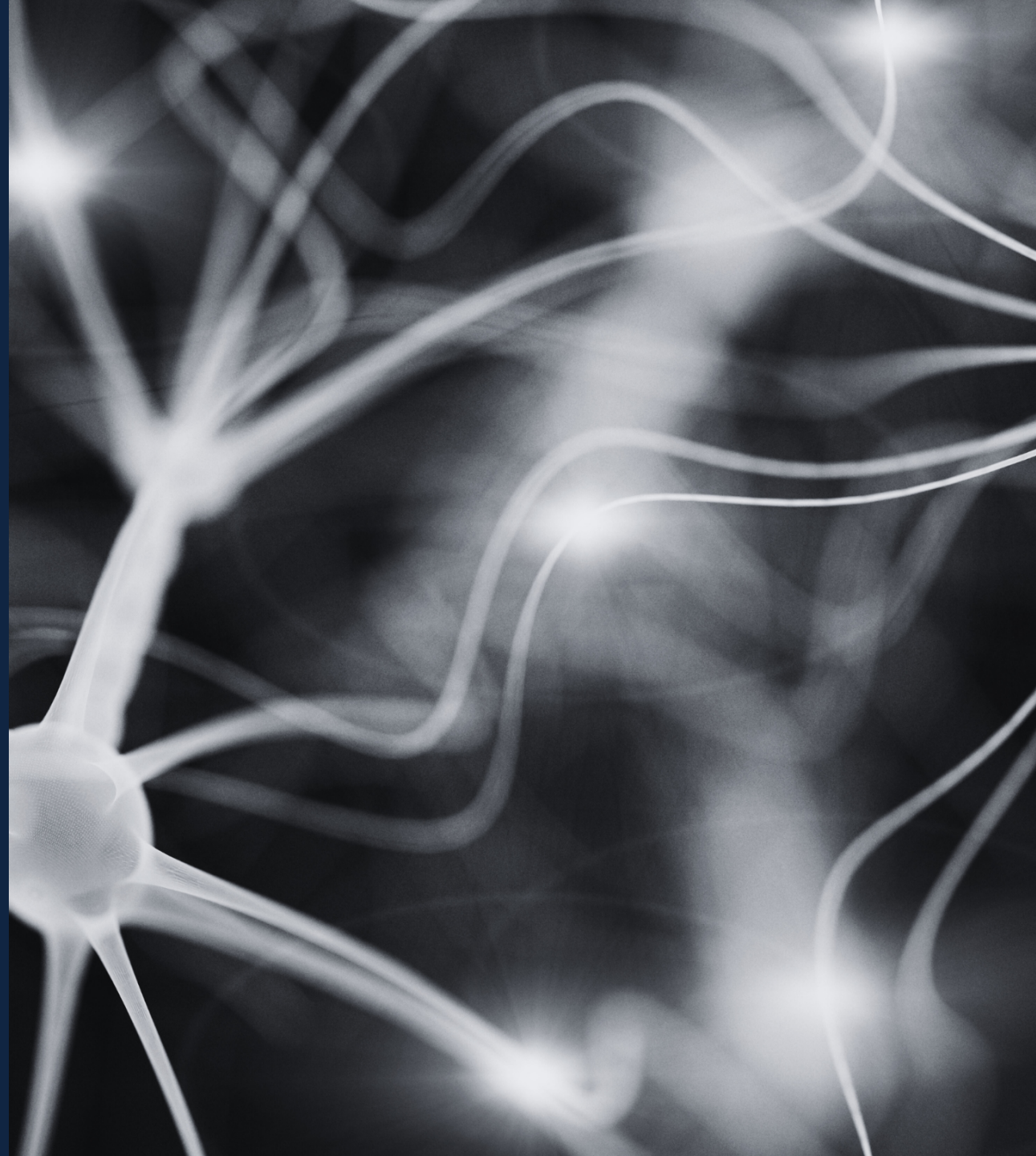


Financial Disclosure

Siddarth Puri, MD

- No relevant disclosures

General Outline

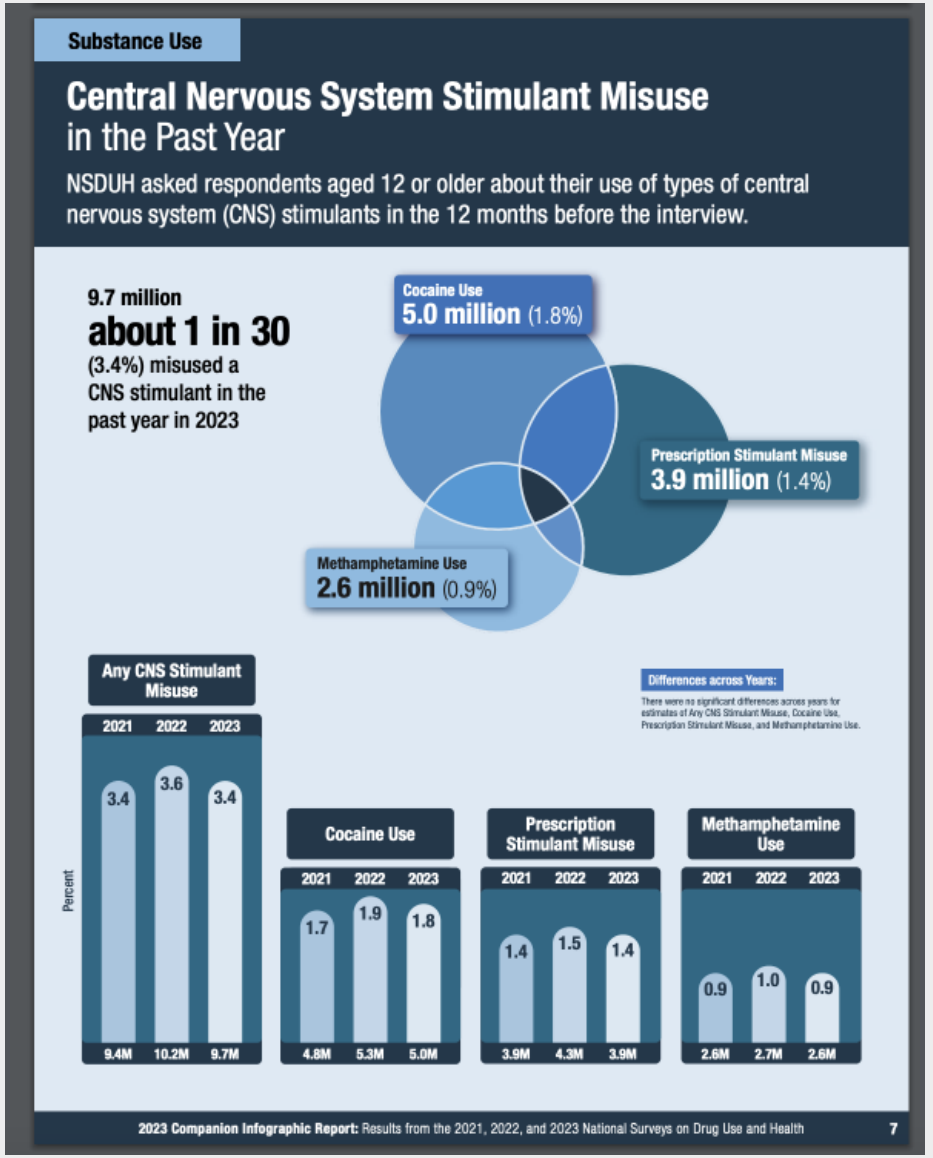
- Cocaine
- Methamphetamine
- MDMA
- Bath Salts

Topics Covered for Each Substance

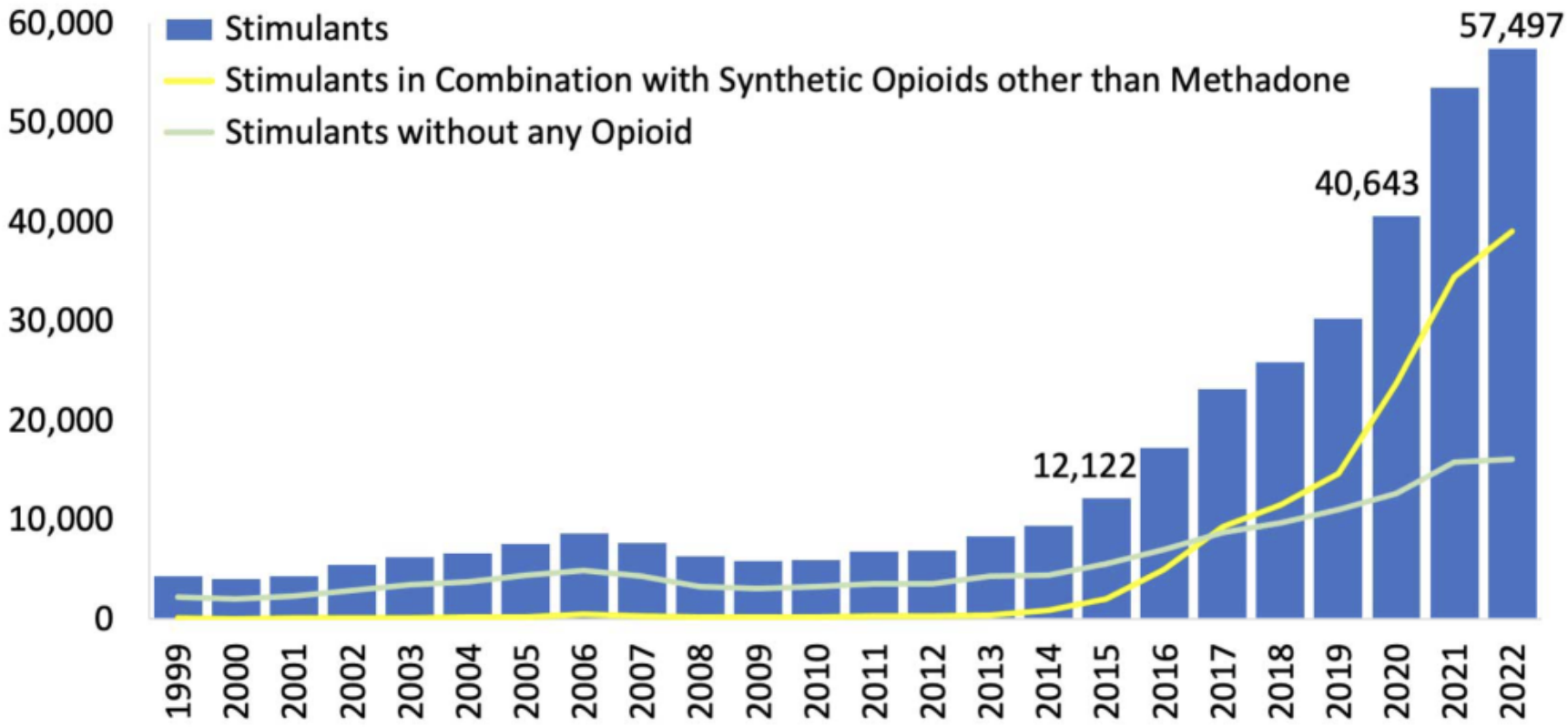
- Formulations and Methods of Use
- Pharmacokinetics and Metabolism
- Desired and Adverse Effects
- Chronic and Withdrawal Effects
- Neurobiology
- Treatments

Epidemiology

- National Survey on Drug Use and Health (NSDUH)
- The majority of people using stimulants are using Cocaine.
- Slight reduction in stimulant misuse.



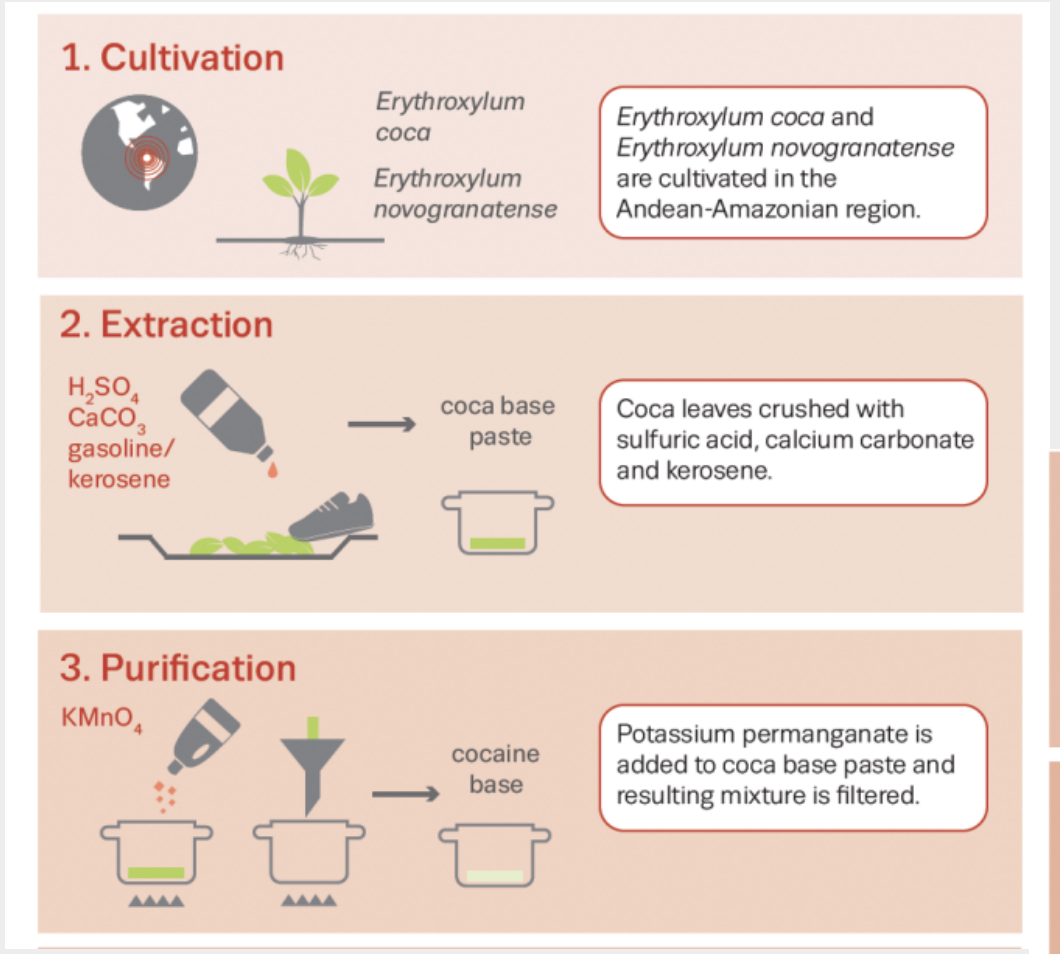
US Overdose Deaths Involving Stimulants (cocaine and psychostimulants)

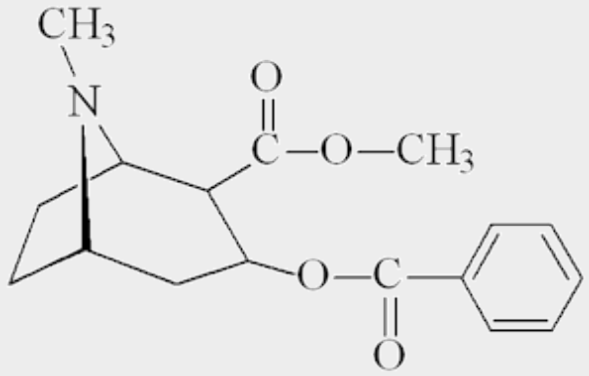


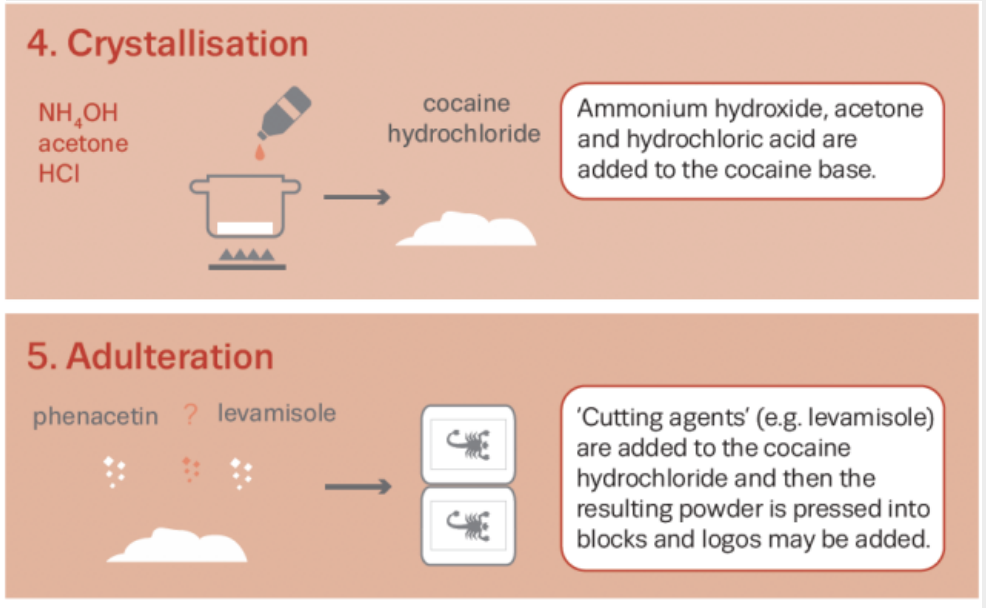
*Among deaths with drug overdose as the underlying cause, the psychostimulants with abuse potential (primarily methamphetamine) category was determined by the T43.6 ICD-10 multiple cause-of-death code. Abbreviated to *psychostimulants* in the bar chart above.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2022 on CDC WONDER Online Database, released 4/2024.

Cocaine

Cocaine: Plant Based Alkaloid



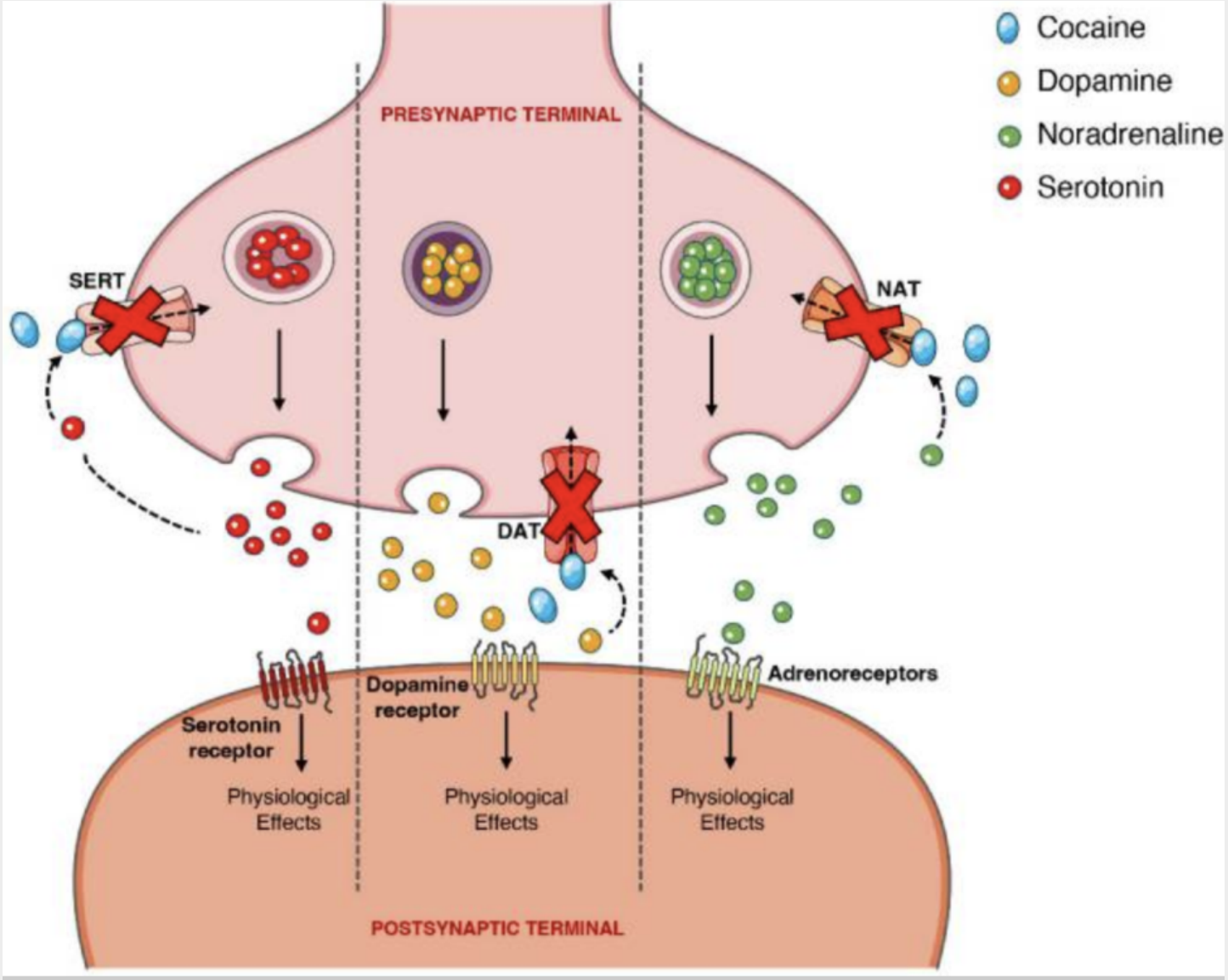




Crack Cocaine vs Cocaine

Category	Crack	Cocaine
Formulation	Powder cocaine mixed with water & baking soda (free base) creating “rocks”	Powder or liquid solution
Method of Use	Smoked	Snorted or Injected
Pharmacokinetics	Instant effects, lasts 5-10 min	Snorting: 3-5 min onset, lasts 15-30 min Injecting: 15-30 sec onset, lasts 20-60 min
Rate Hypothesis and Addiction Potential	Highly psychologically addictive due to **rapid onset**	Less psychologically addictive than crack due to slower onset
Cost depends on location/demand.**	$10-$25 per 1/10 gram ('rock'); $40 per 1/4 gram	$120+ per 1/8 ounce (3.5g) ('8-ball')
Cutting Agents	Glucose, sucrose, talc, inositol, benzocaine, lidocaine, levamisole, ephedrine, Ritalin	Similar to crack; may include boric acid, tetracaine, and procaine

Cocaine: Mechanisms of Action



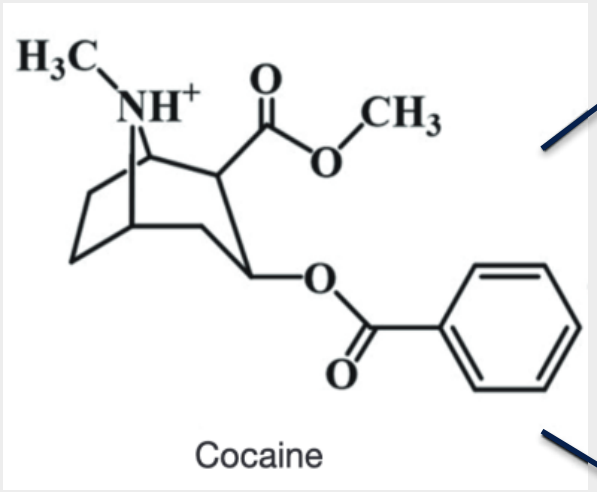
Cocaine: Neurotransmitters

Neurotransmitter	Effect on Neurotransmitter	Impact on Behavior
Dopamine (DA)	Blocks dopamine reuptake in the nucleus accumbens → Increased synaptic dopamine	Euphoria, pleasure, reward, craving
Norepinephrine (NE)	Blocks NE reuptake → Sympathetic nervous system activation	Increased heart rate, blood pressure, energy, alertness
Serotonin (5-HT)	Blocks serotonin reuptake (less pronounced than DA/NE)	Mood elevation, reduced appetite, possible paranoia
Glutamate	Increases glutamate activity in reward circuits	Increased excitability, drug-seeking behavior
GABA	Inhibits GABAergic interneurons, leading to greater dopamine release	Reduced impulse control, heightened stimulation

Cocaine Desired Effects

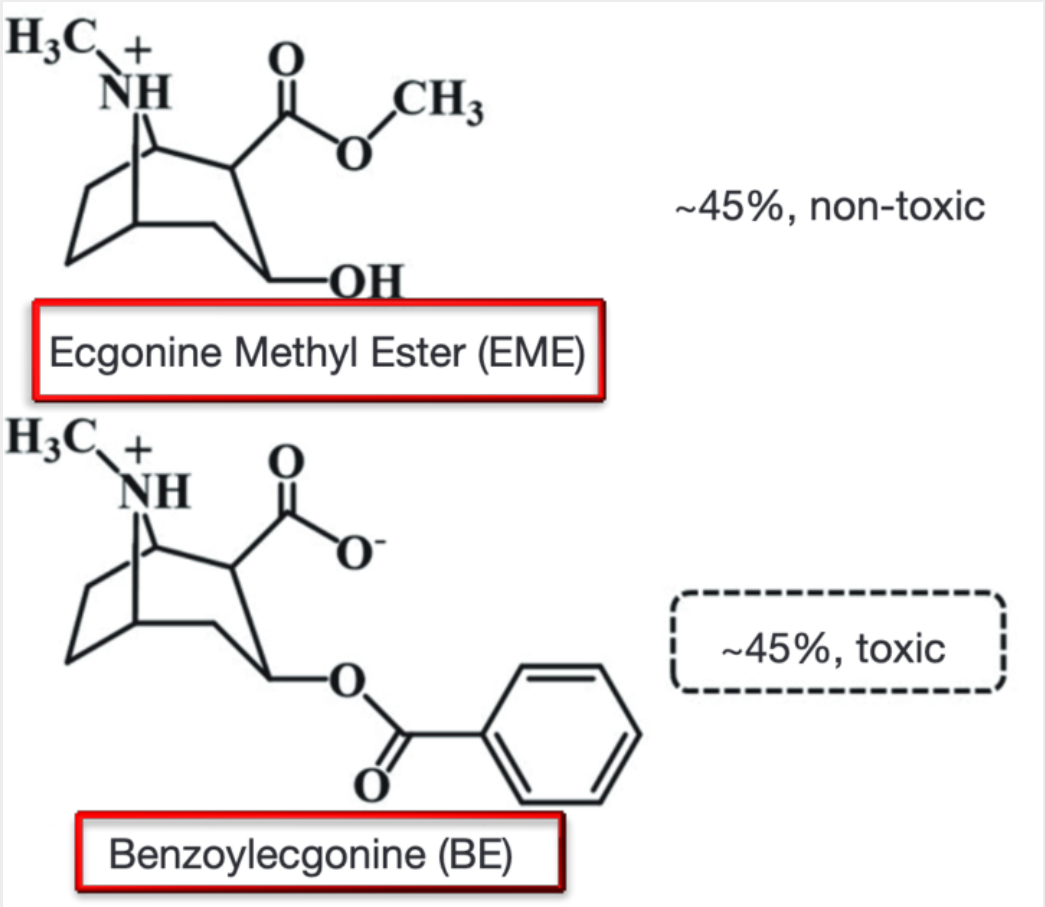
- **Euphoria:** Intense feelings of pleasure, well-being, and confidence.
- **Increased Energy & Alertness:** Reduces fatigue and enhancing wakefulness.
- **Enhanced Focus & Mental Clarity:** Temporary improvements in attention and cognitive function.
- **Increased Sociability & Talkativeness:** Feeling more outgoing, confident, and engaged in conversations.
- **Appetite Suppression:** Reduces hunger and leading to weight loss with chronic use.
- **Improved Physical Performance:** Temporary increase in stamina and strength
- **Heightened Sensory Perception:** Colors may appear brighter, sounds clearer
- **Reduced Need for Sleep:** Prolongs wakefulness
- **Heightened Libido:** Amplifies sexual desire and performance

Cocaine: Metabolism



Plasma cholinesterase

Ester hydrolysis



Other small metabolites: Norcocaine, p-hydroxycocaine, m-hydroxycocaine, p-hydroxybenzoylecgonine

Cocaine Adverse Effects

- Psychological:
  - Paranoia can occur in >50% of heavy users
  - Can persist for hours, even after drug effects wear off.
  - Often includes persecutory delusions, hypervigilance, and tactile hallucinations (e.g., formication, “coke bugs”).
- Tachycardia, Hypertension, MI
- Stroke
- Hyperthermia, Rhabdomyolyses
- Organ Failure

Cocaine: Tolerance

- **Acute Tolerance**: Rapid decrease in response after initial use.
  - **Complete**: Euphoria diminishes with repeated doses in a session.
  - **Incomplete**: Increased heart rate still occurs but to a lesser extent.
- **Reverse Tolerance (Kindling Effect)**: Sensitization to certain CNS effects.
  - **Paranoia, Seizures, Stereotyped Behaviors**: More likely with repeated exposure.

Cocaine and Culture

Affluent & Professional Circles ("High-Functioning" Use)

- Often associated with wealth, power, and status, making it prevalent in corporate, finance, entertainment, and high-income social circles.
- Used to enhance productivity, confidence, and endurance in competitive work environments.
- Often viewed as a "party drug" but can lead to functional dependence over time.

Club , Rave, & Party Scene

- Commonly used with alcohol, MDMA, and ketamine to prolong the party experience.
- Snorted or combined with other drugs, increasing overdose risk.
- Often marketed as a "luxury" stimulant in nightlife settings.

Cocaine and Culture

LGBTQ+ Communities (Club & Chemsex Use)

- Cocaine is popular in gay nightlife and chemsex scenes, though less commonly associated with sexual enhancement than meth.
- Used to increase confidence, social energy, and reduce inhibitions.
- High risk of polysubstance use (alcohol, GHB, poppers, MDMA).

Communities experiencing homelessness/ lower social economic status: Crack Cocaine Use

- Crack cocaine, a cheaper and more potent form of cocaine, is more common in economically disadvantaged populations.
- Crack produces an intense but short-lasting high, leading to frequent re-dosing and compulsive use.
- Historically, racialized drug policies led to disproportionate criminalization of crack cocaine vs. powder cocaine.

Cocaine Intoxication

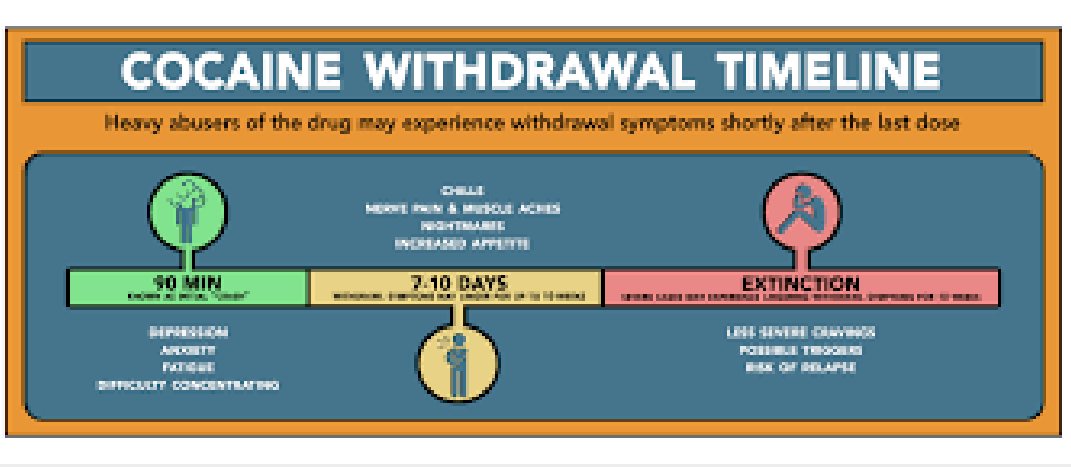
- Recent Stimulant use
- Two or more of the following
  - Tachycardia or bradycardia
  - Pupillary dilation
  - Elevated or lowered blood pressure
  - Perspiration or chills
  - Nausea or vomiting
  - Evidence of weight loss
  - Psychomotor agitation or retardation
  - Muscular weakness, respiratory depression, chest pain or cardiac arrhythmias
  - Confusion, seizures, dyskinesias, dystonia or coma

Cocaine withdrawal

A. Cessation of (or reduction in) prolonged amphetamine-type substance, cocaine or other stimulant use

B. **Dysphoric mood and two (or more)** of the following physiological changes, developing within **hours to several days** after criterion A,

1. **Fatigue**
2. **Vivid, unpleasant dreams**
3. **Insomnia or hypersomnia**
4. **Increased appetite**
5. **Psychomotor retardation, or agitation**

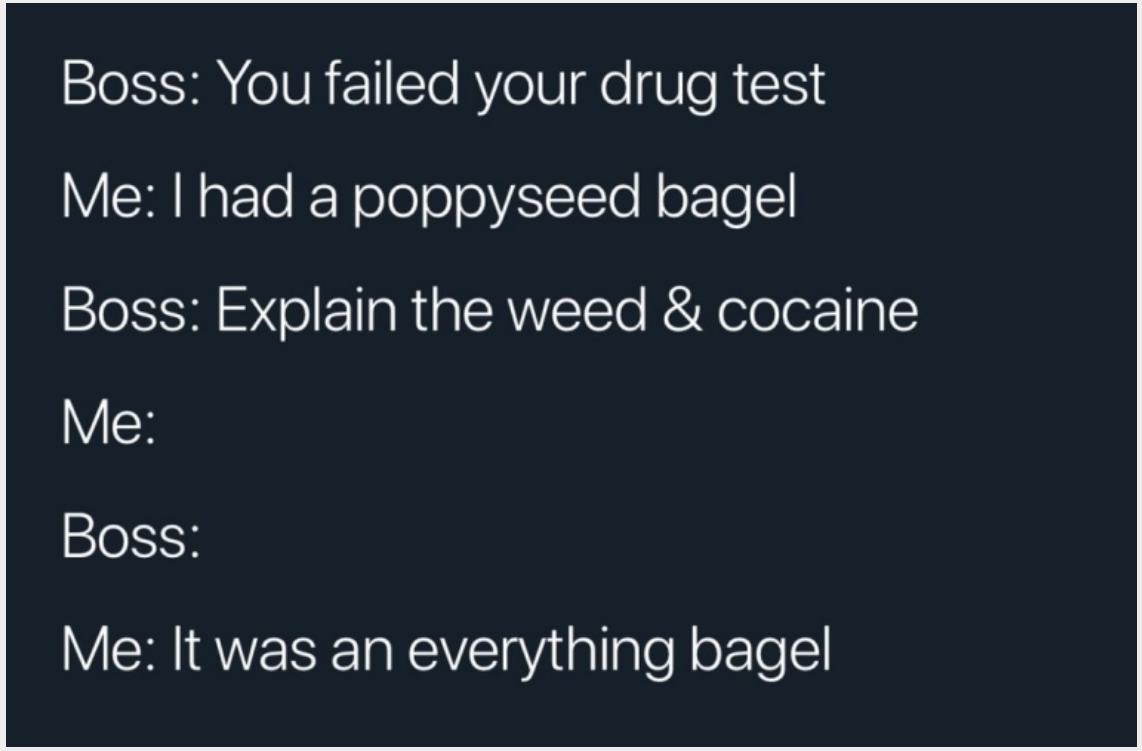


C. Signs and symptoms cause clinically significant distress and impairment in social, occupational, or other important areas of functioning

D. Signs and symptoms not attributable to another medical condition, mental disorder or **intoxication or withdrawal** from another substance

Cocaine Testing: Common False Positive

- Major metabolite, benzoylecgonine, is used in cocaine detection due to longer half-life (t1/2=12 hours) and therefore longer period for detection after use (up to 3-4 days)
- Coca leaf tea or adulterated natural products.
- Generally, cocaine is cocaine +



Cocaine Use Disorder Treatment

- Gold Standard: Behavioral Interventions
  - **<u>Contingency Management:</u>**
    - Based on operant conditioning.
    - Providing positive reinforcement ($$$) for testing without stimulants in a urine drug screen
  - Cognitive Behavioral Therapy
  - Community Reinforcement Approach

Cocaine Use Disorder Treatment

- **Positive Signaling, though low strength evidence for increasing abstinence at 2 weeks or more:**
  - Bupropion
  - Topiramate
  - Dextroamphetamine and mixed amphetamine salts
- **No difference in cocaine use outcomes with or without ADHD**
- **Negative Signals that do not improve abstinence, use, or retention**
  - Antidepressants (SSRIs, SNRIs or TCAS)
  - Anticonvulsants (except topiramate),
  - Neuroleptics
  - SSRIs and disulfiram: lower retention than placebo

JAMA Network | Open

Original Investigation | Substance Use and Addiction

Comparison of Treatments for Cocaine Use Disorder Among Adults
A Systematic Review and Meta-analysis

Brandon S. Bentzley, MD, PhD; Summer S. Han, PhD; Sophie Neuner, BS; Keith Humphreys, PhD; Kyle M. Kampman, MD; Casey H. Halpern, MD

Research Question: What treatments for cocaine use disorder are associated with objective reductions in cocaine use among adults?

	Without imputed data				With imputed data			
	No.				No.			
Treatment category	Studies	Treatment groups	Participants	OR (95% CI)	Studies	Treatment groups	Participants	OR (95% CI)
Anticonvulsants	14	17	570	2.32 (1.15-4.67)[a]	16	20	683	1.39 (0.59-3.29)
Antidepressants	8	15	482	1.96 (0.91-4.25)	11	18	574	1.36 (0.63-2.91)
Antipsychotics	8	11	241	1.59 (0.68-3.71)	9	12	281	1.02 (0.41-2.53)
Contingency management	38	69	2744	2.09 (1.59-2.75)[b]	50	88	3301	2.13 (1.62-2.80)[b]
Dopamine agonists	10	18	645	1.55 (0.80-3.00)	12	20	710	1.04 (0.51-2.14)
Miscellaneous medications	26	38	1455	1.64 (0.88-3.06)	37	54	1751	1.14 (0.60-2.17)
Opioids	49	142	4686	2.32 (1.54-3.49)[b]	55	159	5139	1.70 (0.98-2.94)
Other therapies	12	21	1577	2.19 (1.07-4.49)[c]	15	26	1805	1.35 (0.72-2.53)
Placebo	65	78	2889	1.48 (0.86-2.53)	80	96	3381	1.03 (0.59-1.80)
Psychostimulants	13	19	645	2.48 (1.27-4.85)[d]	17	24	702	1.74 (0.81-3.74)
Psychotherapy	98	258	10 773	1.08 (0.74-1.58)	131	330	13 213	1.18 (0.81-1.73)

Abbreviation: OR, odds ratio.

[a] $P = .02$.

[b] $P < .001$.

[c] $P = .03$.

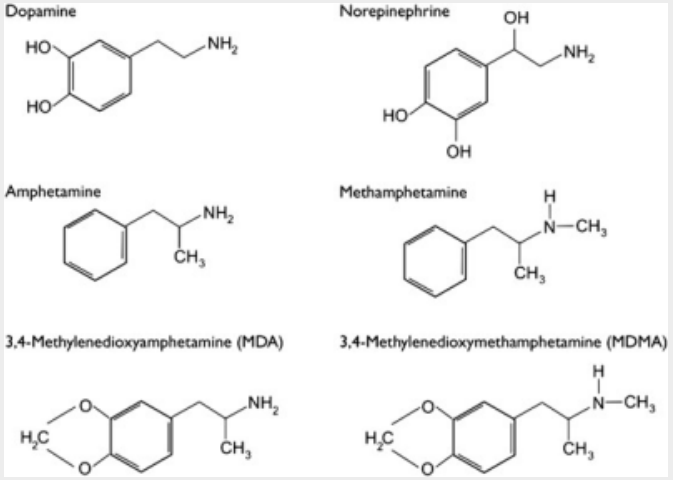
[d] $P = .008$.

SOURCE: DOI: 10.1001/jamanetworkopen.2021.8049

Methamphetamine

Methamphetamine: Synthetic Amphetamine

- Pseudoephedrine route

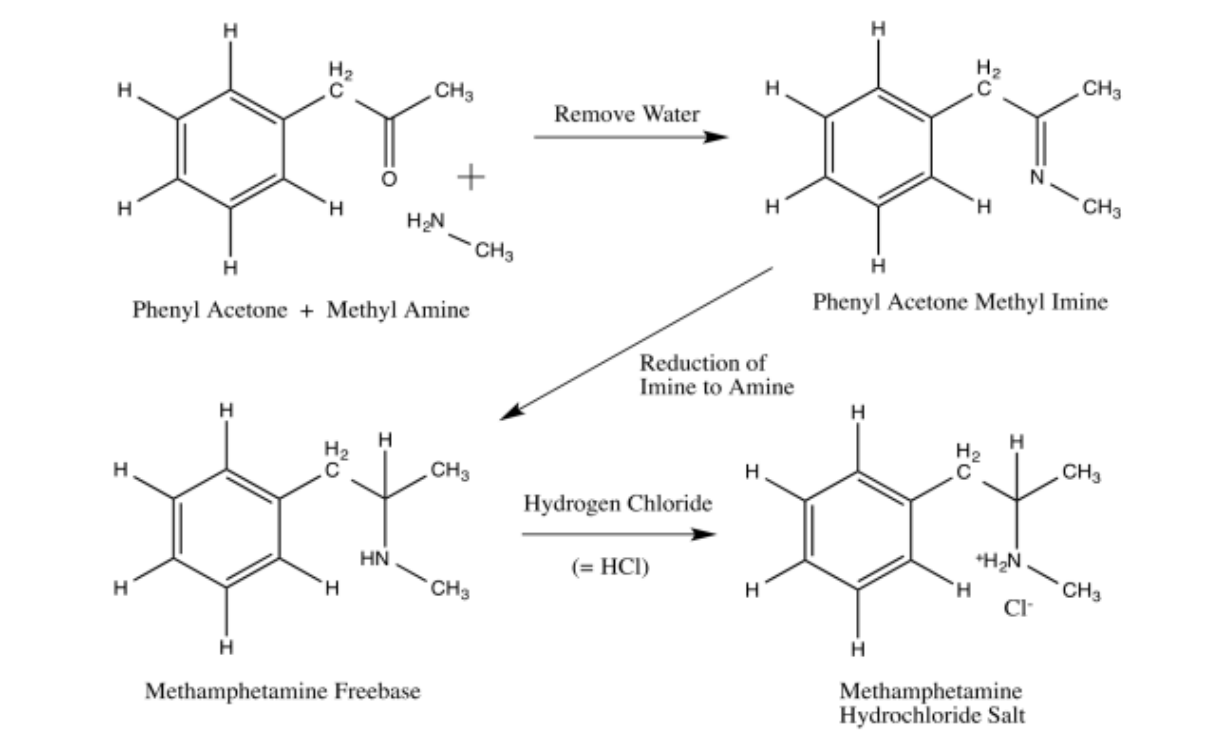


Methamphetamine: Synthetic Amphetamine

- Pseudoephedrine route: "Shake and Bake:" One pot!
  - Pseudoephedrine + ammonium nitrate + organic solvent + lithium mixed together in a cannister. Then add 1 capful of sodium hydroxide (lye). Then add water.
  - Swirl bottle. Take cap off every few minutes (release ammonia)
  - Keep swirly, venting for 1-2 hours
  - Filter fluid, dry filtrate, meth!

Methamphetamine: Synthetic Amphetamine

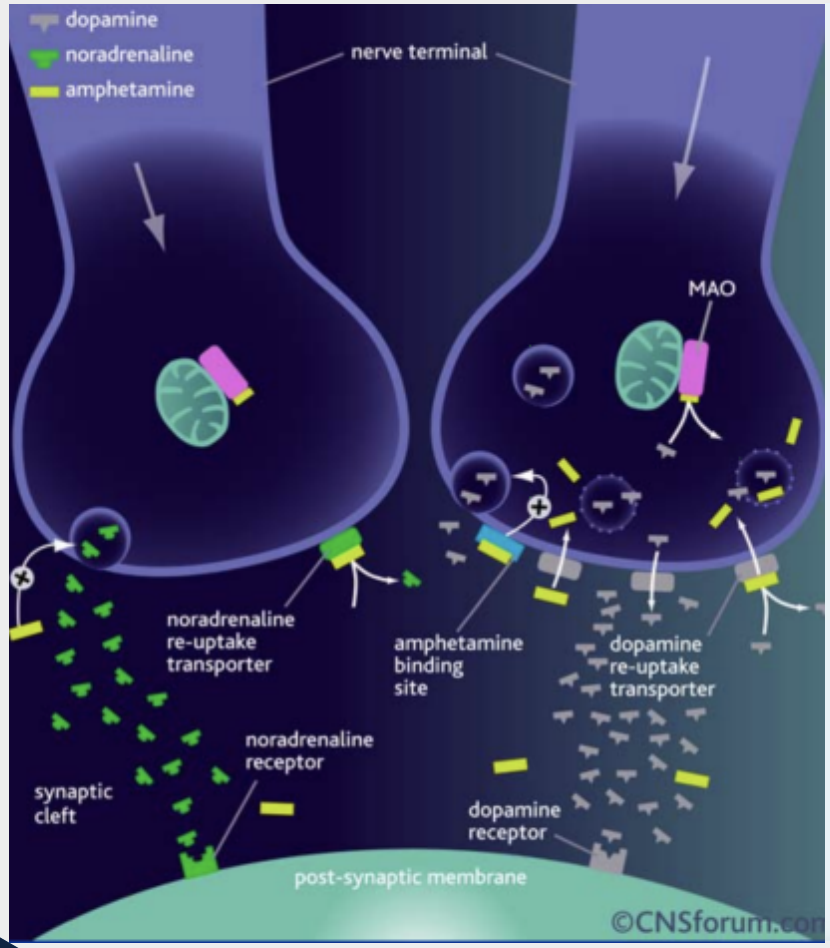
- Phenyl 2 Butane/ Phenyl Acetone Route:
  - Cooked in large laboratories in Mexico with expert chemists

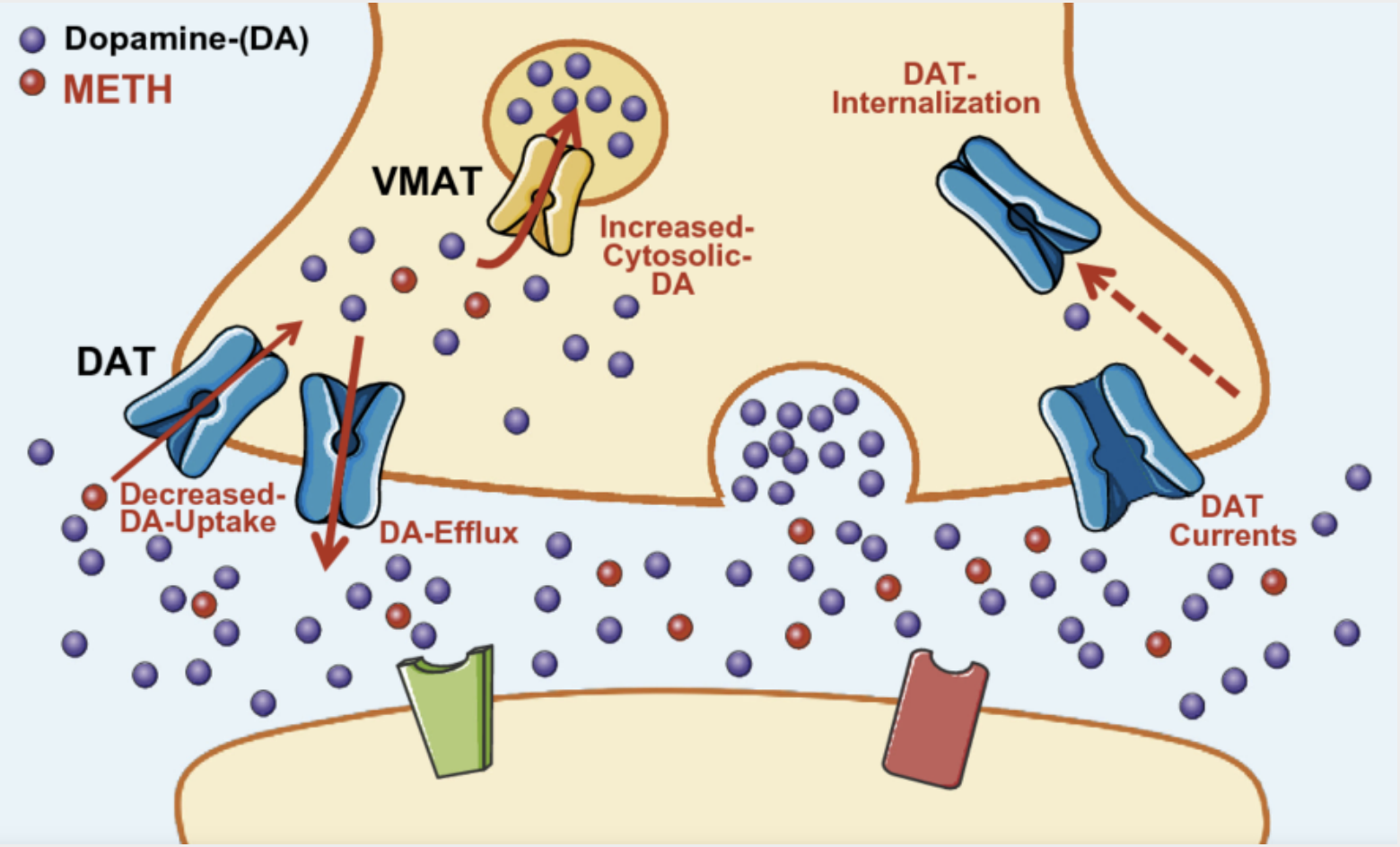


Methamphetamine

Formulation	Synthetic stimulant; crystal (crystal meth) or powder form
Method of Use	Smoked, snorted, injected, or taken orally
Pharmacokinetics	Smoking/Injecting: Immediate intense rush, lasts 6-12 hours Snorting: Effects within minutes, lasts up to 12 hours Oral: Slower onset, effects last up to 24 hours
Rate Hypothesis and Addiction Potential	Extremely addictive due to long duration & high dopamine release
Cost (depends on location/demand)	$20-$80 per gram; varies widely by region
Cutting Agents	Lactose, MSM (methylsulfonylmethane), acetone, ephedrine, pseudoephedrine, lithium, red phosphorus

Methamphetamine: Mechanism of Action





Methamphetamine: Neurotransmitters

Neurotransmitter	Effect on Neurotransmitter	Impact on Behavior
Dopamine (DA)	Releases DA from vesicles & reverses dopamine transporter (DAT)	More intense euphoria than cocaine, addiction, and cravings
Norepinephrine (NE)	Massive NE release from nerve terminals	Extreme energy, alertness, sympathetic overdrive
Serotonin (5-HT)	Releases 5-HT → Longer-lasting effects than cocaine	Elevated mood, hallucinations, possible aggression
Glutamate	Excitotoxicity & synaptic remodeling	Cognitive deficits, compulsive drug-seeking
GABA	Decreased GABAergic inhibition, leading to prolonged stimulant effects	Hyperstimulation, impulsivity, paranoia

Methamphetamine Desired Effects

- **Euphoria** – Intense feelings of pleasure, well-being, and confidence.
- **Increased Energy & Alertness** – Reduces fatigue and enhancing wakefulness.
- **Increased Sociability & Talkativeness** – Feeling more outgoing, confident, and engaged in conversations.
- **Appetite Suppression** – Reduces hunger and leading to weight loss with chronic use.
- **Improved Physical Performance** – Temporary increase in stamina and strength
- **Heightened Sensory Perception** – Colors may appear brighter, sounds clearer
- **Reduced Need for Sleep** – Prolongs wakefulness
- **Heightened Libido** – Meth **amplifies sexual desire and performance**

- **Prolonged Effects (12+ Hours)** – Unlike cocaine (which lasts ~30-60 minutes), **meth effects persist for 6-12 hours**, leading to extended binge use.

Methamphetamine Adverse Effects

- Psychological:
  - Paranoia, agitation, anxiety
  - Hallucinations (visual, tactile, and auditory)
  - Aggression & violent behavior
  - Hyperactivity & restlessness
- Tachycardia, Hypertension, MI
- Stroke
- Hyperthermia, Rhabdomyolyses
- Multiorgan Failure
- Severe teeth grinding and jaw clenching

Methamphetamine Intoxication

- Recent Stimulant use
- Two or more of the following
  - Tachycardia or bradycardia
  - Pupillary dilation
  - Elevated or lowered blood pressure
  - Perspiration or chills
  - Nausea or vomiting
  - Evidence of weight loss
  - Psychomotor agitation or retardation
  - Muscular weakness, respiratory depression, chest pain or cardiac arrhythmias
  - Confusion, seizures, dyskinesias, dystonia or coma

Methamphetamine Withdrawal

A. Cessation of (or reduction in) prolonged amphetamine-type substance, cocaine or other stimulant use

B. **Dysphoric mood and two (or more)** of the following physiological changes, developing within **hours to several days** after criterion A,

1. **Fatigue**
2. **Vivid, unpleasant dreams**
3. **Insomnia or hypersomnia**
4. **Increased appetite**
5. **Psychomotor retardation, or agitation**

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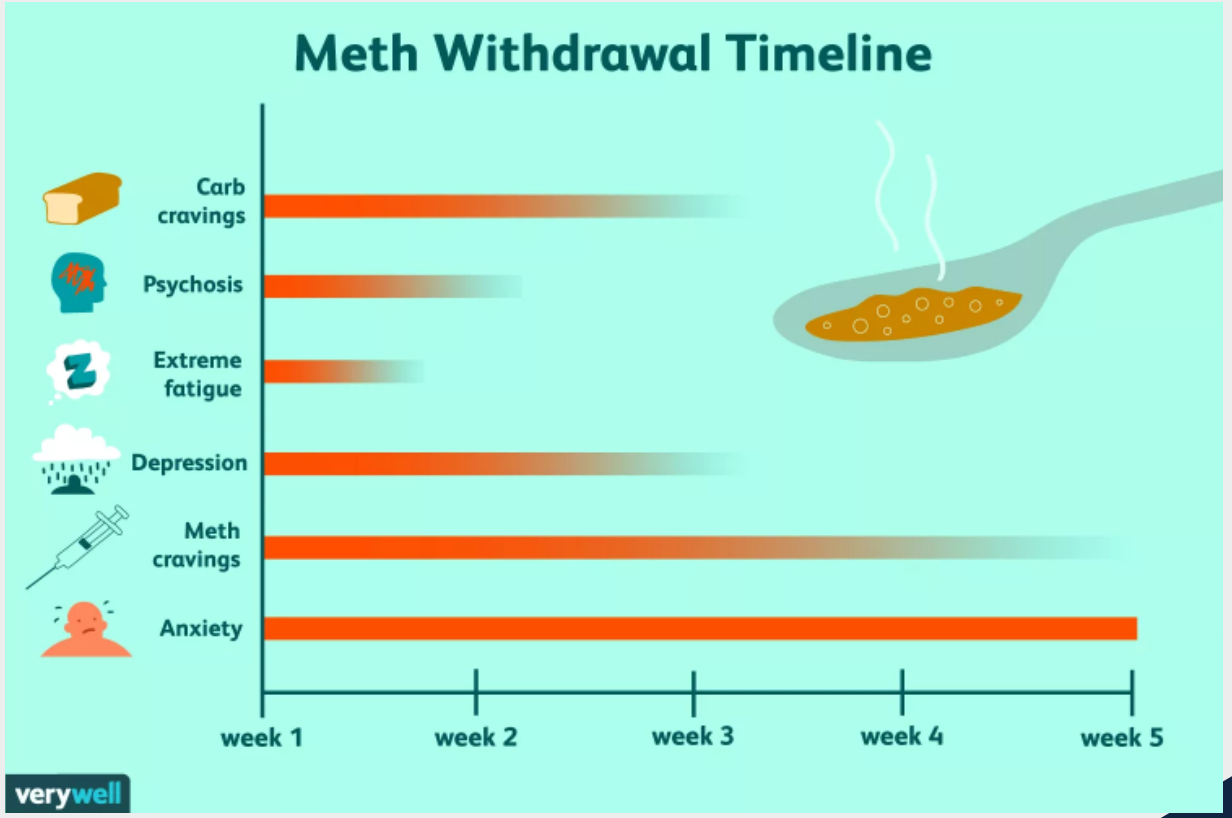


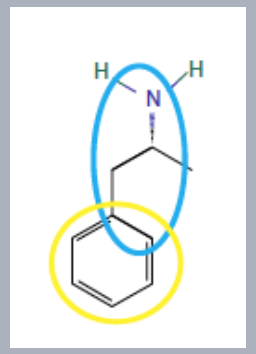
Methamphetamine Testing: Common False Positives

UDS: + Up to 72 hours after use
Confirmation for methamphetamine with Gas Chromatography Mass spectrometry (GC MS)

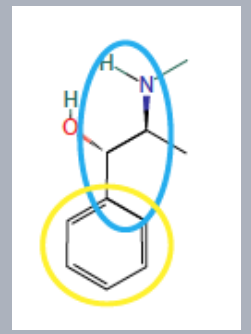
Amine Group Connected with Carbon Chain

Phenyl ring moiety

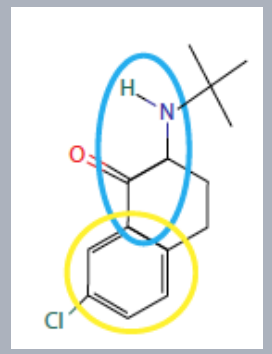
Amphetamine



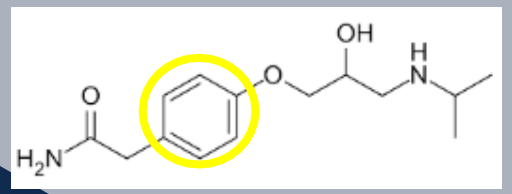
Pseudophedrine



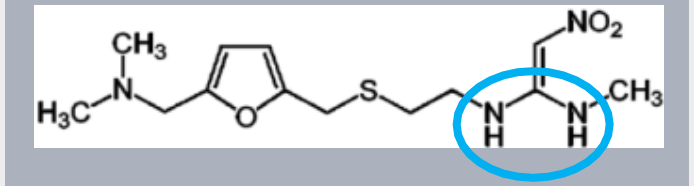
Bupropion



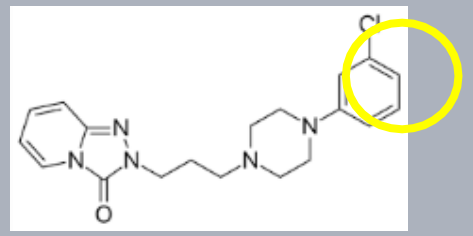
Atenolol



Ranitidine



Trazodone



Methamphetamine and Culture

Rural Communities

- Prevalent due to availability, economic stress, and lack of access to other stimulants (e.g., cocaine).
- Used to sustain long work hours in physically demanding jobs (e.g., agriculture, trucking, manual labor).
- Limited access to healthcare & treatment → Higher rates of meth-related health complications.

LGBTQ+ Communities (Chemsex/Substance Use in Party Scenes)

- Methamphetamine is commonly used in “chemsex” (sexualized drug use) settings, particularly among gay, bisexual, and other men who have sex with men (MSM).
- Reasons for use: Enhanced sexual experiences, increased confidence, prolonged stamina
- High-risk behaviors: Increased likelihood of unprotected sex, multiple partners, and transmission of HIV/STIs.
- Barrier to treatment: Fear of stigmatization from healthcare providers.

Methamphetamine and Culture

Homeless & Marginalized Populations

- Meth is used to stay awake at night for safety (avoiding assault, robbery, or sexual violence).
- Helps cope with trauma, PTSD, and mental illness.
- Commonly smoked or injected, leading to higher risks of infection and dental deterioration.

Club & Rave Scene

- Used as an alternative to MDMA/ecstasy to enhance energy and euphoria.
- Often mixed with other substances (e.g., GHB, ketamine, alcohol), increasing overdose risk.

Methamphetamine Use Disorder Treatment

- Gold Standard: Behavioral Interventions
  - **<u>Contingency Management:</u>**
    - Based on operant conditioning.
    - Providing positive reinforcement ($$$) for testing without stimulants in a urine drug screen
  - Cognitive Behavioral Therapy
  - Community Reinforcement Approach

Methamphetamine Use Disorder Treatment

- Some Positive Results: All considered “off label”
  - **Bupropion** [1]

    Better evidence in low severity/frequency users
  - **Mirtazapine** [2]
  - Methylphenidate [4]
  - **Topiramate** [6]

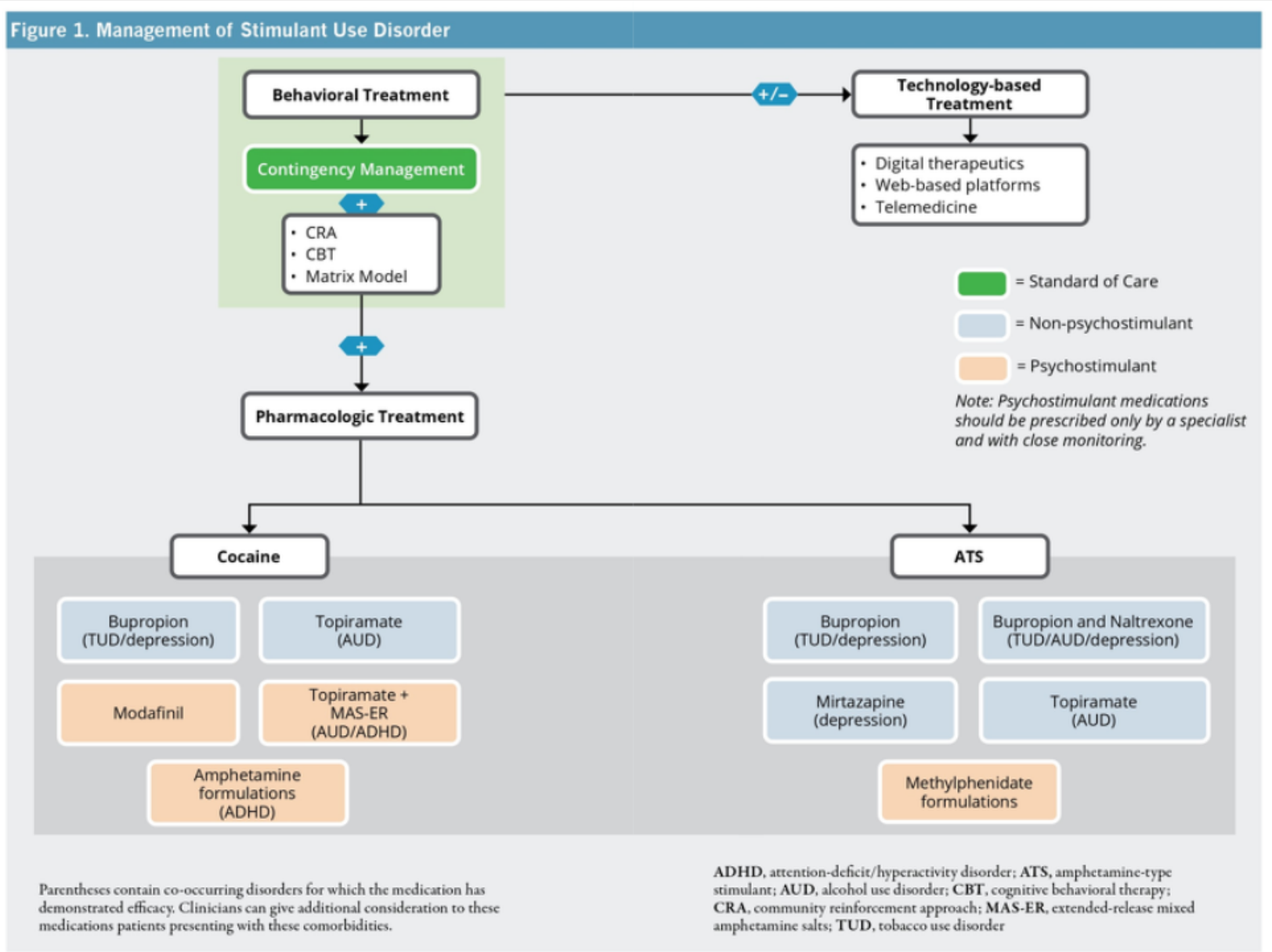
    Better outcomes if abstinent at treatment start
  - **Combination Treatment (Bupropion + Naltrexone)**
- **Mostly Negative Results**
  - Imipramine, Desipramine, Fluoxetine, Sertraline, Paroxetine, Tyrosine, Ondansetron
  - Aripiprazole, Gabapentin
  - N-Acetylcysteine, Varenicline

[1] Elkashaef et al. 2008, Shaptow et al. 2008; Heinzerling et al. 2014; Anderson et al. 2015. [2] Colfax et al. 2012, Coffin et al., 2020; [3] Jayaram-Linstrom et al., 2008; [4] Tiihonen et al., 2007; Ling et al. 2014; [5] Galloway et al. 2011; [6] Elkashef et al., 2011; [7]Heinzerling et al., 2010; Anderson et al., 2012.

Cocaine vs Methamphetamine Summary

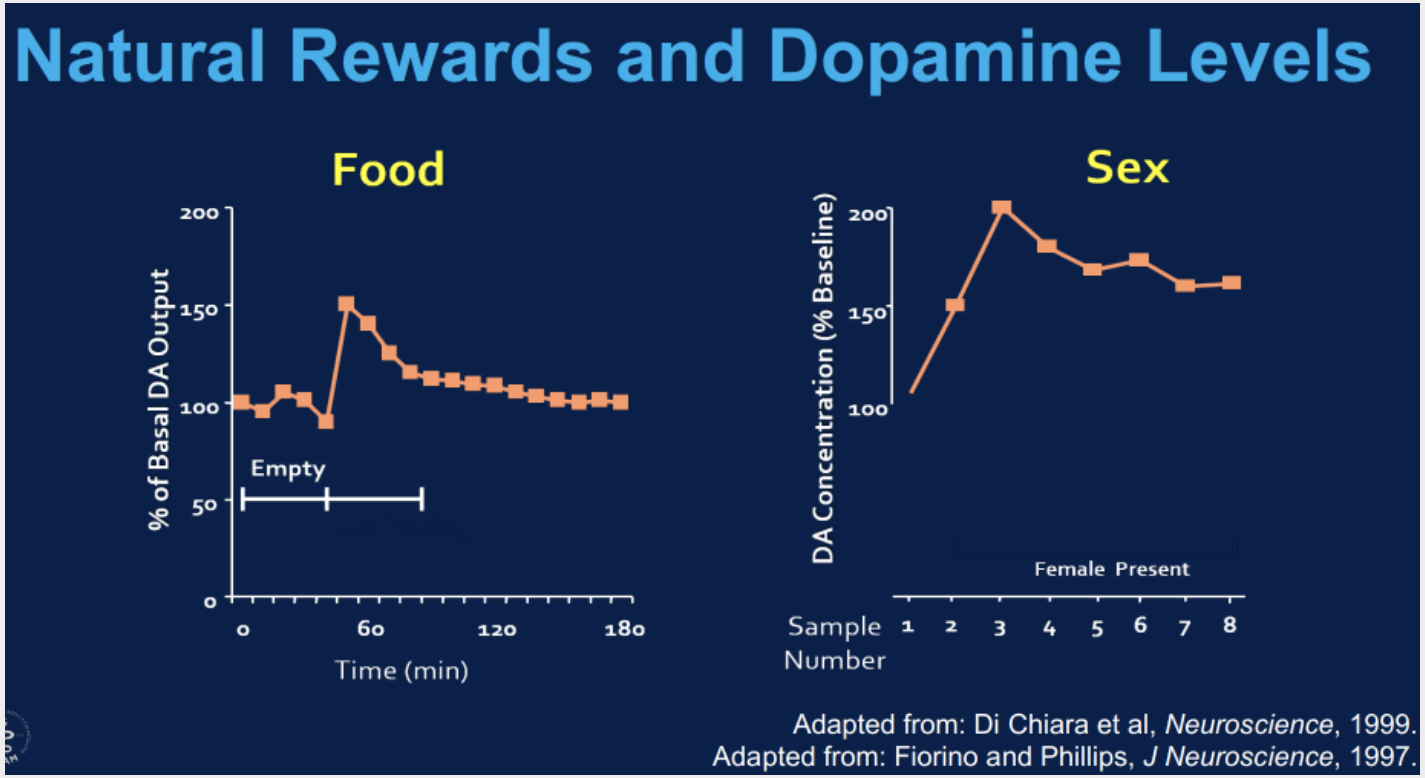
Feature	Cocaine	Methamphetamine
Development	Plant-derived	Synthetic
Length of high	Lasts 10-30 mins	Lasts 8-24 hours
Half-life	1 hour	12 hours
Primary Action	Blocks monoamine reuptake transporters	Increases monoamine release (DA, NE, 5-HT)
Reuptake Inhibition	Prevents neurotransmitter reuptake into presynaptic terminals	Partially blocks reuptake but mainly reverses transporter function
Neurotransmitter Release	No direct release; increases extracellular levels by **blocking reuptake**	Forces neurotransmitters out of vesicles and into synaptic cleft
Effects on Dopamine Transporters (DAT)	Blocks DAT, increasing synaptic DA	Reverses DAT, actively pumping DA out
Effects on Monoamine Oxidase (MAO)	No direct MAO inhibition	Inhibits MAO, preventing neurotransmitter breakdown
Effects on VMAT (Vesicular Monoamine Transporter)	No effect on VMAT (unlike reserpine)	Disrupts VMAT, causing release of stored neurotransmitters
Lipid Solubility & BBB Penetration	Passes BBB quickly, but less lipid-soluble than meth	Highly lipid-soluble, crosses BBB very rapidly
Additional Toxic Effects	Blocks Na+, K+, and Ca2+ channels at high doses (cardiotoxic)	Increases DA synthesis promoting long-term neurotoxicity
Sympathomimetic Effects	Prolonged monoamine accumulation leads to enhanced sympathetic effects (↑HR, ↑BP, ↑alertness)	Prolonged sympathetic activation similar to cocaine, but longer-lasting due to transporter reversal & MAO inhibition
Medical uses:	Vasoconstrictor	Derivatives for ADHD

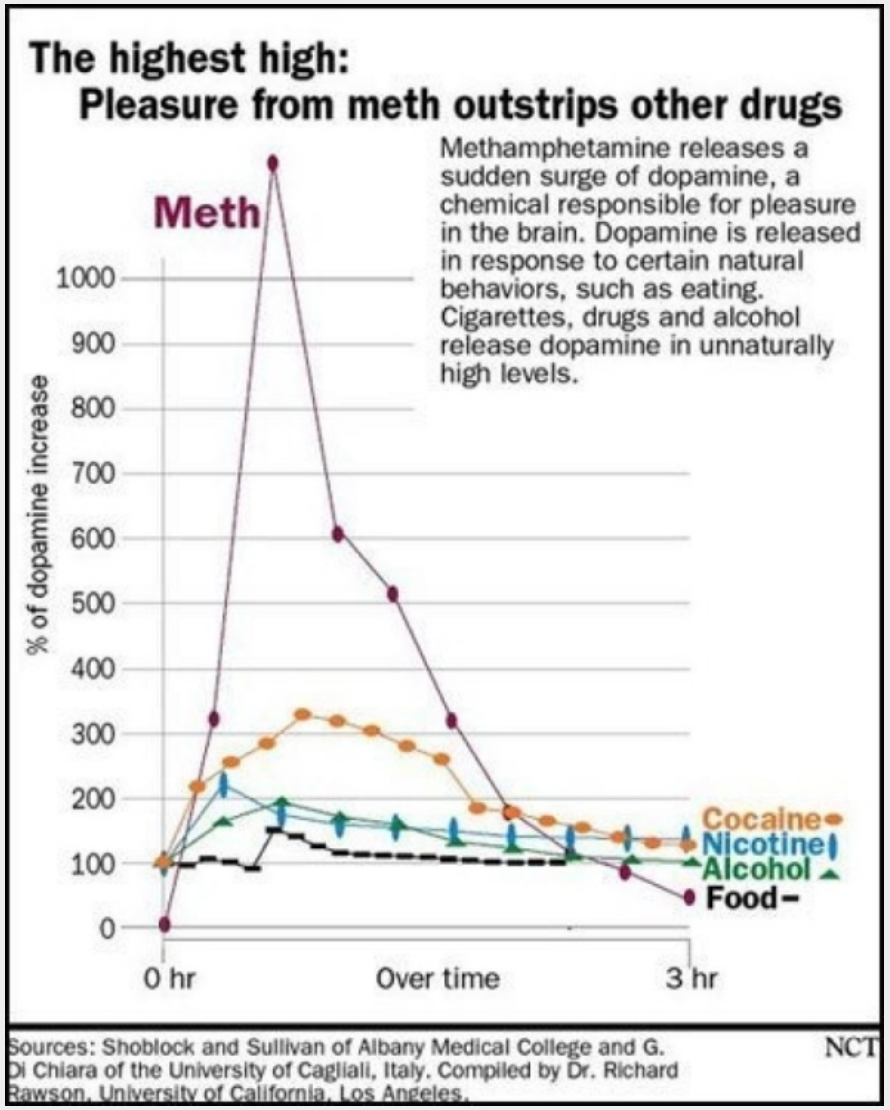
ASAM Stimulant Use Treatment Guidelines



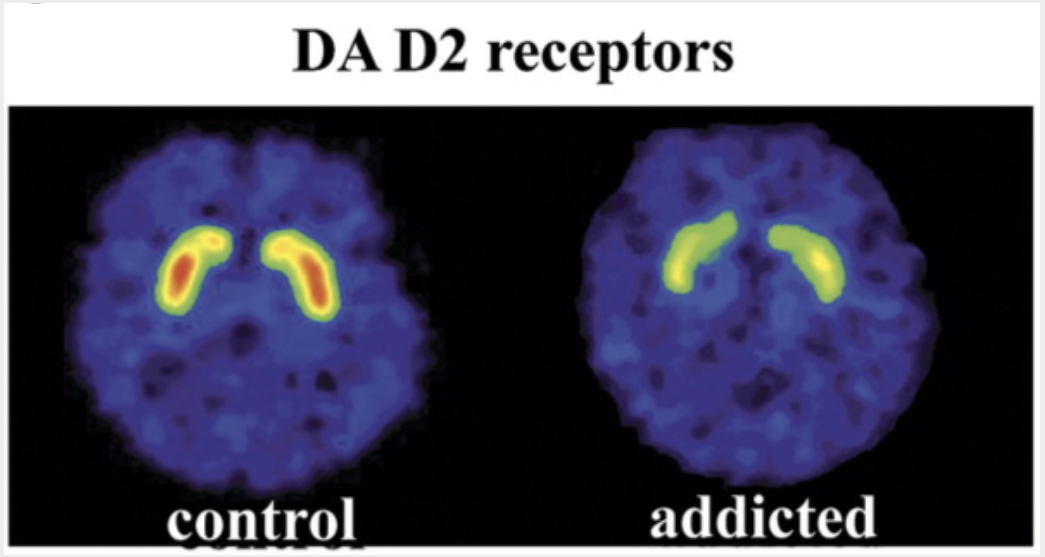
Neurobiology of Stimulant Use

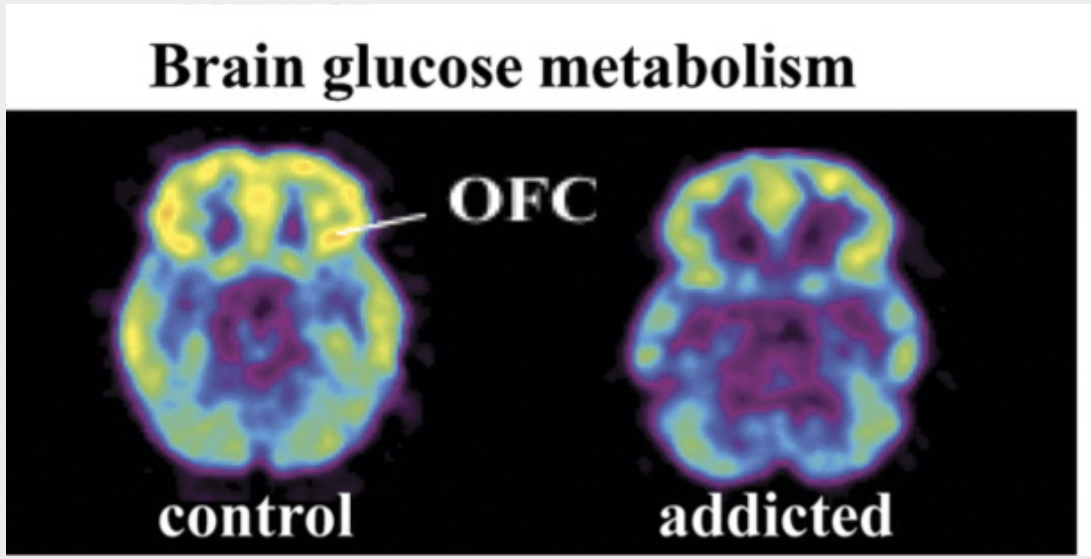
Dopamine Levels





Impact on Dopamine & Glutamate Pathways



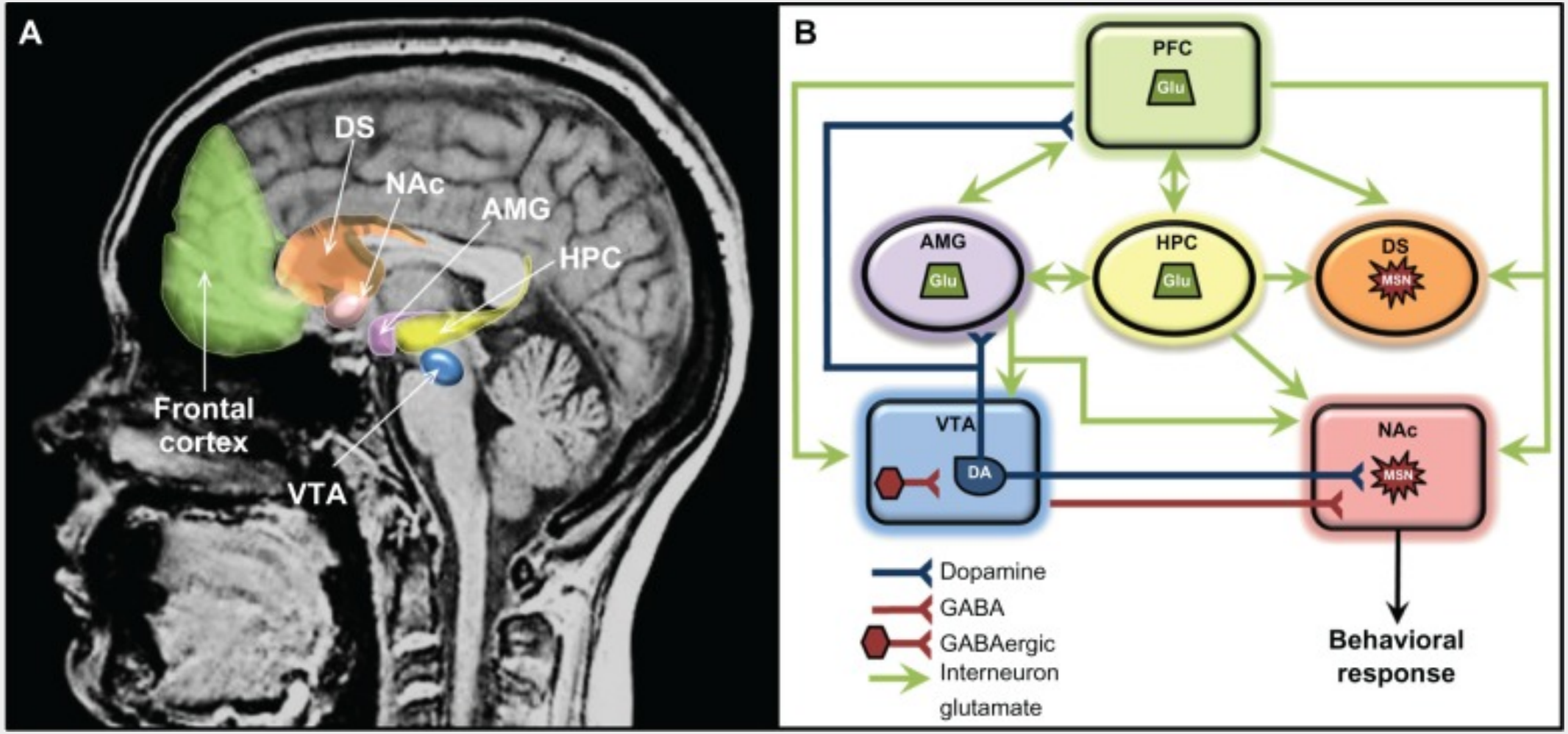


↓ Dopamine transporters:
↓ Ability to respond to non-drug rewards, ↑ impulsivity, immediate>delayed rewards[1]

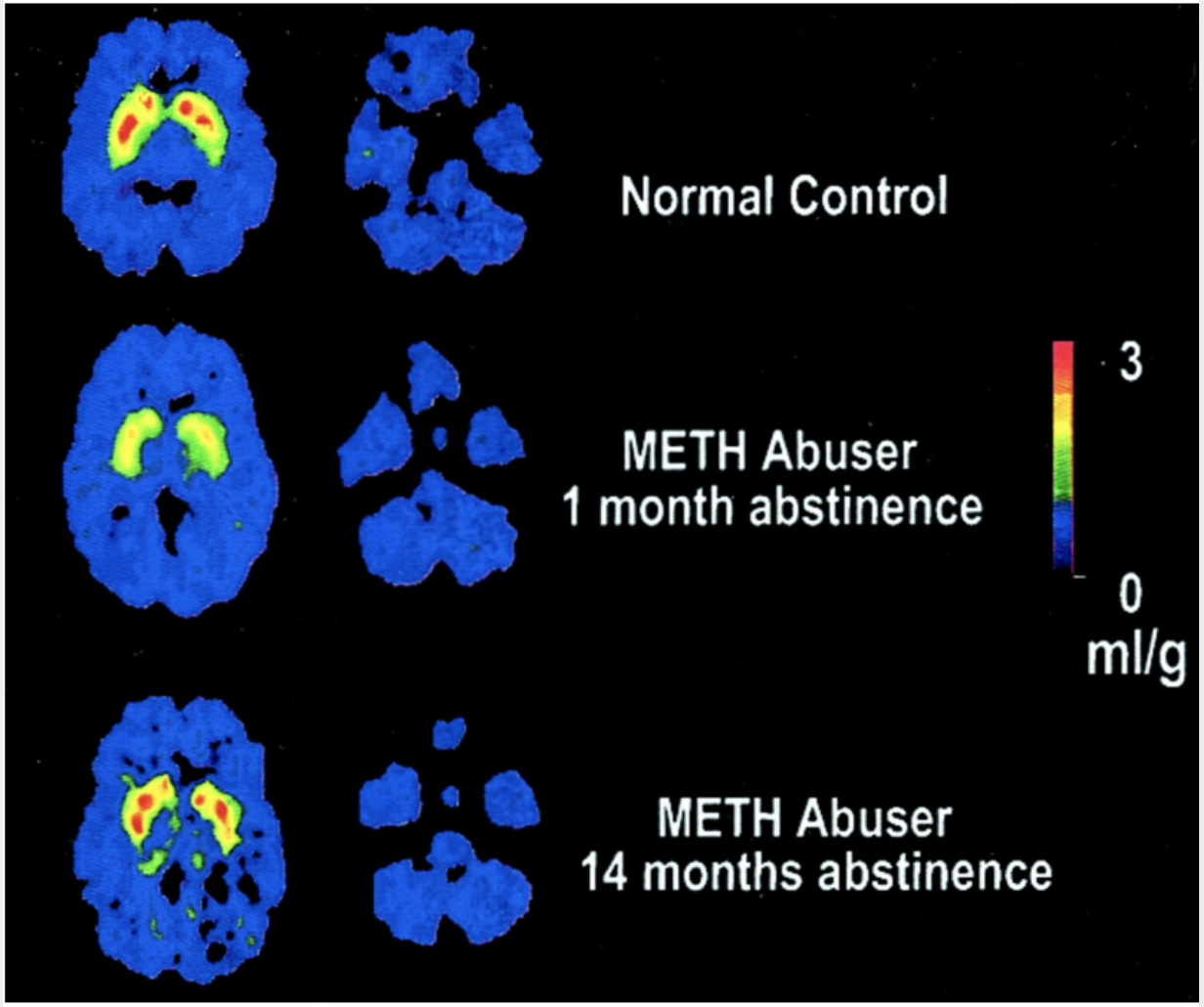
↓ Orbitofrontal Cortex Function, GLUT
- Poor decision making, ↓ resistance to urges[2]

[1]Volkow ND, Am J Psychiatry. 2001 [2] Volkow ND, Nature Review Neuroscience 12/2004

Mesocorticolimbic Reward Pathway



The Brain can Heal!



Volkow, ND. J Neuroscience 2001

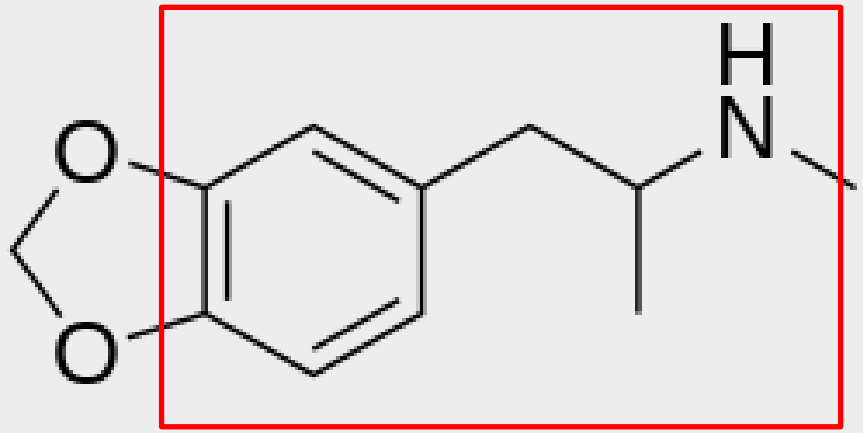
Cocaine vs Methamphetamine Neurobiology

Neuroadaptation	Cocaine	Methamphetamine
Dopamine D2 Receptor Downregulation	Decreased D2 receptors → Blunted reward response & anhedonia	More severe D2 receptor loss → Severe anhedonia & cognitive impairment
Prefrontal Cortex Dysfunction	Reduced PFC activity → Impaired impulse control & decision-making	Greater neurotoxicity in PFC → More severe cognitive & executive function deficits
Glutamate Dysregulation	Increased glutamate in NAc → Stronger drug-seeking behavior	More severe glutamate toxicity → Widespread synaptic damage & cravings
Dendritic Spine Remodeling	Increased Structural changes in NAc & PFC → Persistent drug-seeking	More profound loss of dendritic spines → Contributes to cognitive decline
Neurotoxicity & Brain Damage	Less neurotoxic compared to methamphetamine	Highly neurotoxic → Causes dopaminergic neurodegeneration (like Parkinson's)

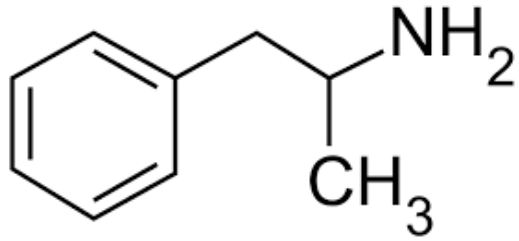
MDMA
3,4-Methylenedioxymethamphetamine

MDMA

- Entactogen/Empathogen
- Synthetic
  - Structurally similar to Amphetamine
  - Started as “Club Drug”
  - Psychedelic Assisted Therapy Agent



Amphetamine



MDMA

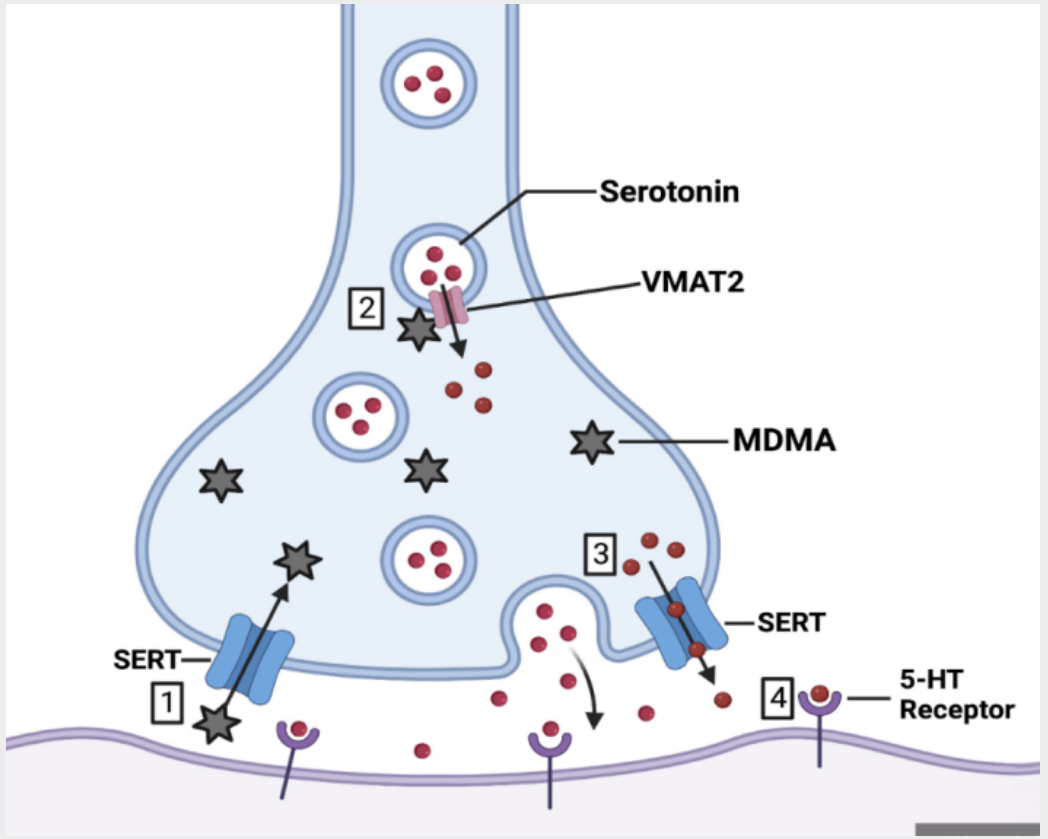
Formulation	**Tablets/Pills (often mixed with adulterants)** **Powder/Crystals (claimed to be "pure" MDMA, but may contain other substances)** **Capsules (powder-filled)**
Method of Use	**Oral (Most Common)** – Swallowed as a pill or capsule **Intranasal** – Powder/Crystal Bumping: Repeated oral or intranasal doses Stacking: Taking multiple doses at the same time
Cutting Agents	Can contain methamphetamine, caffeine, synthetic cathinones ("bath salts"), ketamine, or PMA (para-methoxyamphetamine, a toxic substitute).

MDMA Pharmacokinetics

- **Absorption:** Rapidly absorbed from the gastrointestinal tract or intranasally
- **Peak Effects:** 1-3 hours after ingestion, 15-30 mins after intranasal
- **Half-Life:** ~7-9 hours, but varies due to nonlinear metabolism
- **Duration of Effects:**
  - Psychoactive effects: 3-6 hours
  - Aftereffects ("comedown"): Up to 24 hours
  - Residual mood effects ("Tuesday blues"): Days to a week

MDMA: Mechanism of Action

- Increases release and reuptake inhibition of serotonin (5-HT) (SERT)
- To a lesser extent, dopamine (DA) and norepinephrine (NE).



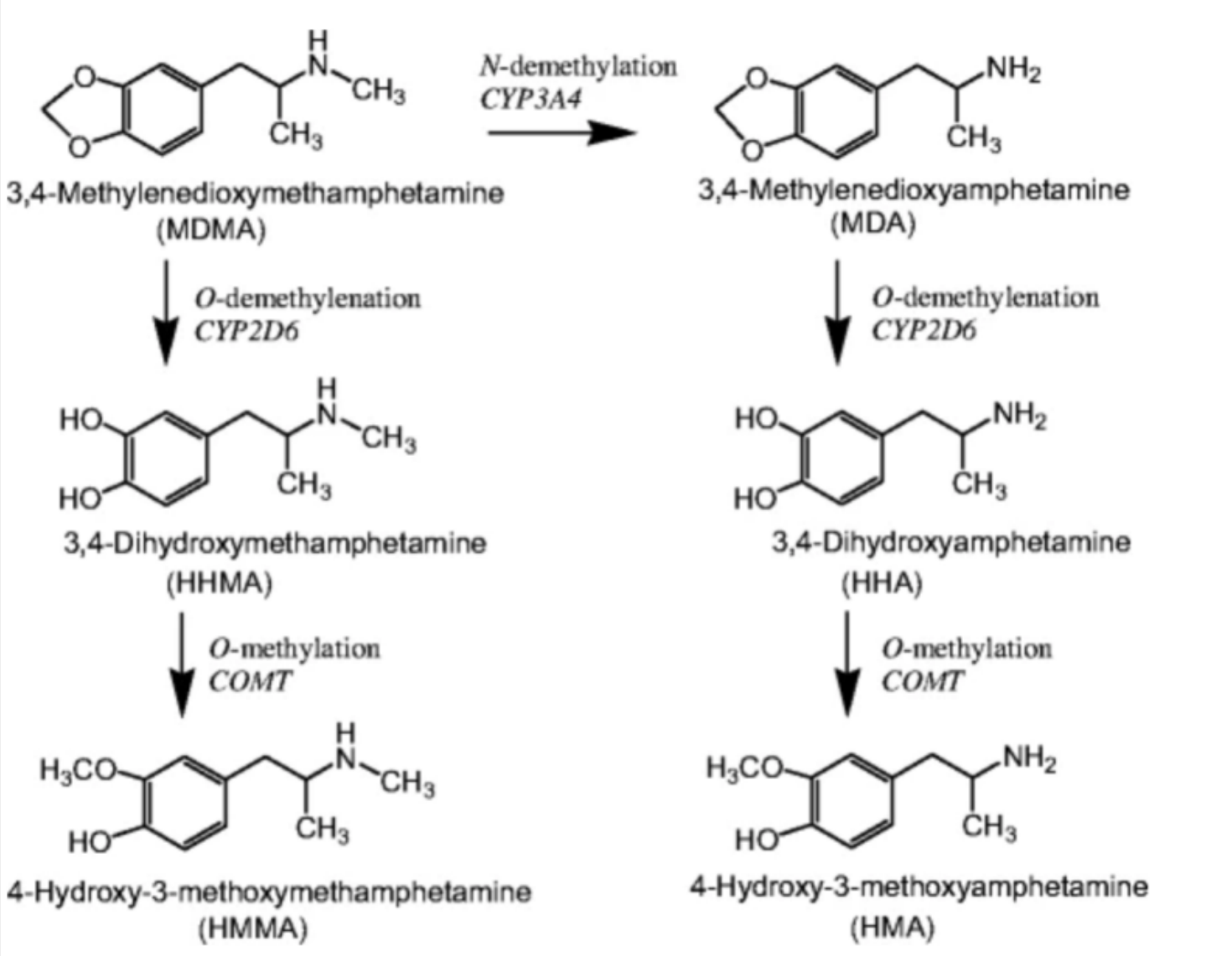
MDMA: Desired Effects

- **Euphoria & Empathy** – Heightened feelings of happiness, emotional openness, and connection with others
- **Increased Energy & Alertness** – Mild stimulant effects, generally less jittery than cocaine/meth
- **Enhanced Sensory Perception** – Brighter colors, increased tactile sensitivity, intensified music appreciation
- **Reduced Anxiety & Increased Sociability** – Promotes relaxation and bonding

MDMA Metabolism

- **Primary Enzyme: CYP2D6** (hepatic metabolism)
- **Major Metabolites:**
  - **3,4-Dihydroxymethamphetamine (HHMA)**
  - **3,4-Methylenedioxyamphetamine (MDA)** (active metabolite with more psychedelic effects)
- **Excretion:**
  - Mainly via **urine**, with **~20-50% excreted unchanged**

MDMA Metabolism



MDMA: Neurotransmitters

Neurotransmitter	Effect on Neurotransmitter	Impact on Behavior
Serotonin (5-HT)	**Massive serotonin release** → Blocks reuptake & reverses transporter function	Elevated mood, hallucinations, possible aggression
Dopamine (DA)	Moderate DA release (less than cocaine/meth)	Mild stimulation, motivation, reward-seeking behaviors
Norepinephrine (NE)	Increased NE	Elevated HR, BP, sweating
Oxytocin	Increased Oxytocin	Emotional warmth, social bonding

MDMA: Desired Effects

- **Euphoria & Well-Being** – Users feel intense happiness, pleasure, and emotional openness.
- **Increased Empathy & Emotional Bonding** – Often described as a "love drug," MDMA enhances feelings of connection and trust.
- **Reduced Anxiety & Fear Response** – Suppresses activity in the amygdala, decreasing social anxiety and emotional distress.
- **Increased Sociability & Talkativeness** – Users feel more outgoing, affectionate, and expressive.
- **Enhanced Self-Awareness & Emotional Processing** – May facilitate introspection and trauma processing, contributing to its therapeutic potential.

MDMA: Adverse Effects

Short-Term Risks

- Jaw Clenching & Teeth Grinding (Bruxism)
- Hyperthermia
- Dehydration & Electrolyte Imbalance (Risk of water intoxication if overhydrated)
- Anxiety, Restlessness, or Agitation
- Blurred Vision & Nystagmus

Long-Term Risks (Frequent Use)

- Serotonin Depletion → "Tuesday Blues" (Depression, fatigue, irritability for days to weeks post-use)
- Cognitive Impairment (Memory, learning deficits with chronic use)
- Neurotoxicity (Potential serotonin system damage with high-dose or frequent use)
- Dysphoria, anhedonia, psychomotor slowing, prolonged fatigue lasting weeks.

MDMA Toxicity

- **Symptoms of MDMA Overdose (Serotonin Syndrome & Hyperthermia)**
  - Severe Hyperthermia (>104°F, 40°C) → Organ failure, rhabdomyolysis
  - Seizures
  - Severe Hypertension & Cardiovascular Collapse
  - Serotonin Syndrome (Agitation, confusion, muscle rigidity, high fever)
- **Factors Increasing Overdose Risk:**
  - High doses or frequent re-dosing ("stacking")
  - Mixing with other stimulants (e.g., meth, cocaine)
  - Overhydration (causing hyponatremia)
  - Genetic CYP2D6 polymorphisms (poor metabolizers have increased risk of toxicity)

MDMA Toxicity Treatment

- **Medical Emergency! Supportive Care & Symptom Management:**
  - **Hyperthermia** → Rapid cooling measures, hydration with electrolyte-balanced fluids (avoid excessive water intake)
  - **Hypertension & Tachycardia** → Benzodiazepines (lorazepam, diazepam)
  - **Serotonin Syndrome** → Cyproheptadine (serotonin antagonist)
  - **Seizures** → Benzodiazepines, supportive care

MDMA: Culture

- **Rave, Club, & Festival Scene**
  - MDMA is deeply associated with electronic dance music (EDM) festivals, raves, and nightclub culture.
  - Used to enhance music appreciation, increase sensory perception, and boost energy for prolonged dancing.
  - Often taken in group settings, reinforcing its reputation as a "social drug."
- **LGBTQ+ & Queer Party Culture**
  - MDMA has been popular in gay nightlife & underground club scenes since the 1980s.
  - Used to promote emotional connection, self-expression, and intimacy.
  - Some crossover with chemsex culture, where it may be mixed with other substances (e.g., GHB, ketamine).

MDMA: Culture

- **Psychedelic & Consciousness Exploration Communities**
  - Some use MDMA for spiritual experiences, introspection, and therapy.
  - Often integrated into psychedelic retreats, Burning Man, and underground therapy sessions.
  - Microdosing MDMA is being explored for mental health benefits.
- **Therapeutic & Research Settings**
  - MDMA-assisted psychotherapy is being studied for PTSD, trauma, and couples therapy.
  - MAPS (Multidisciplinary Association for Psychedelic Studies) is leading clinical trials for FDA approval of MDMA-assisted therapy.
  - Unlike recreational use, therapeutic MDMA is carefully dosed, monitored, and combined with therapy.

MDMA: FDA Update

Background:

- Clinical trials aimed to evaluate the efficacy and safety of MDMA-assisted therapy in alleviating PTSD symptoms.

FDA Advisory Panel Decision (June 2024):

- An 11-member FDA advisory committee reviewed the clinical trial data for MDMA-assisted therapy. The panel voted 9-2 against the therapy's effectiveness and 10-1 against its benefits outweighing the risks. Concerns highlighted included:
  - Potential unblinding of study participants.
  - Adverse cardiovascular effects associated with MDMA.
  - Insufficient data on MDMA's misuse potential within the trial context.

FDA's Official Response (August 2024):

- Following the advisory panel's recommendation, the FDA declined approval of MDMA-assisted therapy for PTSD. The agency requested additional data to address the identified concerns, including the conduct of a third Phase 3 clinical trial.

MDMA Treatment

Long-Term Stimulant Use Disorder Treatment (MDMA Addiction):

- **Psychosocial Interventions**:
  - Cognitive Behavioral Therapy (CBT) – Address impulsivity, relapse prevention
  - Motivational Interviewing (MI) – Enhance motivation to quit
  - Harm Reduction Strategies – Education on hydration safety, avoiding polydrug use, and dosing precautions
- No FDA-Approved Options:
  - Can Consider SSRIs to restore serotonin balance in chronic users and Mirtazapine (5-HT antagonist) to reduce withdrawal symptoms, anxiety

Bath Salts
Synthetic Cathinones

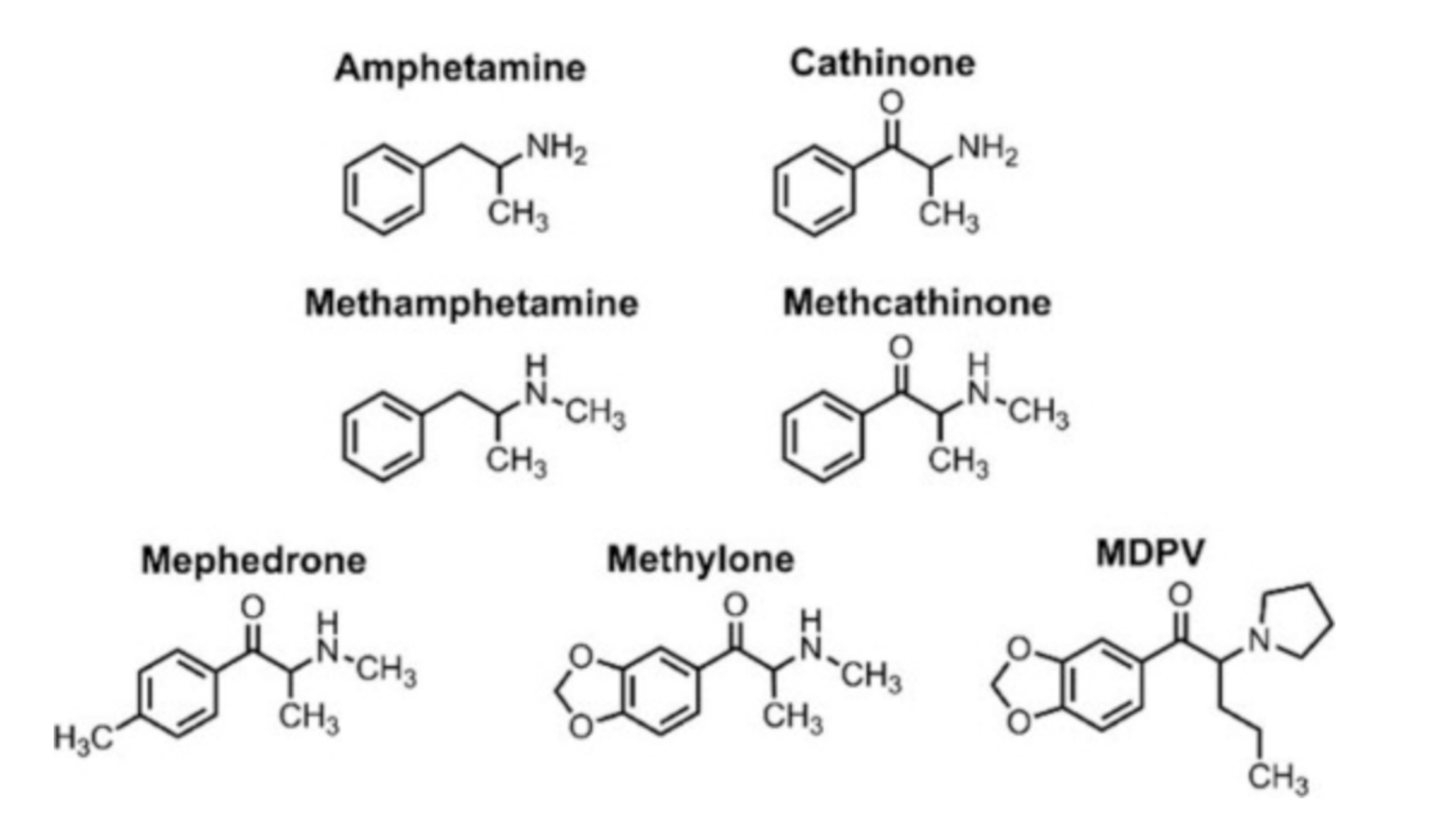
Bath Salts: Formulations

- **Common Names:** "Bath salts," Flakka, Cloud 9, Vanilla Sky, White Lightning
- **Chemical Class: Synthetic Cathinones** (structurally related to cathinone, the active compound in **khat**, a plant chewed for stimulant effects).
- **Common Ingredients:**
  - **Methylenedioxypyrovalerone (MDPV)**
  - **Mephedrone ("Meow Meow")**
  - **α-Pyrrolidinopentiophenone (α-PVP, "Flakka")**
- **Forms:**
  - **White or tan powder**
  - **Crystals, capsules, or pressed pills**
  - **Liquid formulations (e-cigarettes, vaping solutions)**

Bath Salts: Khat Plant Origin

- Khat is a flowering evergreen shrub that has two active ingredients:
  - Cathine and Cathinone.
- Khat is typically chewed like tobacco, then retained in the cheek and chewed intermittently to release the active drug.
- Dried khat leaves can be made into tea or a chewable paste, and khat can also be smoked and even sprinkled on food.
- Desired effects: Increased energy, euphoria.

Bath Salts: Cathinone Family



Bath Salts & Cathinones: Desired Effects

- Euphoria
- Increased energy and alertness
- Boost in confidence or invincibility
- Heightened sociability
- Increased libido

Bath Salts & Cathinones: Adverse Effects

Psychiatric:

- Agitation, Panic attacks
- Psychosis: Paranoia, Auditory or visual hallucinations: Often lasting weeks after use.
- Delirium
- Aggressive behavior

Physical:

- Tachycardia, hypertension
- Hyperthermia
- Seizures
- Muscle breakdown (rhabdomyolysis)
- Kidney failure
- Death (due to overdose, cardiac issues, or behavioral harm)

Bath Salts & Cathinones: Mechanism of Action

- Synthetic cathinones block **reuptake of dopamine, norepinephrine, and serotonin**
- Some (like mephedrone) also increase release of monoamines (like MDMA)
- **MDPV** (3,4-methylenedioxypyrovalerone):
  - Acts as a **potent reuptake inhibitor of dopamine and norepinephrine**
  - **10x more potent than cocaine** in dopamine transporter inhibition
  - Minimal effect on serotonin (unlike MDMA)
  - MDPV is one of the most dangerous cathinones due to its potency and long duration (up to 8 hours).
  - MDPV's mechanism closely resembles cocaine but with much higher affinity for dopamine transporters—leading to intense stimulation and paranoia.

Bath Salts & Cathinones: Metabolism

- Primarily metabolized in the **liver** via **CYP450 enzymes**
- Excreted in **urine**, both as parent compound and metabolites
- Difficult to detect in standard drug screens — requires **specialized testing**
- MDPV has a half-life of around **3-4 hours**, but effects may last longer due to **slow clearance from the brain**
- Some can be detected using advanced GC-MS or LC-MS/MS methods in forensic or toxicology labs.

Bath Salts & Cathinones: Complications and Treatment

- High risk of severe HTN, seizures, kidney injury due to hyperadrenergic states.
- First-line:
  - Benzodiazepines.
  - Supportive care for hypertension and hyperthermia.

High-Yield Board Review Summary

- **Cocaine**:
  - Plant-based stimulant that blocks dopamine reuptake (DAT) → Short-acting stimulant.
- **Methamphetamine**:
  - Synthetic Amphetamine that releases dopamine + Blocks reuptake → Longer-lasting effects.
- **MDMA**:
  - Primarily serotonin release → Hyperthermia risk.
- **Bath Salts**:
  - Potent synthetic cathinones → Severe paranoia, agitation.
- **Treatments**:
  - Psychosocial and Behavioral treatments are gold standard, but off-label medications can be effective, too!

Summary Slide

Category	Cocaine	Methamphetamine	MDMA	Synthetic Cathinones (Bath Salts)
Neurobiology & Mechanisms	Blocks dopamine reuptake (DAT), increasing dopamine in synapse.	Releases dopamine + blocks reuptake via VMAT2, leading to prolonged effects.	Primarily serotonin release (SERT), with lesser dopamine effects.	Potent dopamine/NE reuptake inhibition; severe stimulant-like effects.
Intoxication Effects	Euphoria, increased energy, vasoconstriction, MI risk, paranoia.	Euphoria, hyperthermia, agitation, paranoia, 'meth mouth'.	Empathogenic effects, sensory enhancement, hyperthermia, hyponatremia.	Extreme agitation, paranoia, violent behavior, 'excited delirium'.
Withdrawal Symptoms	Dysphoria, hypersomnia, fatigue, intense cravings.	Severe anhedonia, psychomotor slowing, prolonged fatigue, mood disturbances.	Serotonin depletion → depression, anxiety, fatigue, irritability.	Severe withdrawal symptoms including dysphoria, insomnia, cravings.
Evidence-Based Treatments	No FDA-approved meds; possible benefit from disulfiram, modafinil, and mixed amphetamine salts.	No FDA-approved meds: Bupropion + naltrexone; methylphenidate for stimulant agonist therapy.	Supportive care: benzodiazepines for agitation, cooling measures, hydration.	First-line: Benzodiazepines; supportive care for hypertension, hyperthermia.

Thank You

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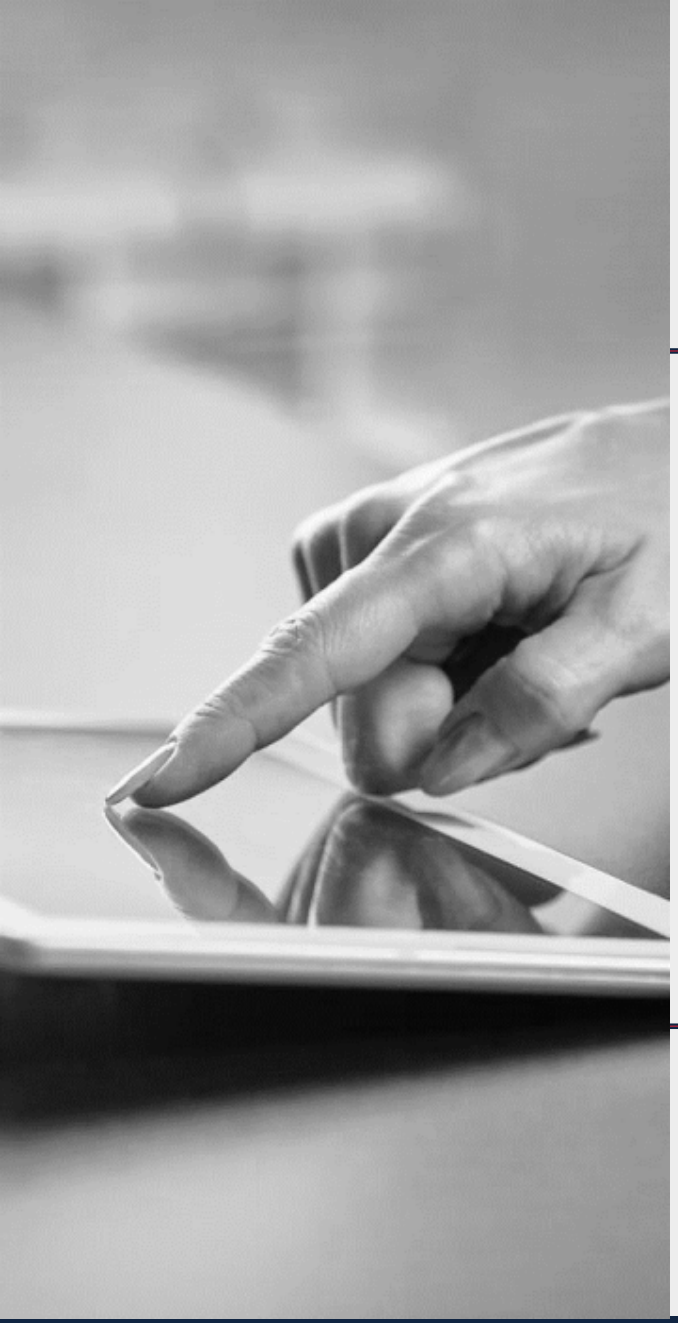

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