



ASAM REVIEW COURSE 2024

Stimulant Use Disorders: From Neurobiology to Public Health

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Financial Disclosure

Michael Baumann, PhD

- No relevant disclosures

General Outline

- Cocaine
- Methamphetamine
- Ecstasy
- Bath Salts and RCs
- Summary

Topics Covered for Each Substance

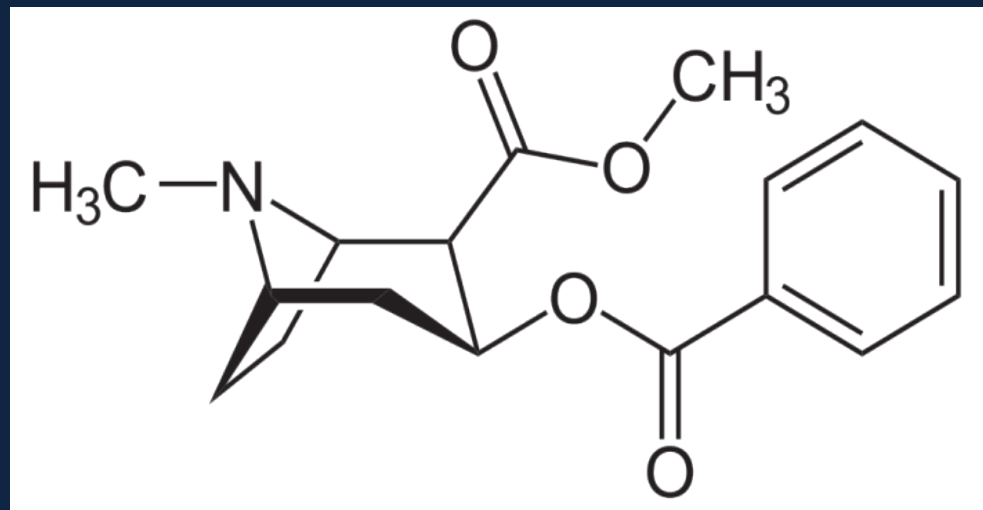
- Drug Trafficking and Epidemiology of Use
- Formulations and Methods of Use
- Pharmacokinetics and Metabolism
- Desired and Adverse Effects
- Chronic and Withdrawal Effects
- Neurobiology
- Treatments

Cocaine

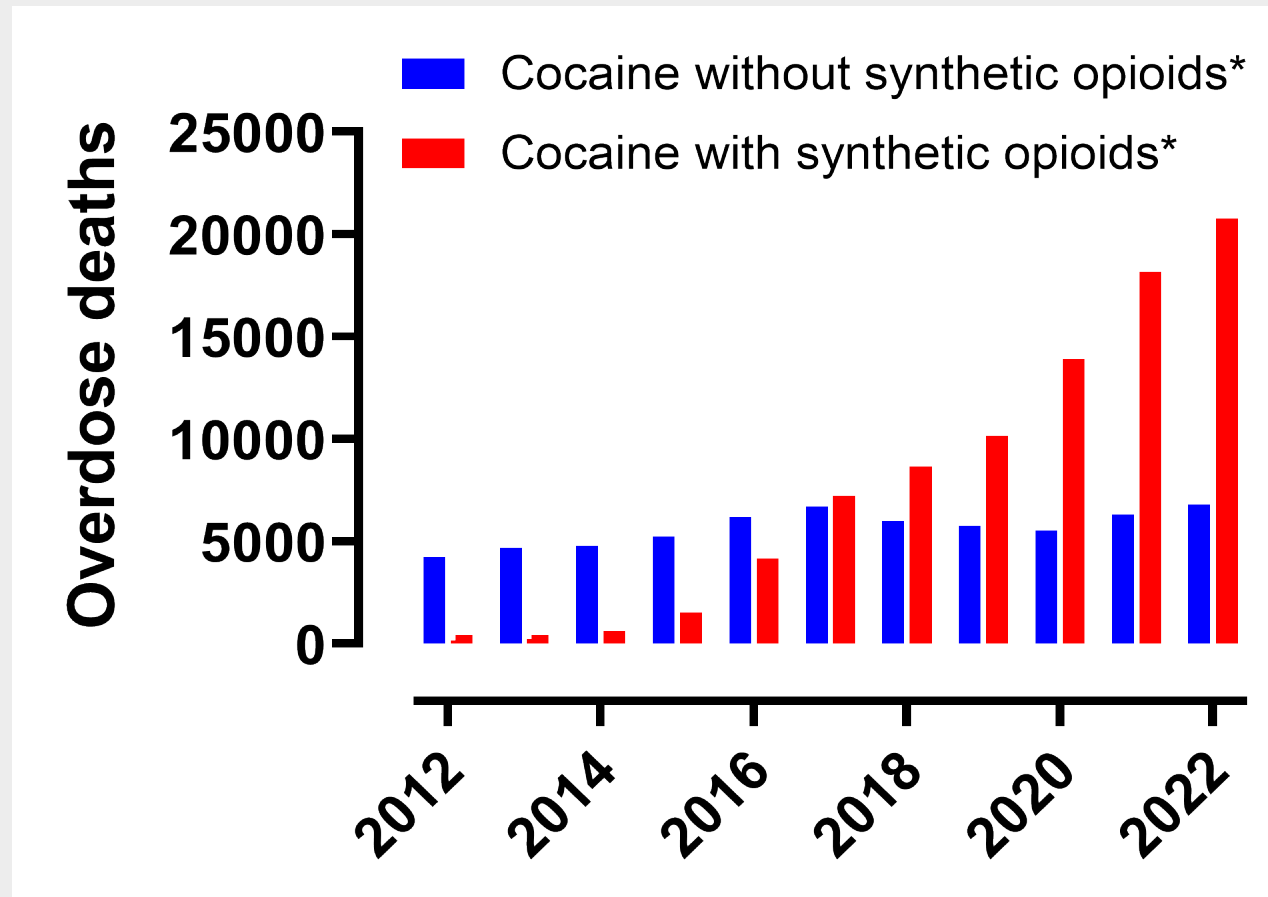




Cocaine is a Plant Based Alkaloid



Cocaine Overdose Deaths Are Increasing



*synthetic opioids other than methadone

Formulations and Methods of Use

- Cocaine Free Base (i.e., Crack)
 - Smoking of free base “rock” using pipes
- Cocaine HCl
 - Intravenous injection of solutions using needle and syringe
 - Intranasal snorting of powder

Pharmacokinetics and Metabolism

- Pharmacokinetics
 - Smoked drug reaches brain within seconds
 - Intravenous drug reaches brain within seconds
 - Intranasal drug reaches brain within minutes
- Metabolism
 - Ester hydrolysis to benzoylecgonine
 - Ecgonine methyl ester

Rate Hypothesis of Drug Reward

- Smoked and Intravenous Routes
 - Faster rate, and greater amount, of drug entry into the brain
 - Enhanced subjective and rewarding effects
- Intranasal and Oral Routes
 - Slower rate, and lesser amount, of drug entry into the brain
 - Reduced subjective and rewarding effects

Desired Effects

- Enhanced Mood and Euphoria
- Increased Attention and Alertness
- Decreased Need for Sleep
- Appetite Suppression
- Sexual Arousal

Adverse Effects

- Psychosis
- Tachycardia, Arrhythmias, Heart Attack
- Hypertension, Stroke
- Hyperthermia, Rhabdomyolysis
- Multisystem Organ Failure

Tolerance- Blunted Effects

- Acute Tachyphylaxis or “First Dose” Effect
 - Cardiovascular effects blunted within a dosing binge
 - Euphoria and sexual arousal diminished
- No longer-term tolerance

Sensitization- Enhanced Effects

- Seizures
- Psychosis
 - Paranoid delusions
 - Visual and auditory hallucinations
 - Indistinguishable from schizophrenia
- Stereotypical Behaviors
 - Compulsive skin picking or scratching
 - Involuntary movements

Withdrawal Effects

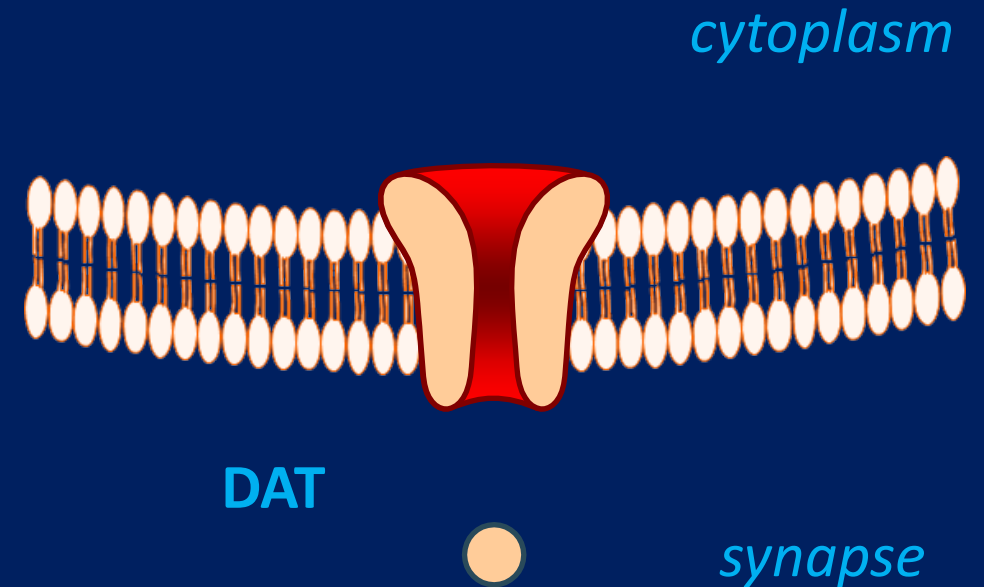
- Anhedonia and Depressed Mood
- Increased Appetite
- Anergia and Fatigue
- Vivid or Unpleasant Dreams
- Insomnia or Hypersomnia

Molecular Sites of Action

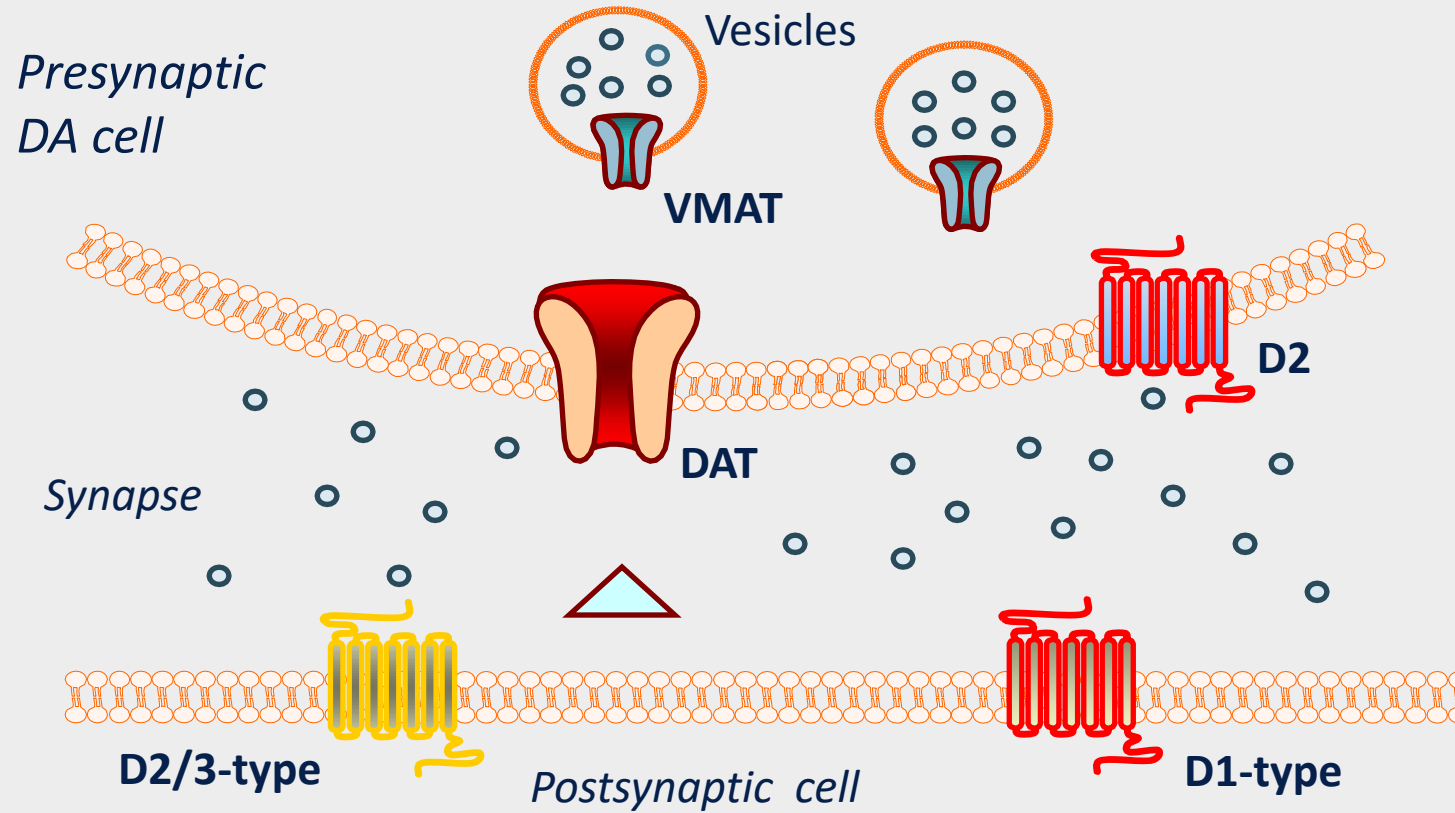
- SLC6 Monoamine Transporters
 - Dopamine transporter (DAT)
 - Norepinephrine transporter (NET)
 - 5-HT transporter (SERT)
- Other sites
 - Sodium channels

DATs Mediate DA Uptake

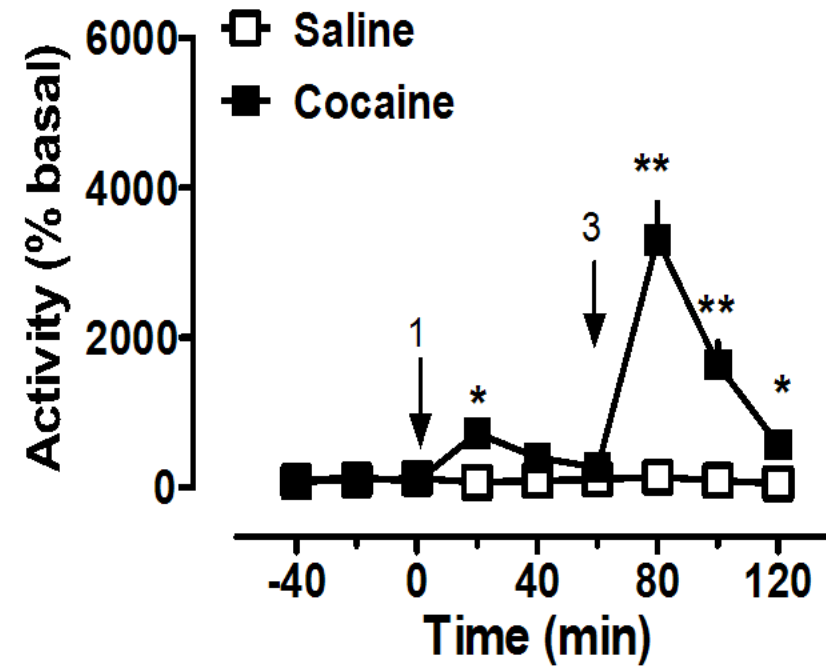
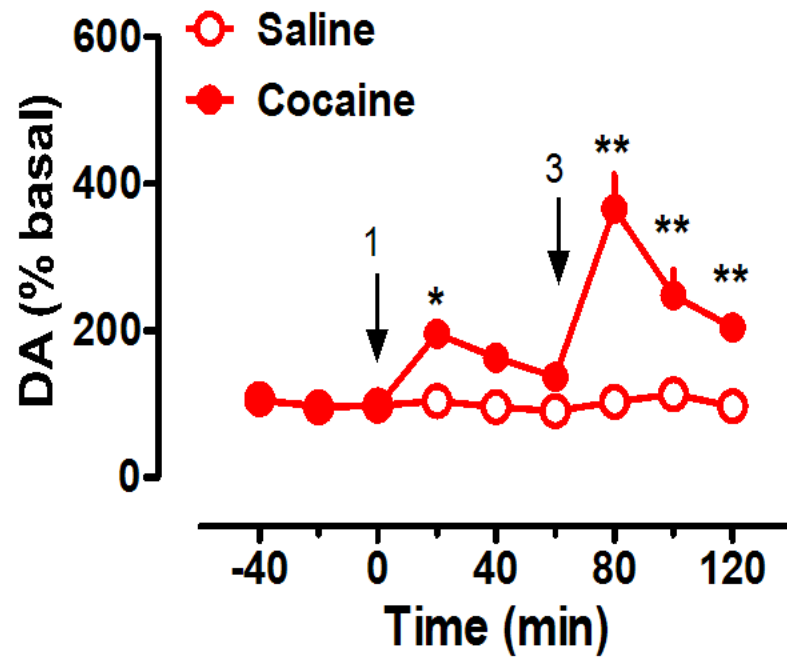
- DATs are membrane proteins responsible for uptake of released dopamine (DA)
- Drugs that disrupt DAT function increase extracellular (EC) DA
- Increases in EC DA are rewarding



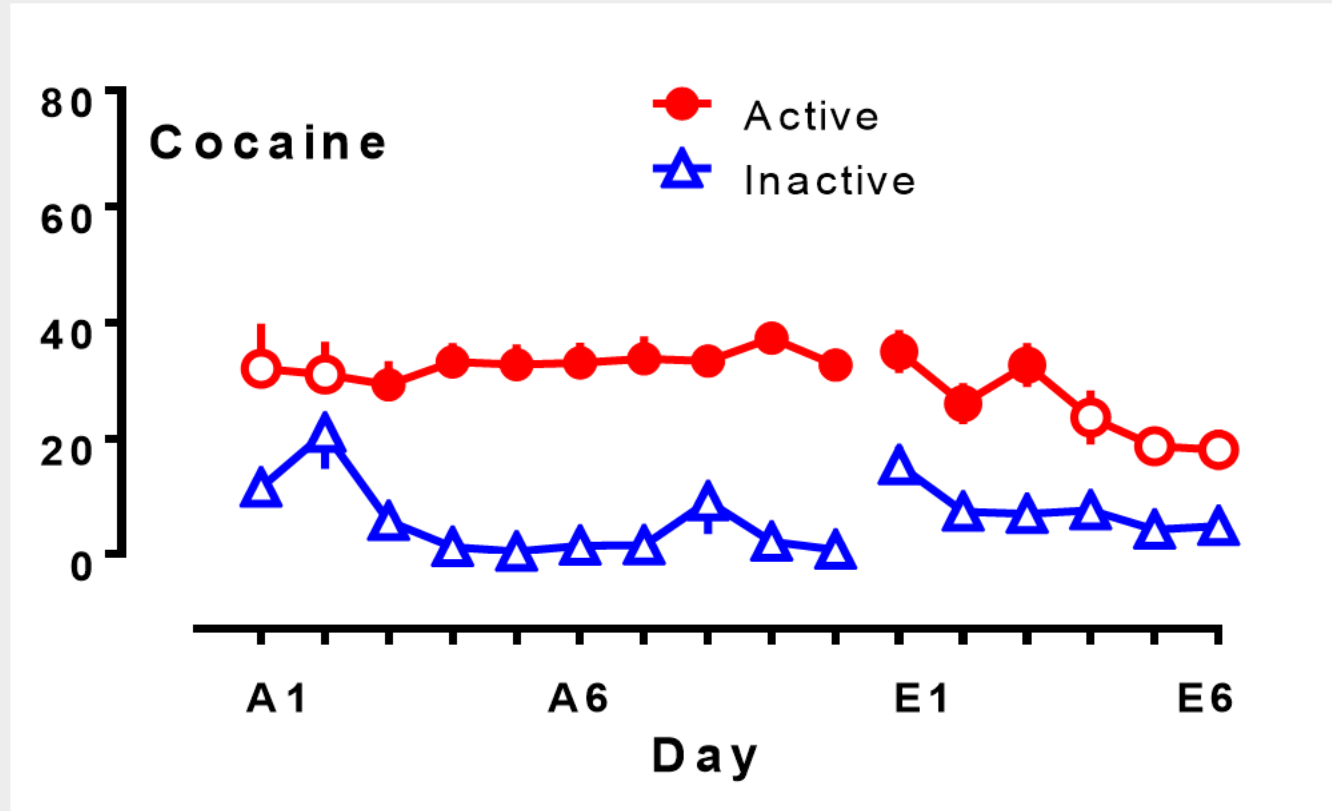
Cocaine is a DAT Blocker (DA Uptake Inhibitor)



Cocaine Increases EC DA in Rat Brain



Rats Learn to Self-Administer Cocaine



Treatment for Cocaine Use Disorder (CUD)

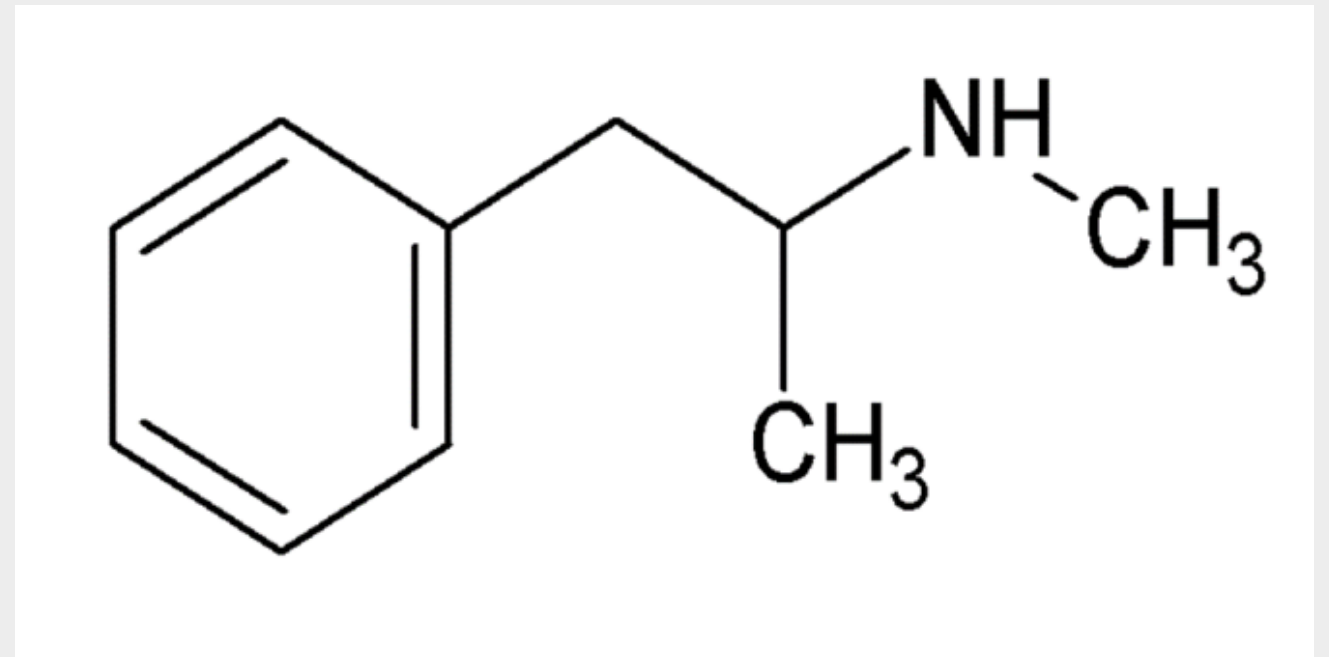
- Pharmacotherapy
 - No FDA-approved medication for CUD
- Psychosocial Therapies
 - Contingency Management
 - Cognitive Behavioral Therapy
 - Group & Community Therapies

Experimental Pharmacotherapies for CUD

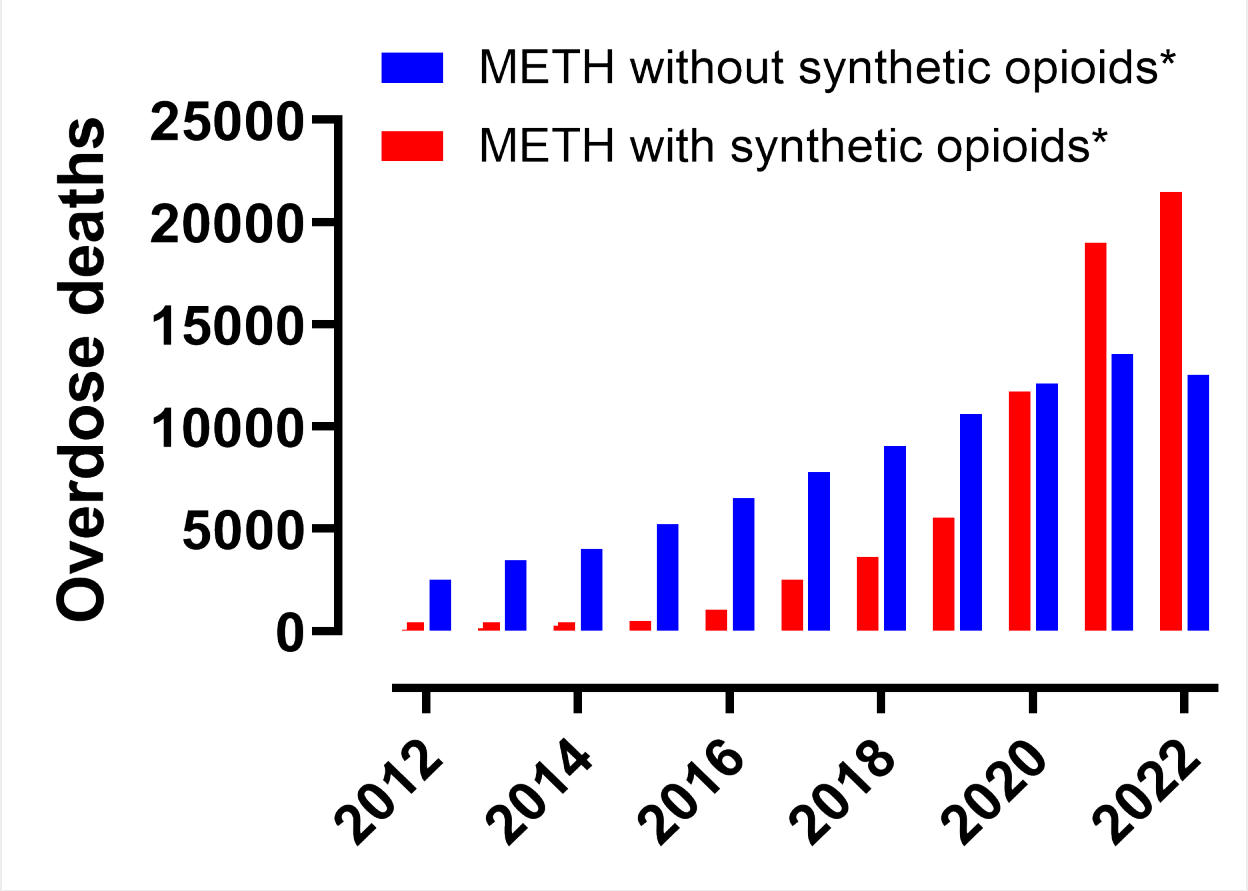
- Single agonist medications
 - Some positive results with stimulant medications, like mixed amphetamine salts (MAS) (*Tardelli et al., 2020*)
- Medication combinations
 - MAS + topiramate (*Levin et al., 2020*)

Methamphetamine

Methamphetamine (METH) is a Synthetic Amphetamine Derivative



METH Overdose Deaths are Increasing



*synthetic opioids other than methadone

Formulations and Methods of Use

- Methamphetamine (i.e., Ice or Crystal)
 - Smoking using pipes
- Methamphetamine HCl
 - Intravenous injection of solutions using needle and syringe
 - Intranasal snorting of crystals

Pharmacokinetics and Metabolism

- Pharmacokinetics
 - Smoked drug reaches brain within seconds
 - Intravenous drug reaches brain within seconds
 - Intranasal drug reaches brain within minutes
- Metabolism
 - *N*-demethylation to form amphetamine (bioactive)
 - Hydroxylation to form inactive metabolites

Desired Effects

- Enhanced Mood and Euphoria
- Increased Attention and Alertness
- Decreased Need for Sleep
- Appetite Suppression
- Sexual Arousal

Adverse Effects

- Agitation, Psychosis
- Arrhythmias, Palpitations, Heart Attack
- Hypertension, Stroke
- Hyperthermia, Rhabdomyolysis
- Multisystem Organ Failure

METH causes adverse health consequences



Chronic METH causes dental problems



Sensitization- Enhanced Effects

- Seizures
- Psychosis
 - Paranoid delusions
 - Visual and auditory hallucinations
 - Indistinguishable from schizophrenia
- Stereotypical Behaviors
 - Compulsive skin picking or scratching
 - Involuntary movements

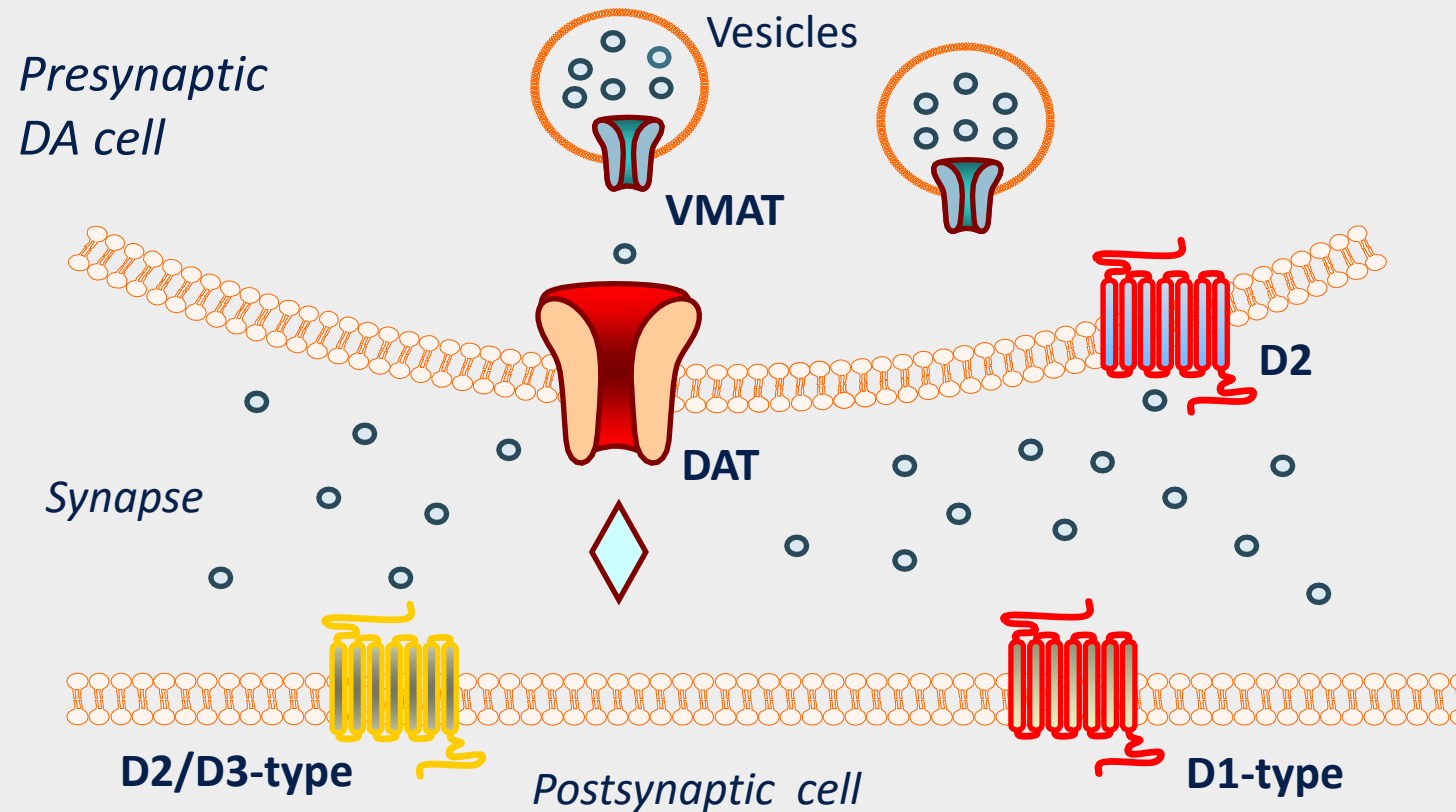
Withdrawal Effects

- Anhedonia and Depressed Mood
- Increased Appetite
- Anergia and Fatigue
- Vivid or Unpleasant Dreams
- Insomnia or Hypersomnia

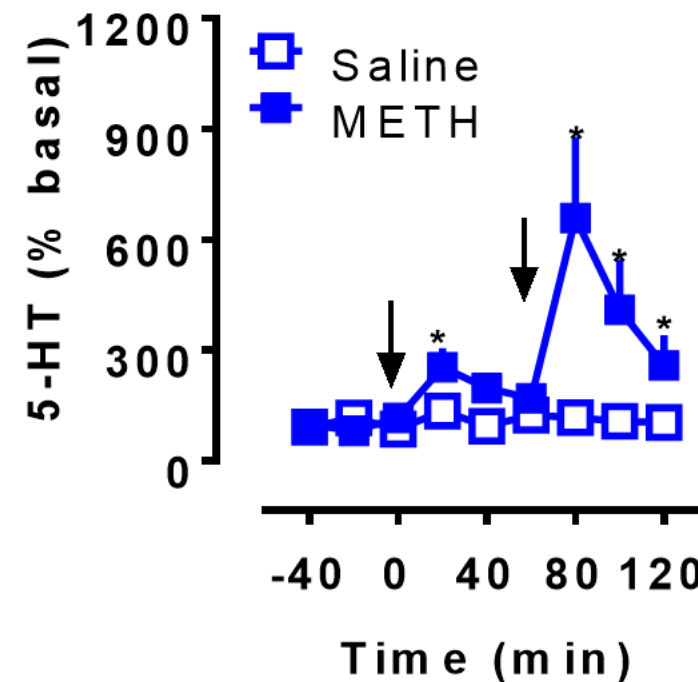
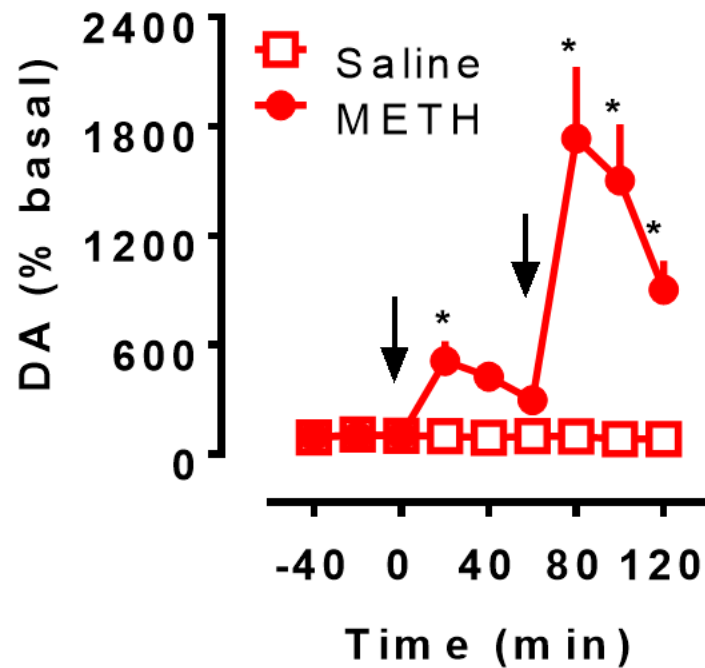
Molecular Sites of Action

- SLC6 Monoamine Transporters
 - Dopamine transporter (DAT)
 - Norepinephrine transporter (NET)
 - 5-HT transporter (SERT)
- Other sites
 - Vesicular Monoamine Transporter 2 (VMAT2)
 - Trace amine-associated receptors (TAAR1)

METH is a DAT substrate (DA releaser)



METH Increases EC DA More Than 5-HT



Cocaine vs Methamphetamine

COCAINE

Inhibits DAT-mediated reuptake of EC DA

METH

Inhibits DAT-mediated reuptake of EC DA

Evokes DAT-mediated release of IC DA by reverse transport

Cocaine vs Methamphetamine

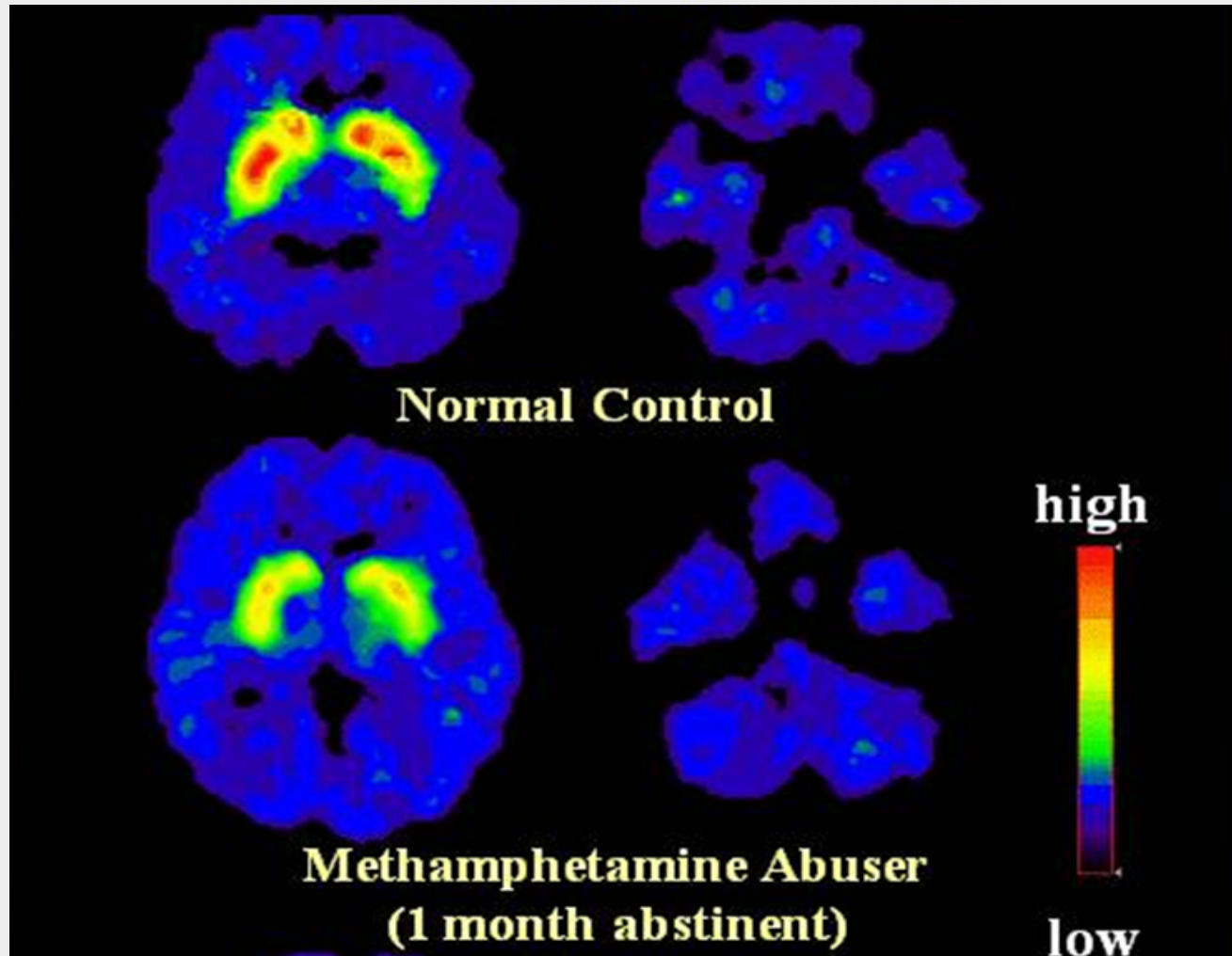
COCAINE

- Rapidly metabolized
- Effects last 1-2 hours
- Withdrawal lasts 1-2 days

METH

- Slowly metabolized
- Effects last 10-20 hours
- Withdrawal lasts many days

Chronic METH decreases DAT sites in brain



Role of METH in Gay Subculture

- METH intoxication
- Decreased inhibitions and judgment
- Increased sensation seeking and sexual arousal
- Unsafe sexual practices
- HIV transmission

Internet Websites Foster Risky Behaviors

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From: LastChanceLife
Added: March 15, 2008
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I'm doing a hit of meth

URL: <http://www.youtube.com/watch?v=xXeFJGeSfS>

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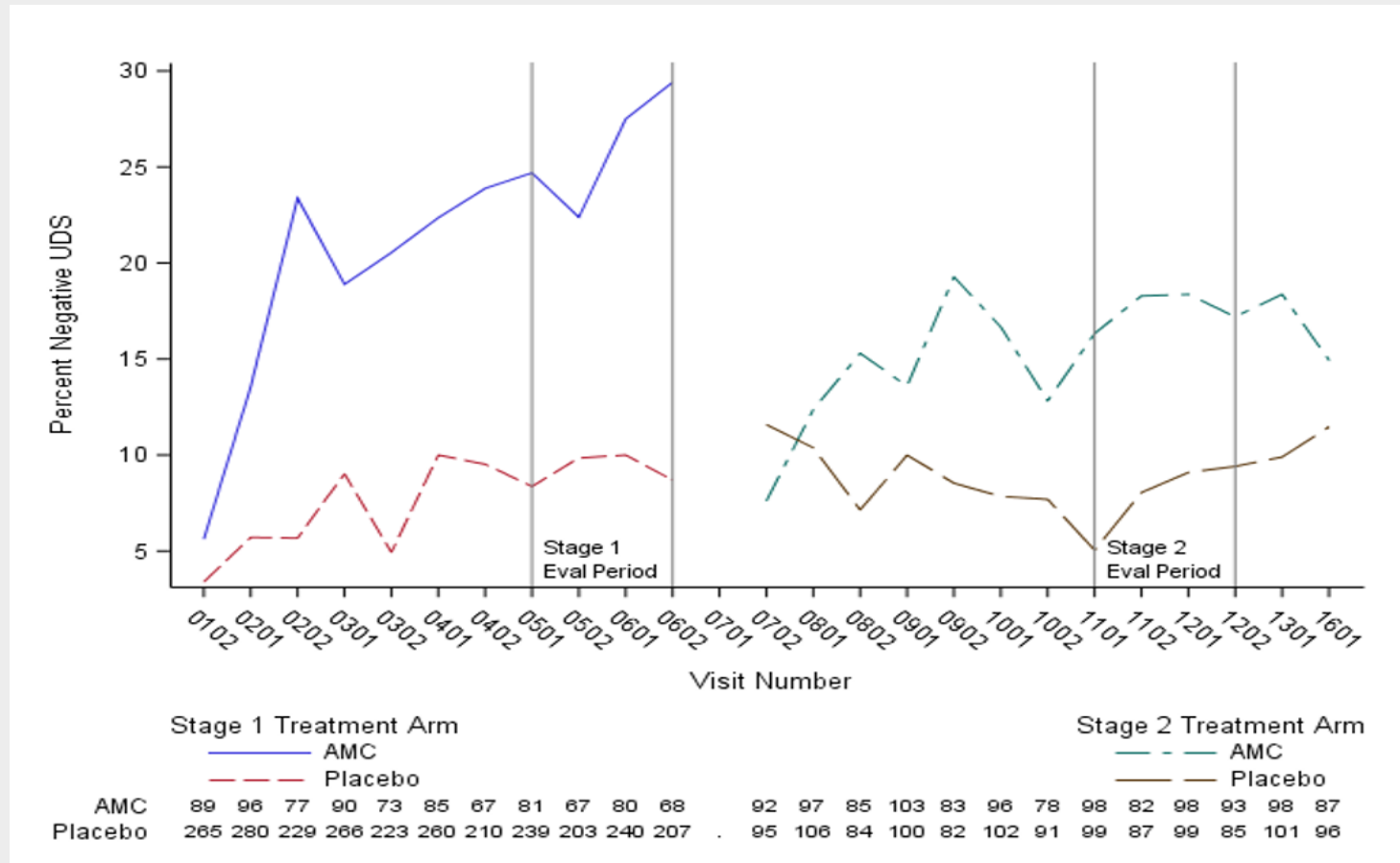
Treatment for METH Use Disorder (MUD)

- Pharmacotherapy
 - No FDA-approved medication for MUD
- Psychosocial Therapies
 - Contingency Management
 - Cognitive Behavioral Therapy
 - Group and Community Therapies

Experimental Pharmacotherapies for MUD

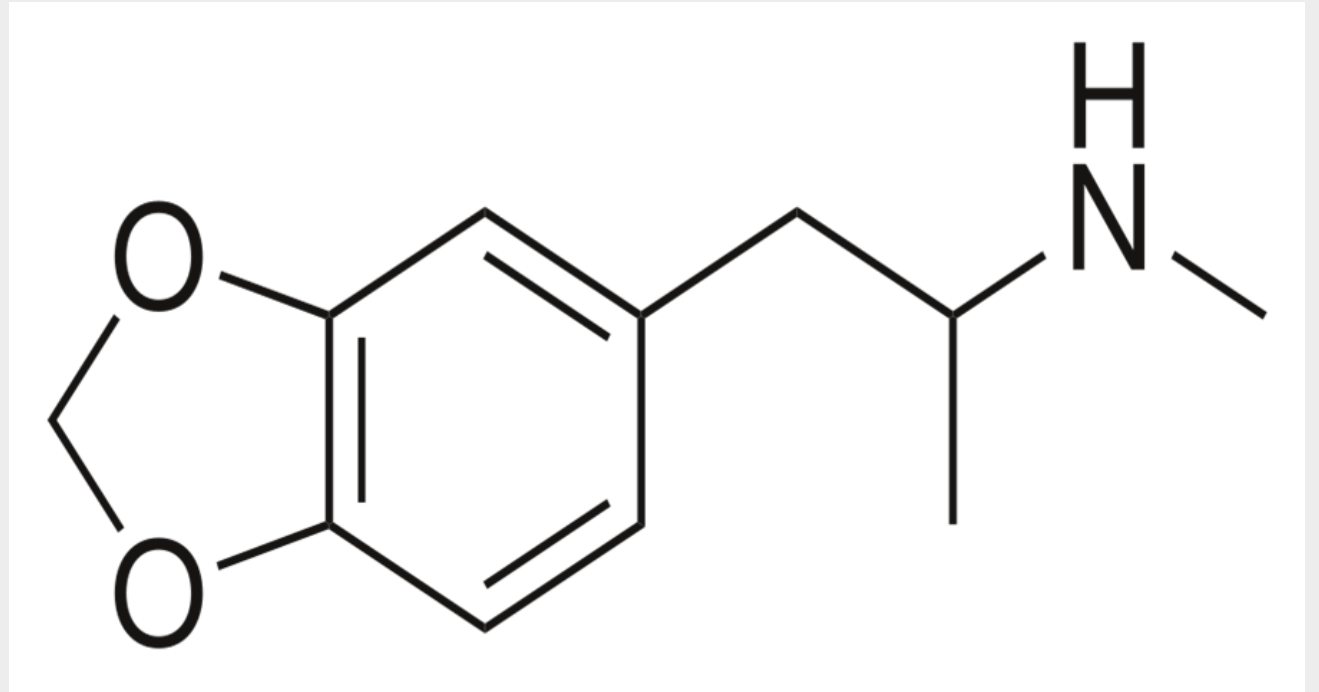
- Single medications
 - Some positive results with tetracyclic antidepressants, like mirtazapine (e.g., *Coffin et al., 2020*)
- Medication combinations
 - Bupropion + extended-release naltrexone (e.g., *Trivedi et al., 2021*)

Bupropion + Naltrexone Reduces METH Use



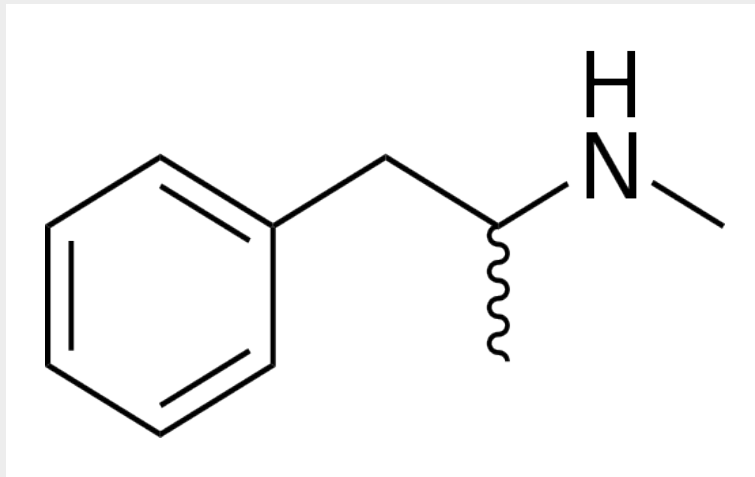
Ecstasy

Ecstasy (MDMA) is a Synthetic Amphetamine Derivative

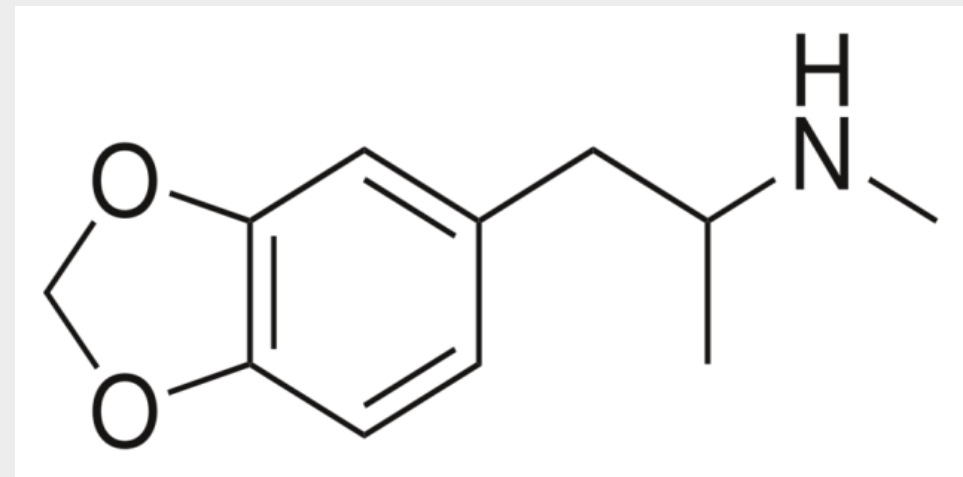


MDMA is a Ring-Substituted Amphetamine

Methamphetamine



3,4-Methylenedioxy
Methamphetamine (MDMA)



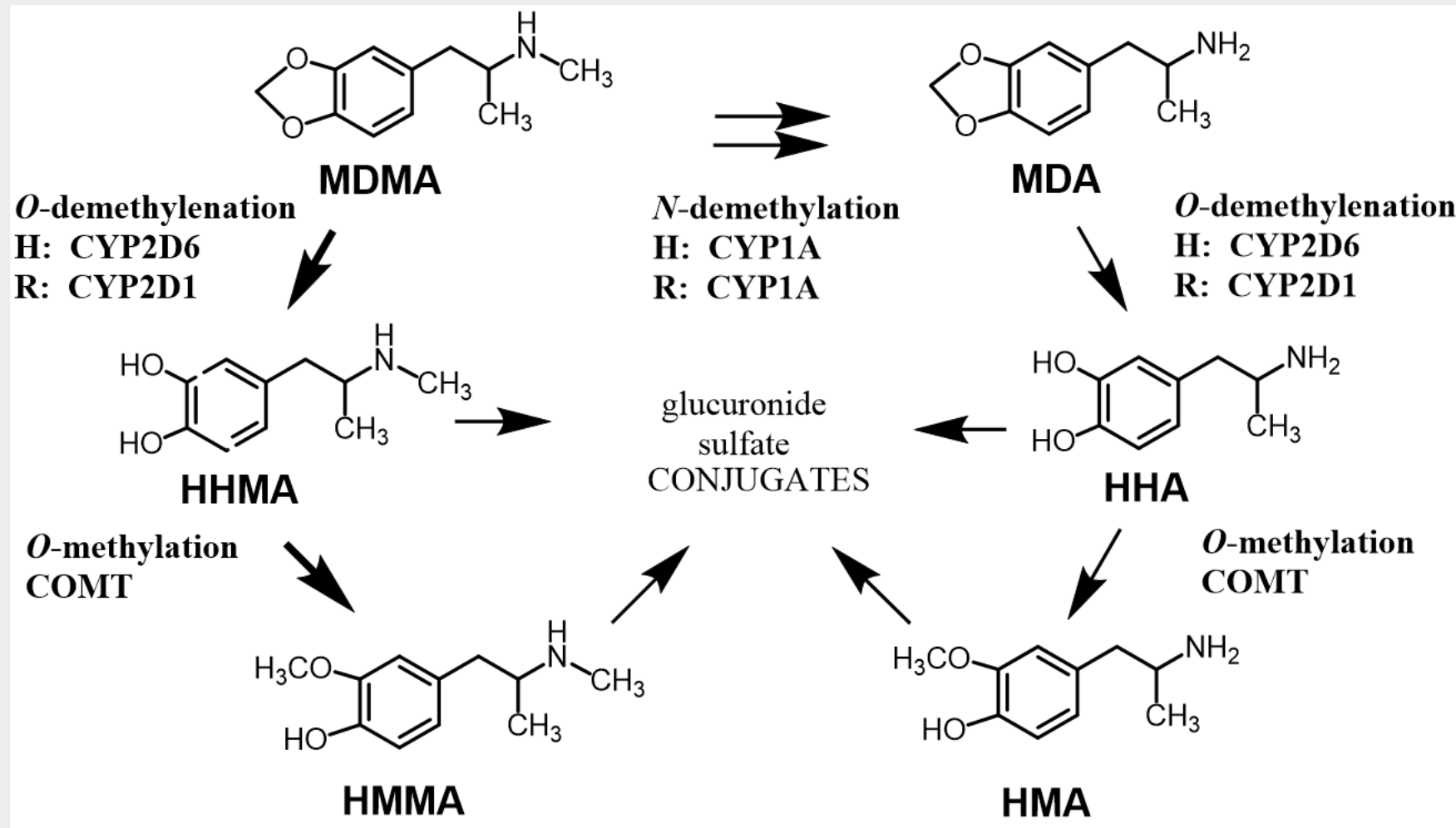
Formulations and Methods of Use

- Powders, capsules and tablets
 - Oral ingestion of tablets most common
 - Some intranasal and intravenous use
- “Bumping” or repeated intermittent dosing
- “Stacking” or taking multiple doses at once
- Binge and crash cycling

Pharmacokinetics And Metabolism

- Pharmacokinetics
 - C_{max} reached within 2 h of oral ingestion
 - Non-linear drug accumulation at doses > 3 mg/kg
- Metabolism
 - N-demethylation to form MDA (bioactive)
 - O-demethylation to form hydroxylated metabolites

MDMA Metabolism is Complex



Desired Effects

- Combined effects of a stimulant and psychedelic
 - Enhanced mood and energy
 - Heightened or altered sensory perception
- Feelings of empathy and closeness to others
- Cardiovascular stimulation
- Appetite suppression

Adverse Effects

- Psychosis
- Sympathetic Stimulation
 - Palpitations and heart attack
 - Hypertension
- 5-HT Syndrome
 - Hyperthermia and dehydration
 - Treat with hydration, cooling, and sedation

Withdrawal

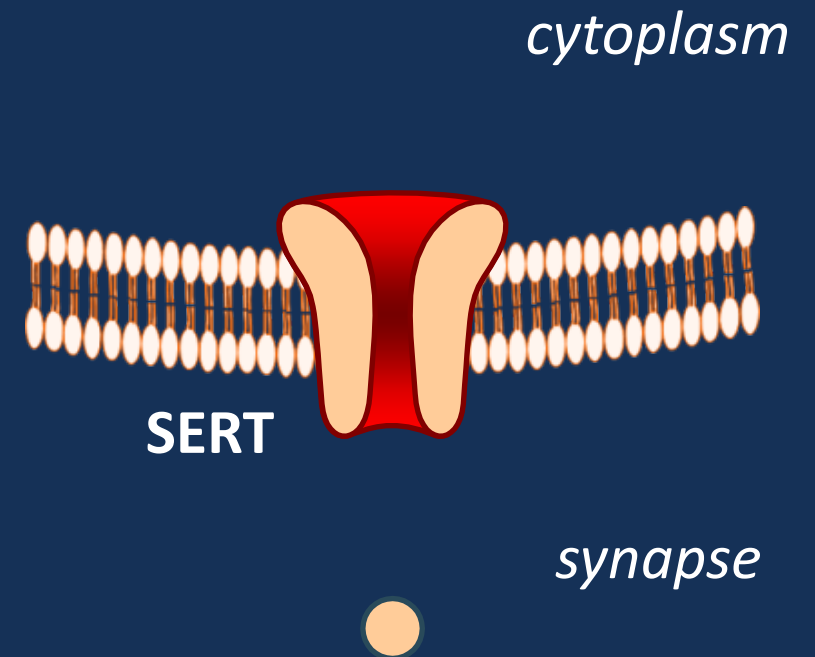
- Anhedonia and depressed mood
- Lethargy and fatigue for several days
- Sleep disturbances
- No indication for treatment

Molecular Sites of Action

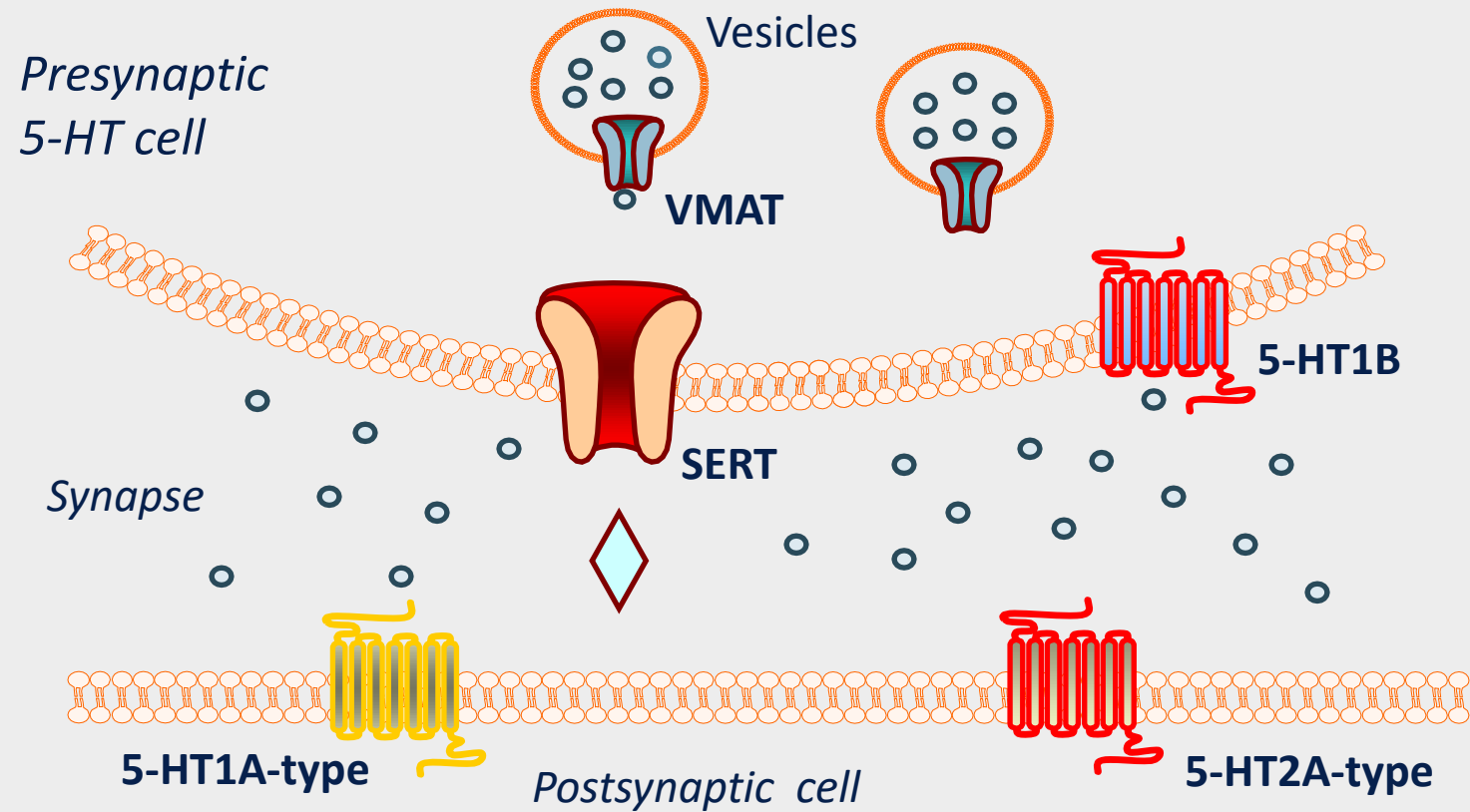
- SLC6 Monoamine Transporters
 - 5-HT transporter (SERT)
 - Dopamine transporter (DAT)
 - Norepinephrine transporter (NET)
- Other sites
 - Vesicular Monoamine Transporter 2 (VMAT2)
 - 5-HT_{2B} receptors

SERTs Mediate 5-HT Uptake

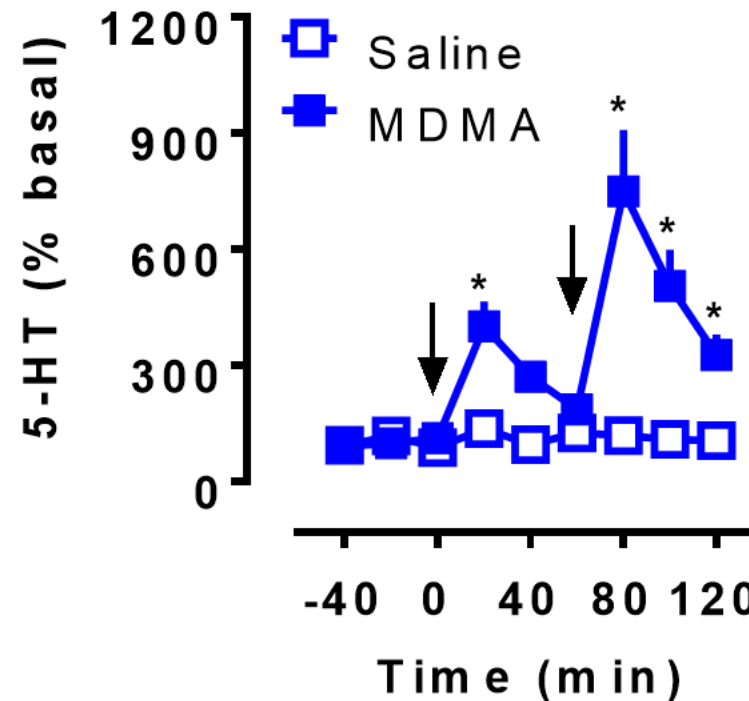
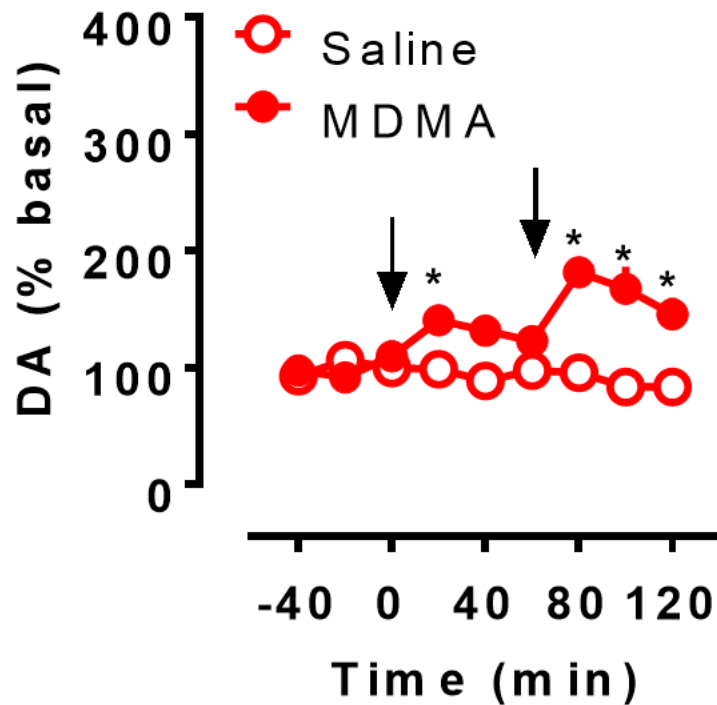
- SERTs are membrane proteins responsible for uptake of 5-HT
- Drugs that disrupt SERT function increase EC 5-HT
- Increases in 5-HT are not rewarding (e.g., SSRIs)



MDMA is a SERT substrate (5-HT releaser)



MDMA Increases EC 5-HT more than DA



Neurotoxic Potential

- MDMA enters 5-HT neurons via SERT
 - Drug accumulates in 5-HT neurons
- MDMA chronically impairs 5-HT neurons
 - Depletion of 5-HT stores
 - Inhibition of 5-HT synthesis
 - Loss of SERT sites in brain
- Neurotoxicity?

MDMA for PTSD

- MDMA induces empathy and prosocial effects
 - SERT-mediated 5-HT release (*Oeri, 2021*)
- MDMA is efficacious as an adjunct for treating PTSD
 - Phase III trial (*Mitchell et al., 2023*)
 - Increased patient-provider alliance
 - Decreased PTSD symptoms

Bath Salts



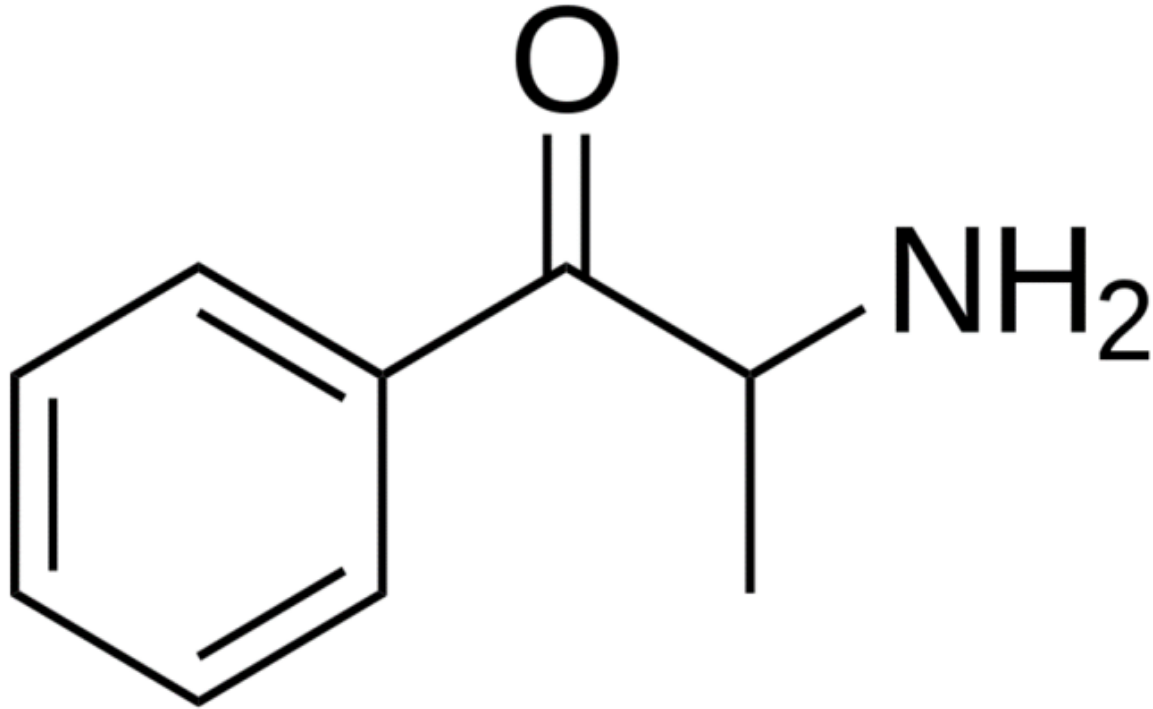
Cathinone is a Plant-Based Alkaloid



Khat Plant *Catha edulis*



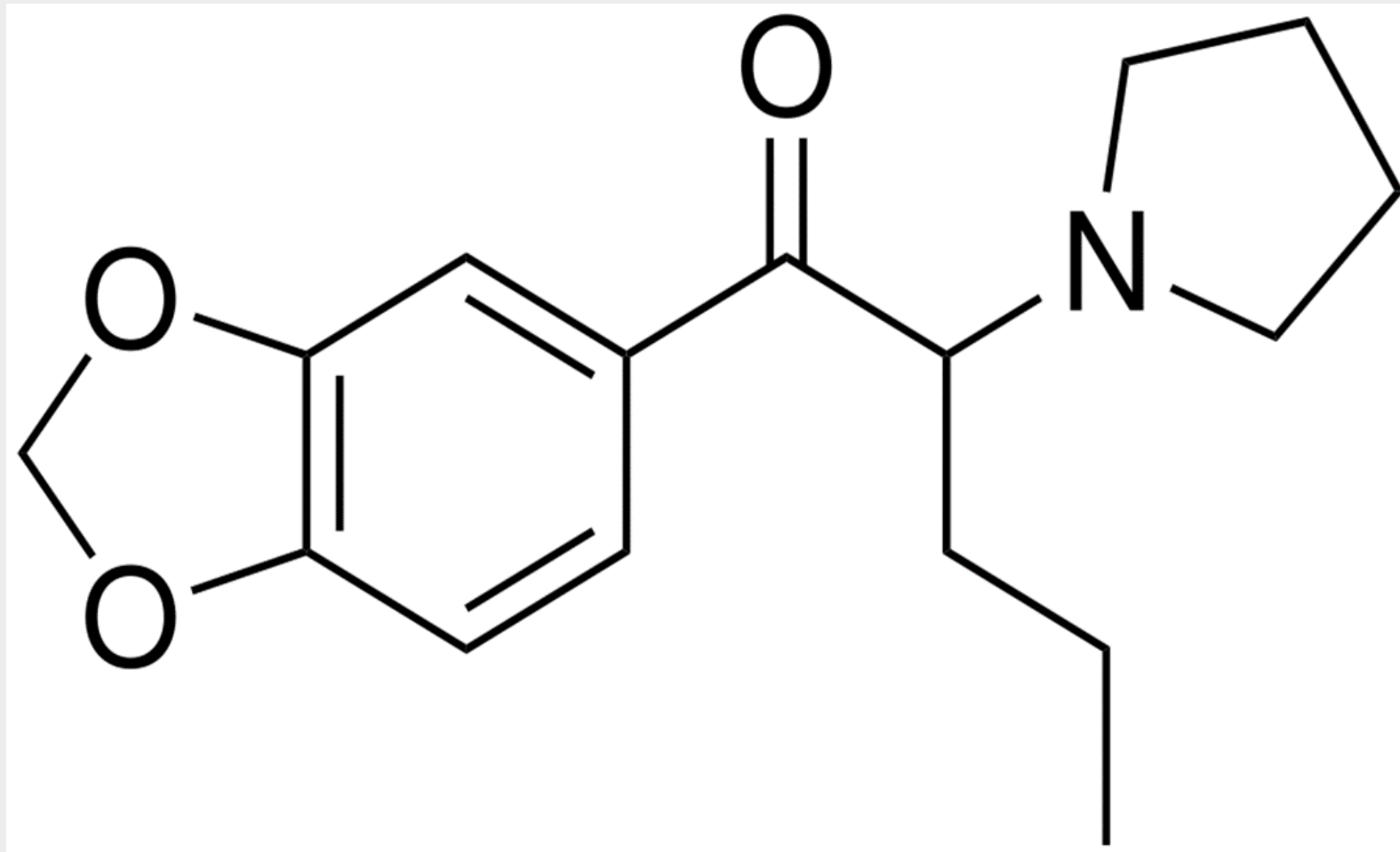
Cathinone is β -Keto Amphetamine



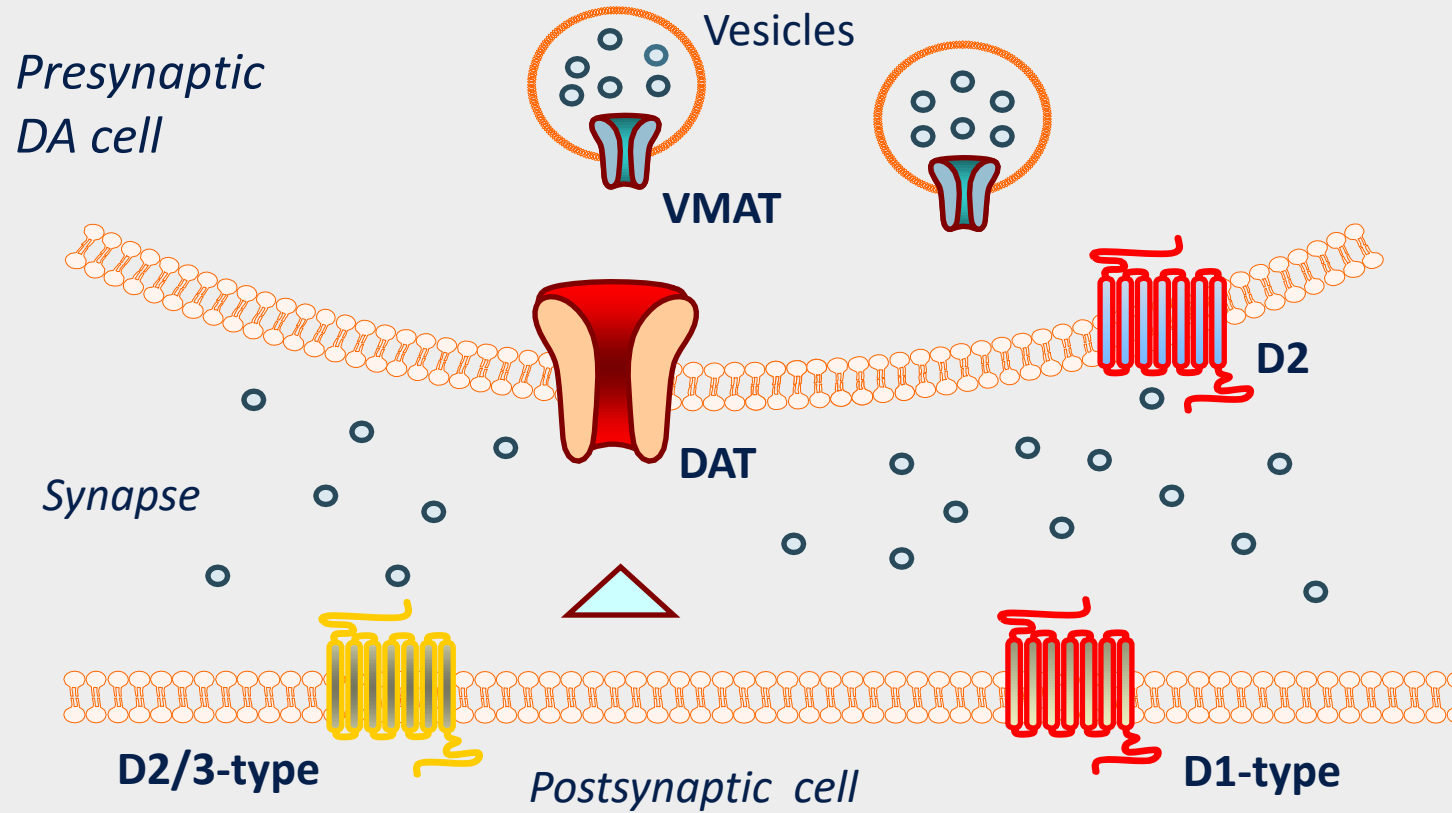
Psychoactive “Bath Salts” Products Contain Synthetic Cathinones



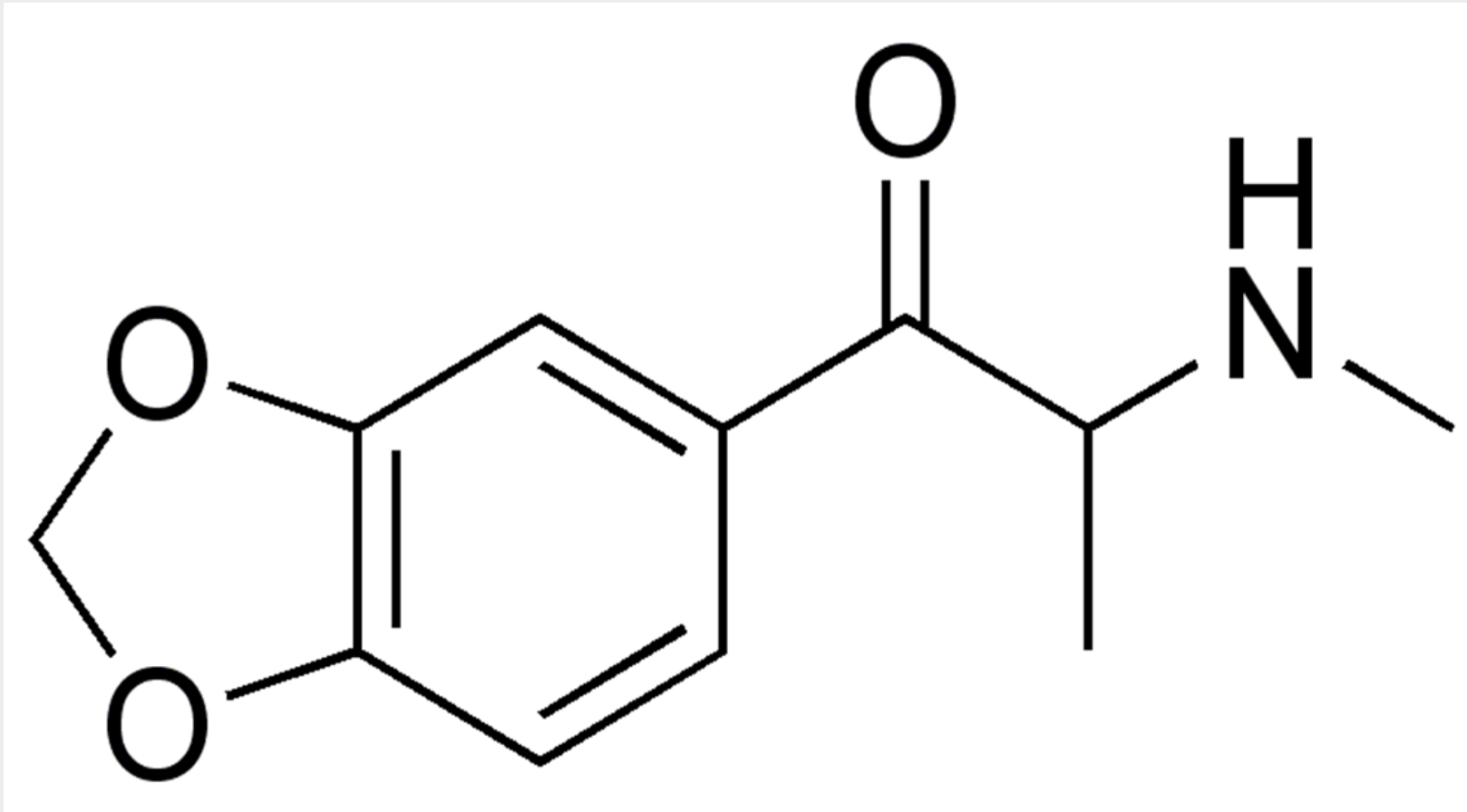
MDPV is an Analog of Pyrovalerone



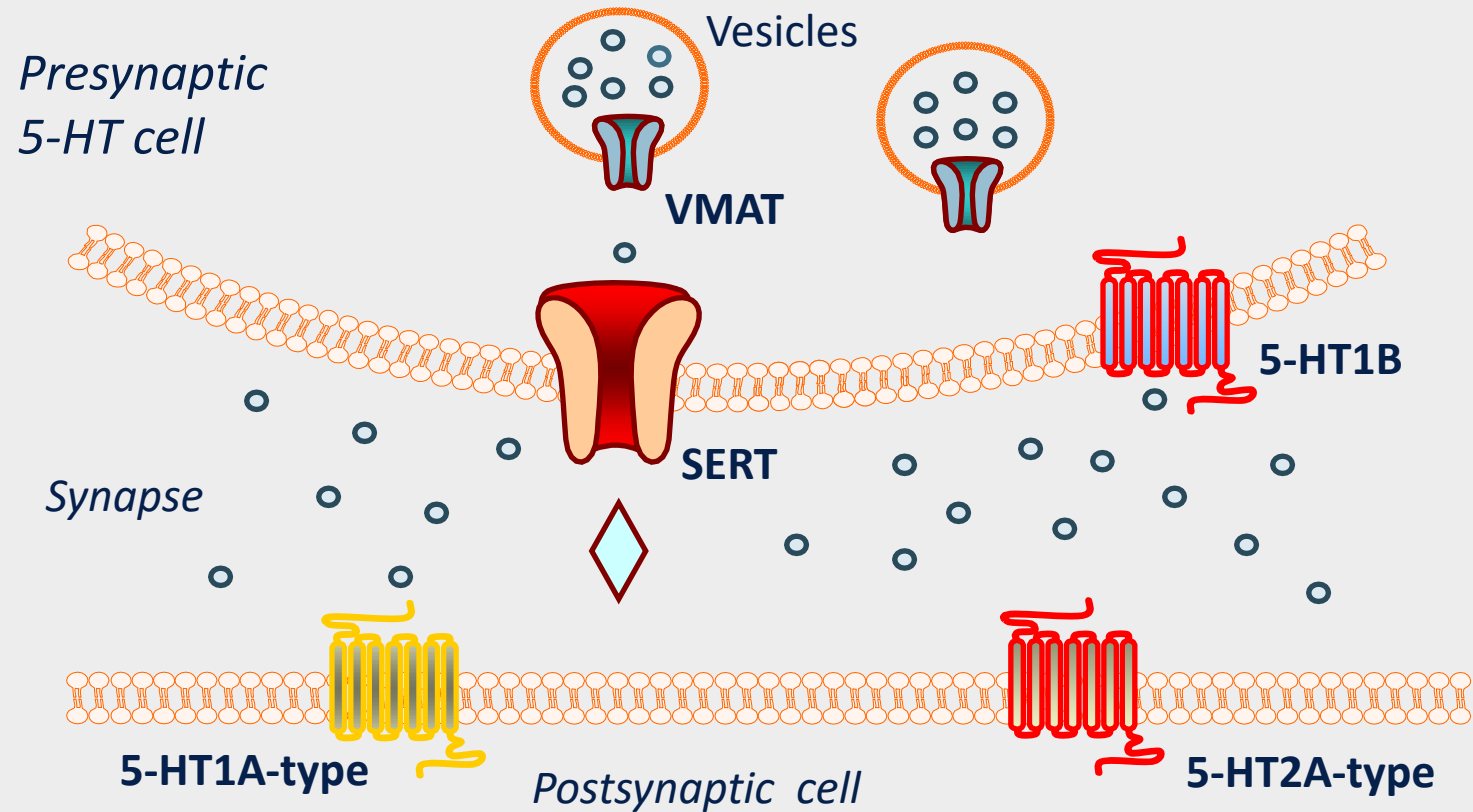
MDPV is a DAT Blocker (DA Uptake Inhibitor)



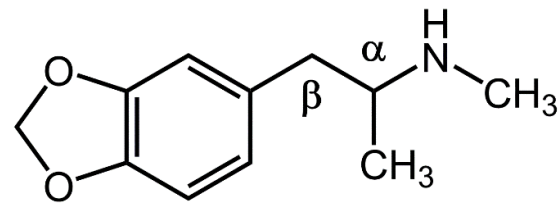
Methylone is β -Keto MDMA



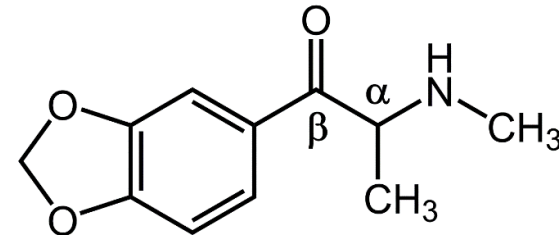
Methylone is a SERT substrate (5-HT releaser)



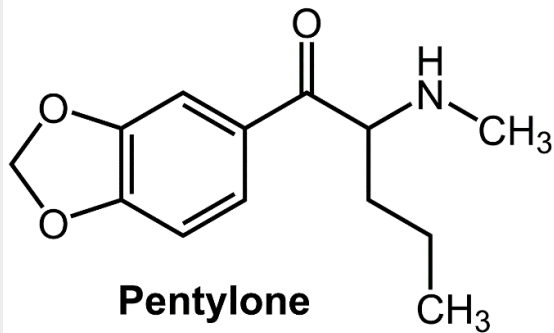
Methylone Analogs are Found as Counterfeit MDMA



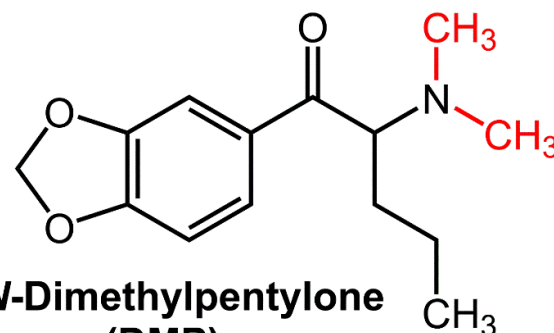
MDMA



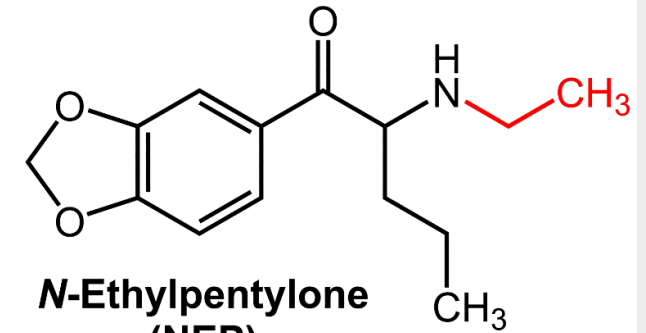
Methylone



Pentylone



**N,N-Dimethylpentylone
(DMP)**



**N-Ethylpentylone
(NEP)**

Summary



Overall Summary

1. Cocaine is a prototypical DAT inhibitor.
2. METH is a powerful stimulant, due to its DAT-mediated dopamine releasing action.
3. MDMA acts as a mild stimulant and psychedelic, due to its SERT-mediated 5-HT release.
4. MDPV is cocaine-like while methylone is MDMA-like.

Clinical Challenges

1. No FDA-approved medications for stimulant use disorders, so treatment is psychosocially-based.
2. No specific antidotes for stimulant intoxication, so treatment is supportive.
3. Stimulant-induced overdose deaths are increasing due to fentanyl co-use... intentional or accidental?

Thank You





Get in Touch



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