

STIMULANTS

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The ASAM Review Course of Addiction Medicine

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Financial Disclosures

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No Disclosures

General Outline

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

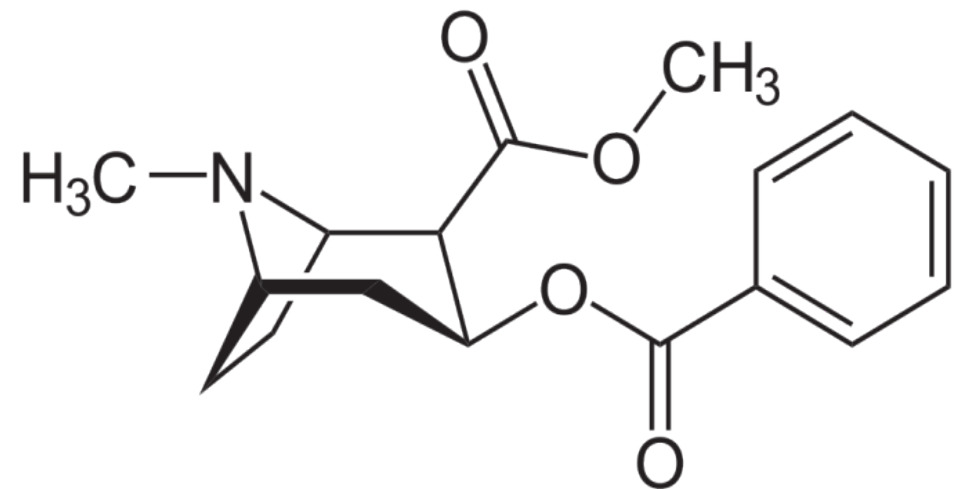
Topics Covered for Each Substance

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

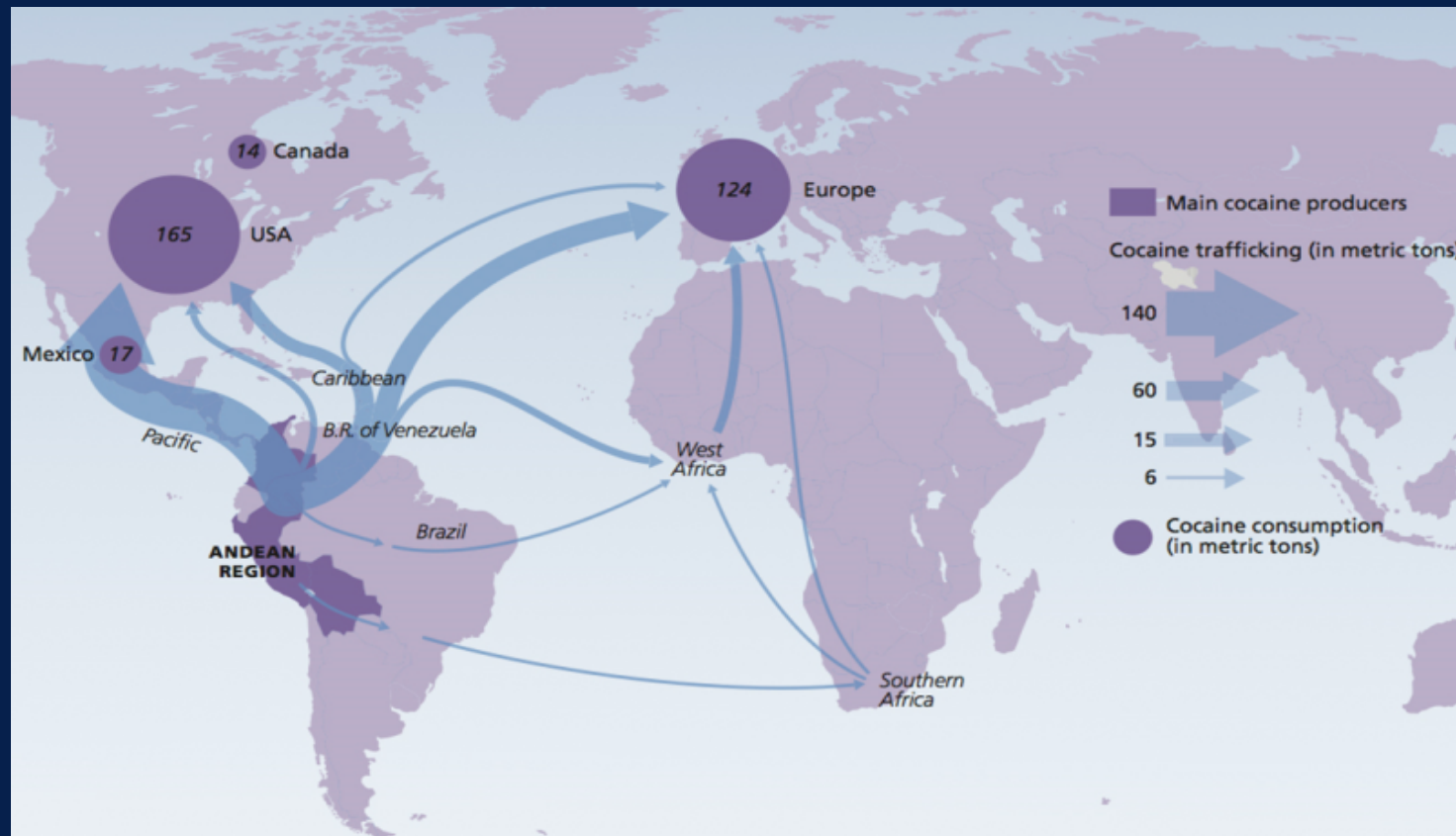
Cocaine



Cocaine is a Plant Based Alkaloid

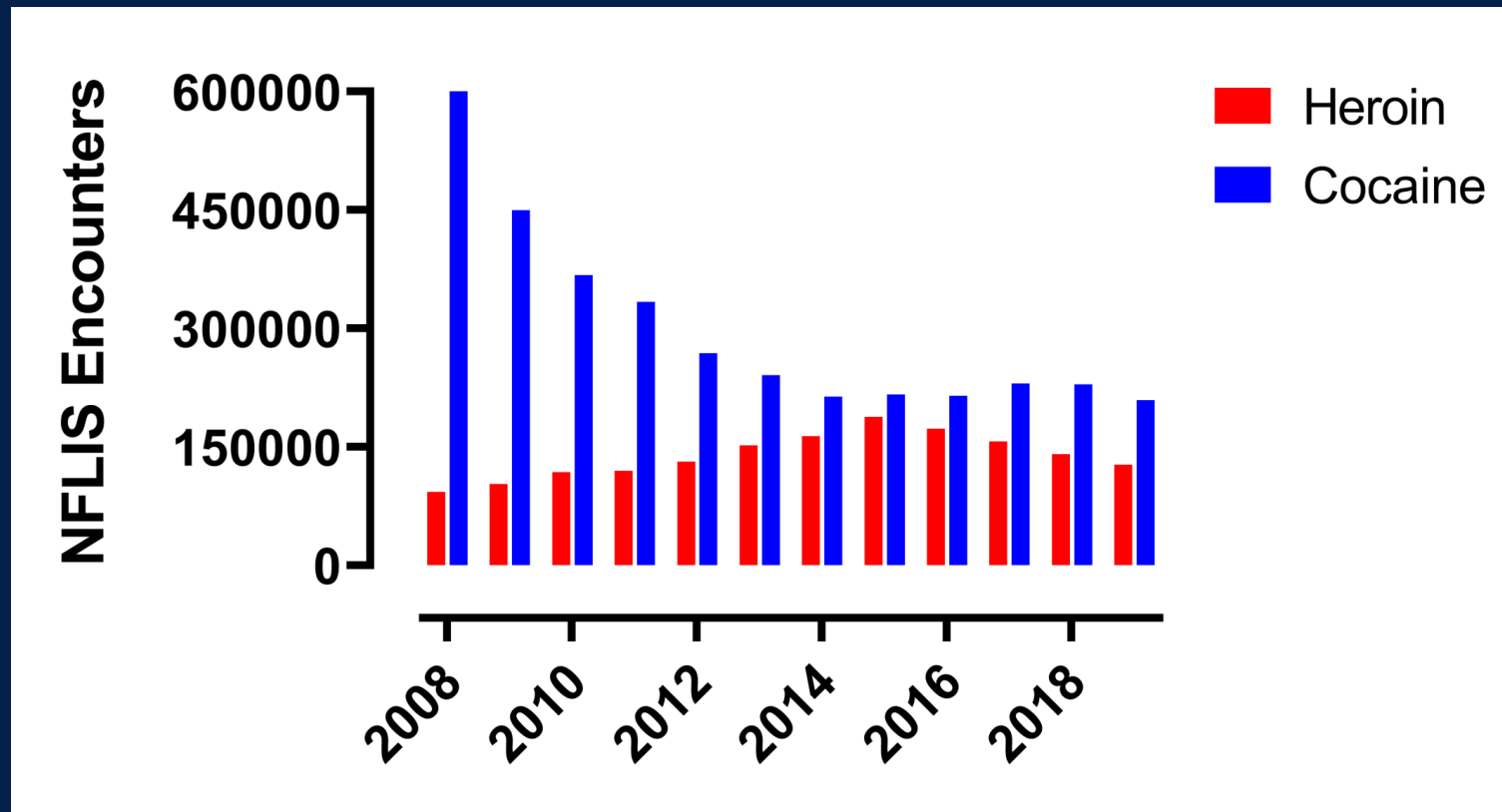


Andean Cocaine is Trafficked on a Global Scale





Cocaine Confiscation Remains Relatively Stable



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 of drug entry into the brain
 - Enhanced subjective and rewarding effects
- Intranasal and Oral Routes
 - Slower rate 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
 - Euphoria and sexual arousal diminished
 - But no longer-term tolerance
- Anorexia

Sensitization- Enhanced Effects

- Seizures
- Psychosis
 - Paranoid delusions
 - Visual, auditory and tactile hallucinations
 - Virtually indistinguishable from schizophrenia
- Stereotypical Behaviors

Withdrawal Effects

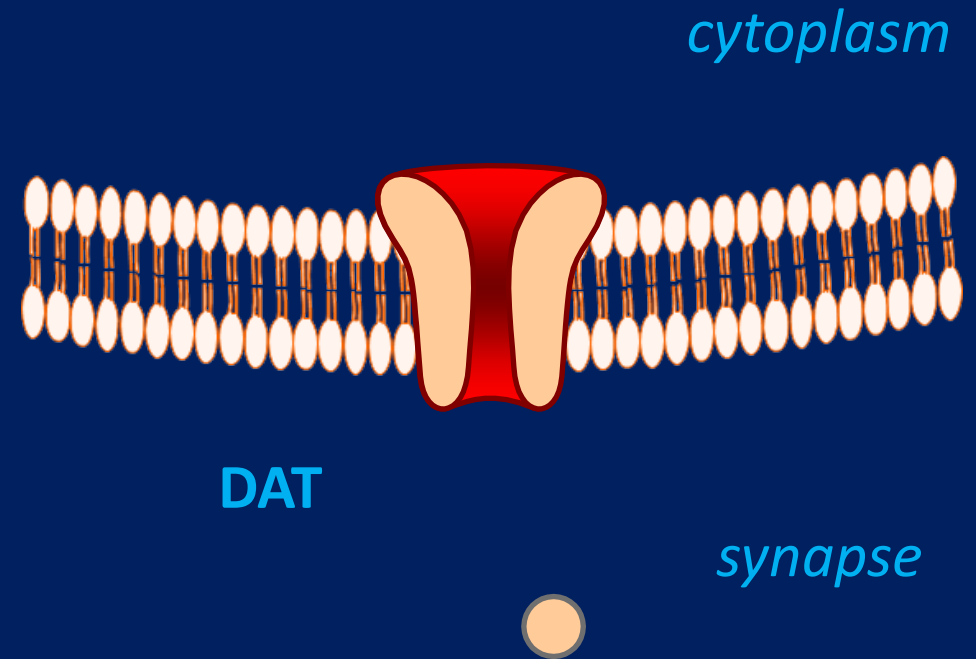
- Anhedonia and Depressed Mood
- Increased Appetite
- Anergia and Fatigue
- Vivid or Unpleasant Dreams
- Insomnia or Hypersomnia

Molecular Sites of Action

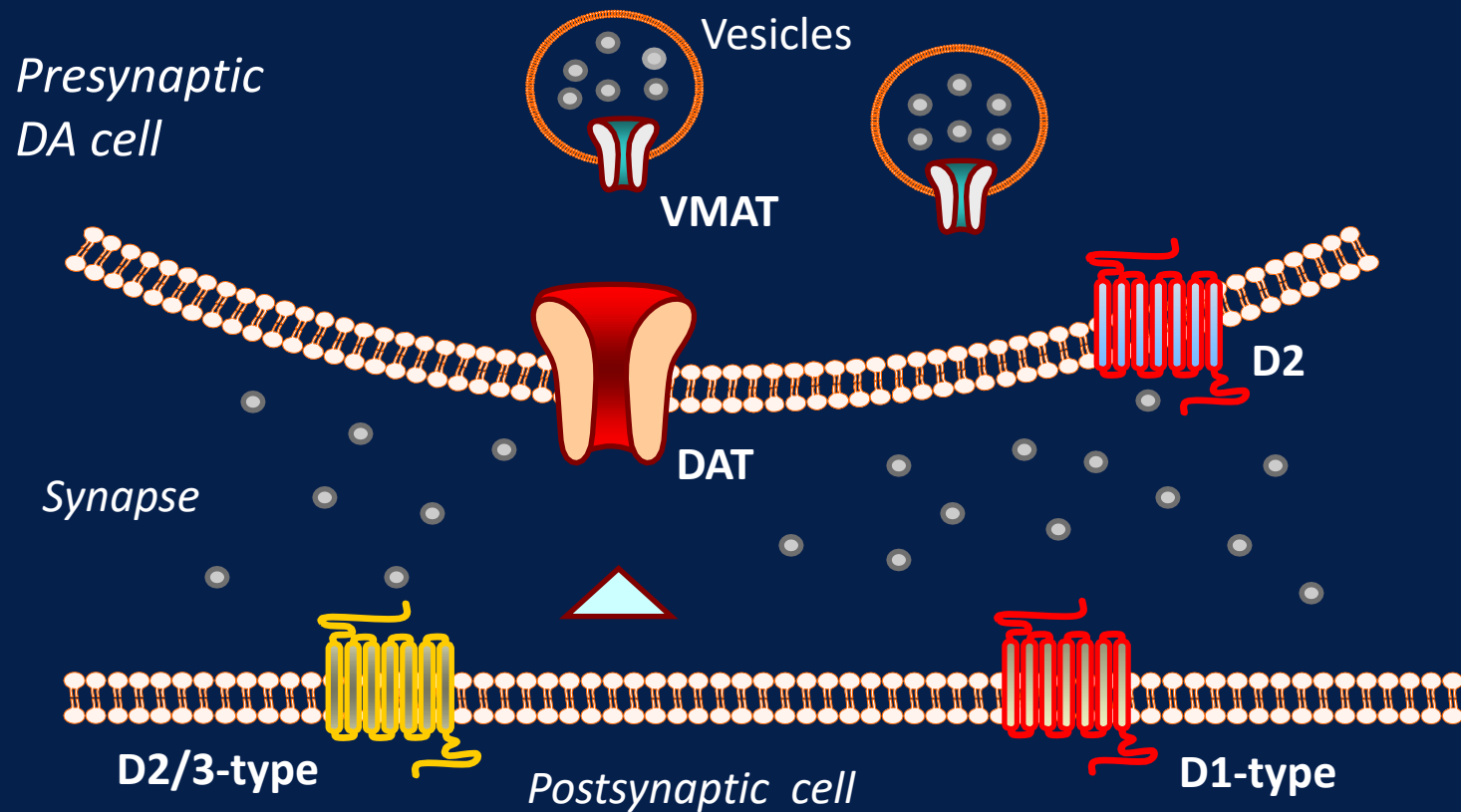
- SLC6 Monoamine Transporters
 - Dopamine transporter (DAT)
 - Norepinephrine transporter (NET)
 - 5-HT transporter (SERT)
- Other sites
 - Sodium channels

DATs Mediate DA Uptake

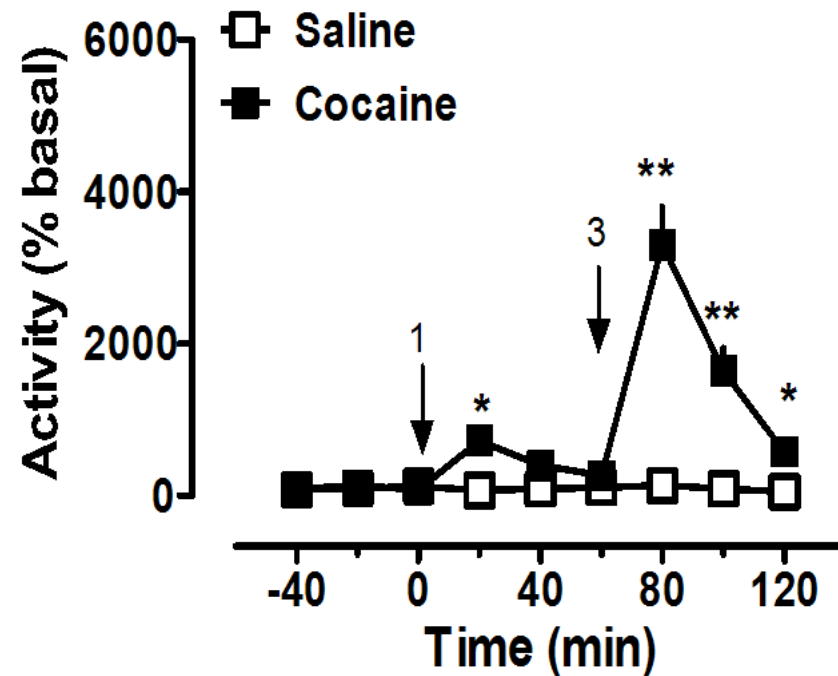
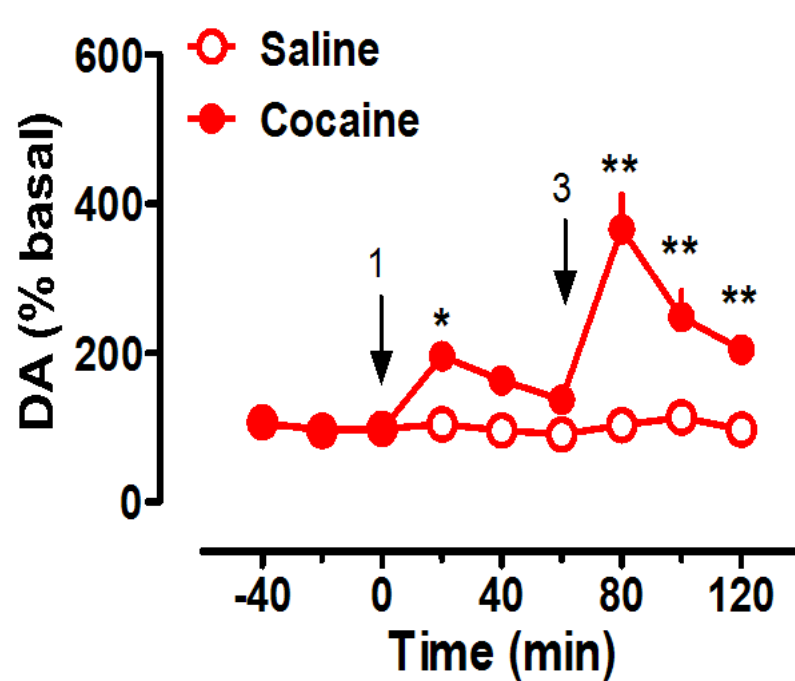
- DATs are membrane proteins responsible for uptake of released dopamine (DA)
- Drugs that disrupt DAT function increase synaptic DA
- Increases in DA are rewarding



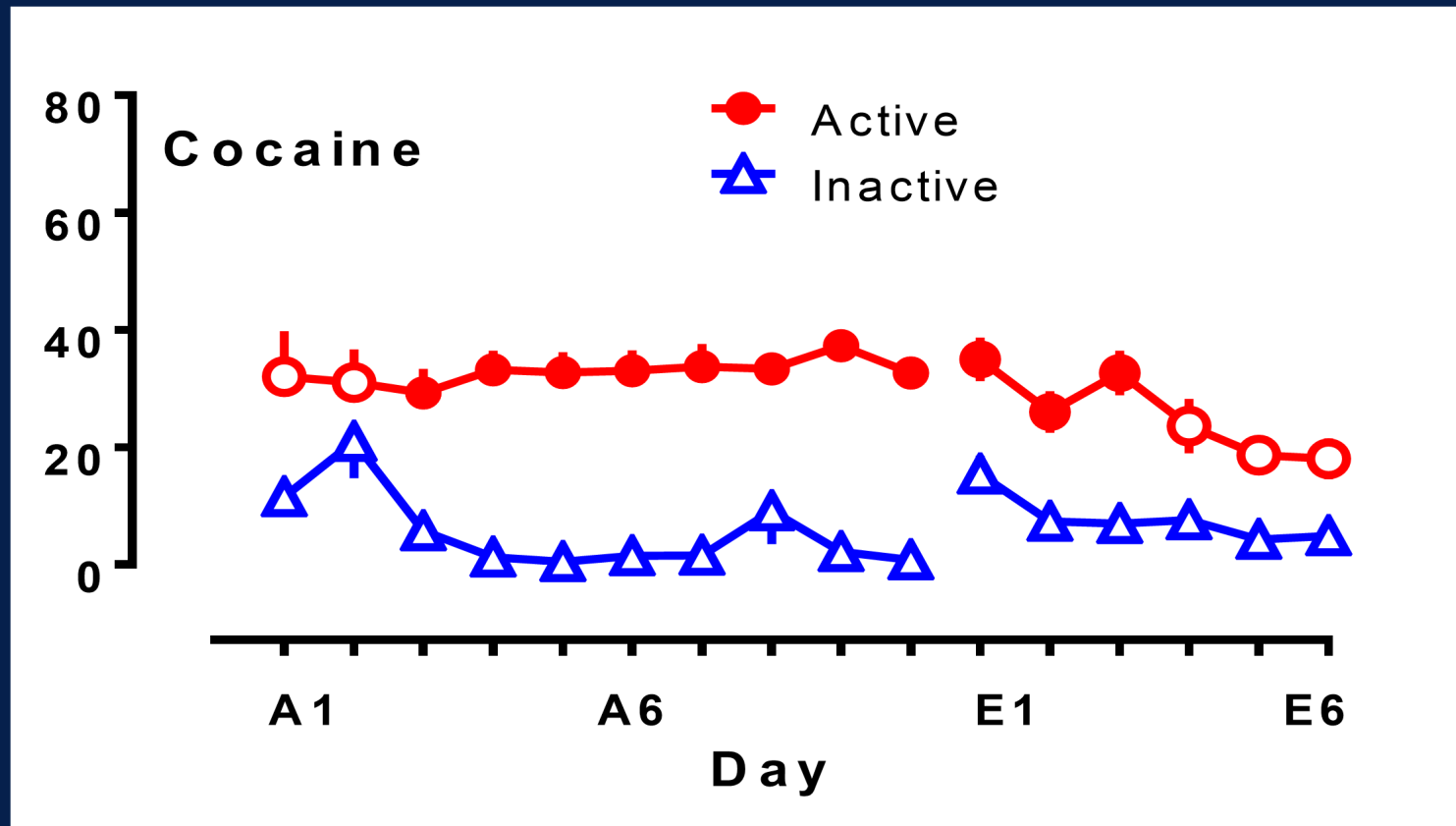
Cocaine is a DAT Blocker (DA Uptake Inhibitor)



Cocaine Increases Extracellular DA in Rat Nucleus Accumbens



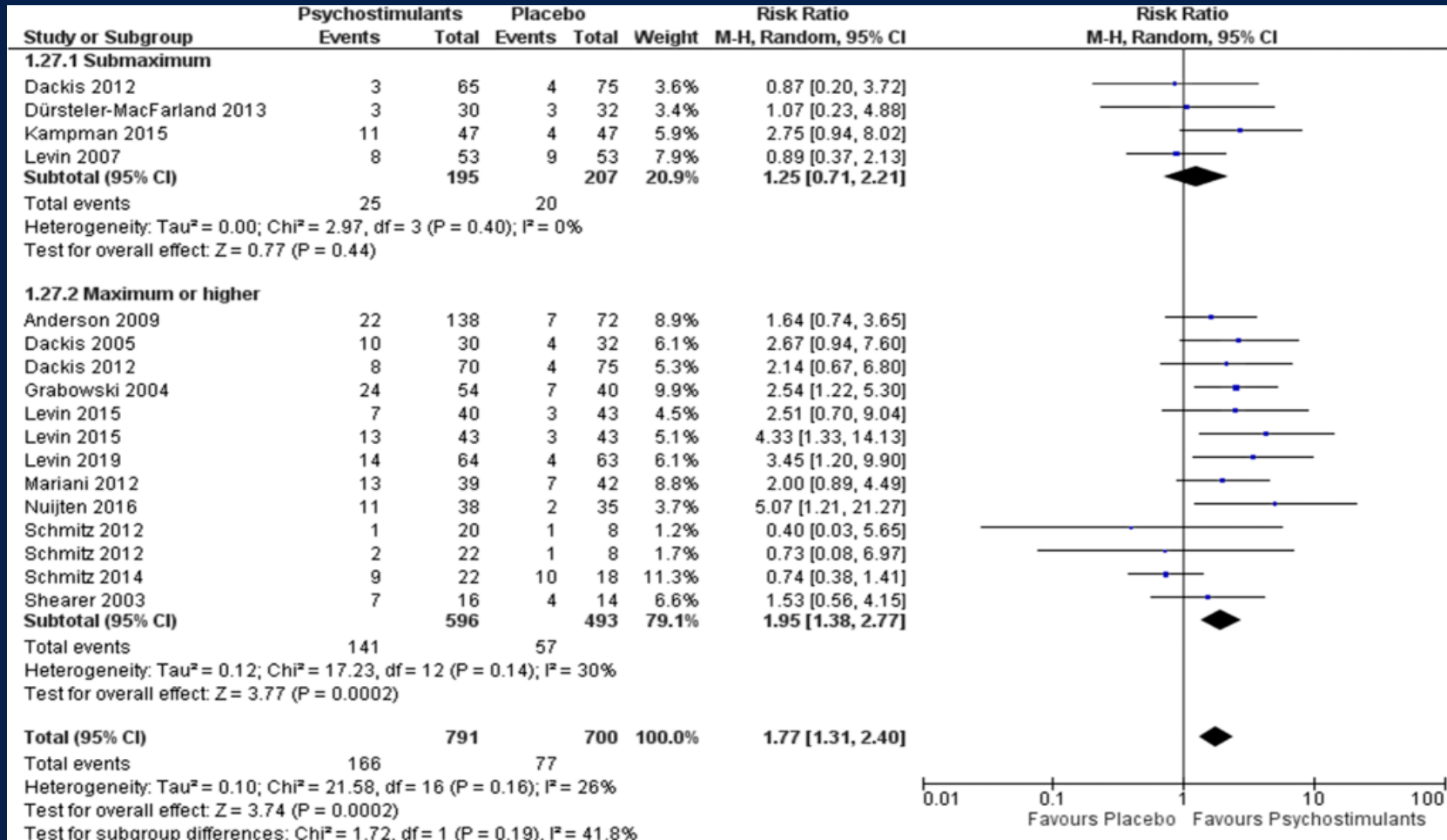
Rats Will Readily Learn to Self-Administer Cocaine



Treatment for Cocaine Dependence

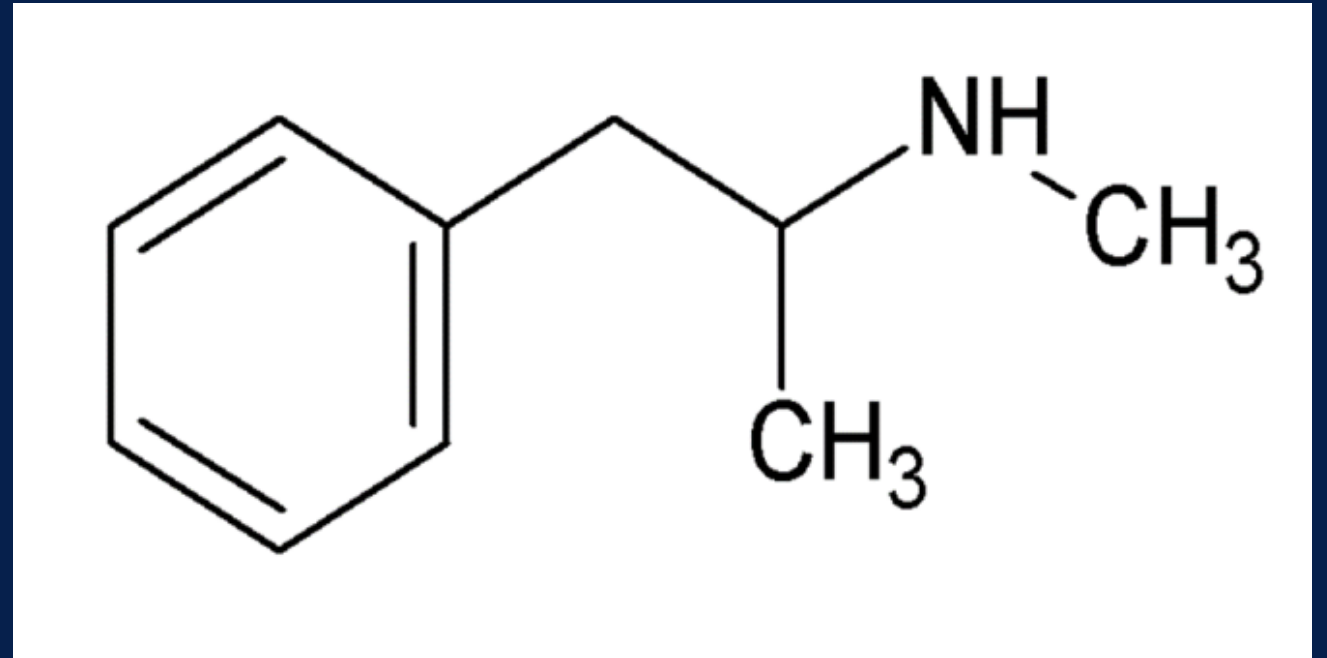
- Pharmacotherapy
 - No FDA-approved medication for cocaine dependence
- Psychologically-Based Therapies
 - Cognitive Behavioral Therapy
 - Contingency Management
 - Group & Community Therapies

Stimulant Meds- Some Success

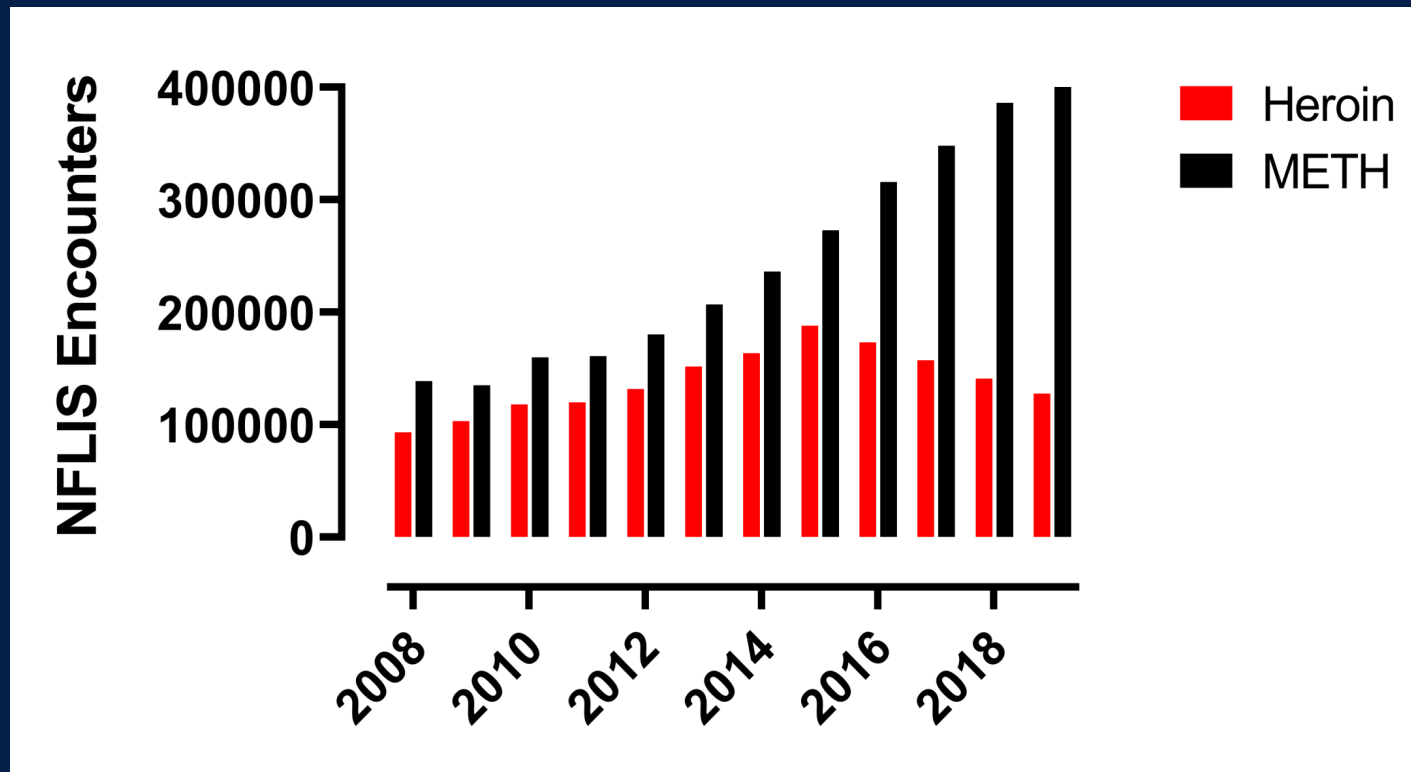


Methamphetamine

Methamphetamine is a Synthetic Amphetamine Analog



METH Confiscation is Increasing Dramatically in Recent Years



Most METH is Now Trafficked by Mexican Cartels



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

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



2005© "Faces of Meth"



1.5 Years

“METH Mouth”



Sensitization- Enhanced Effects

- Seizures
- Psychosis
 - Paranoid delusions
 - Visual, auditory and tactile hallucinations
 - Virtually indistinguishable from schizophrenia
- Stereotypical Behaviors

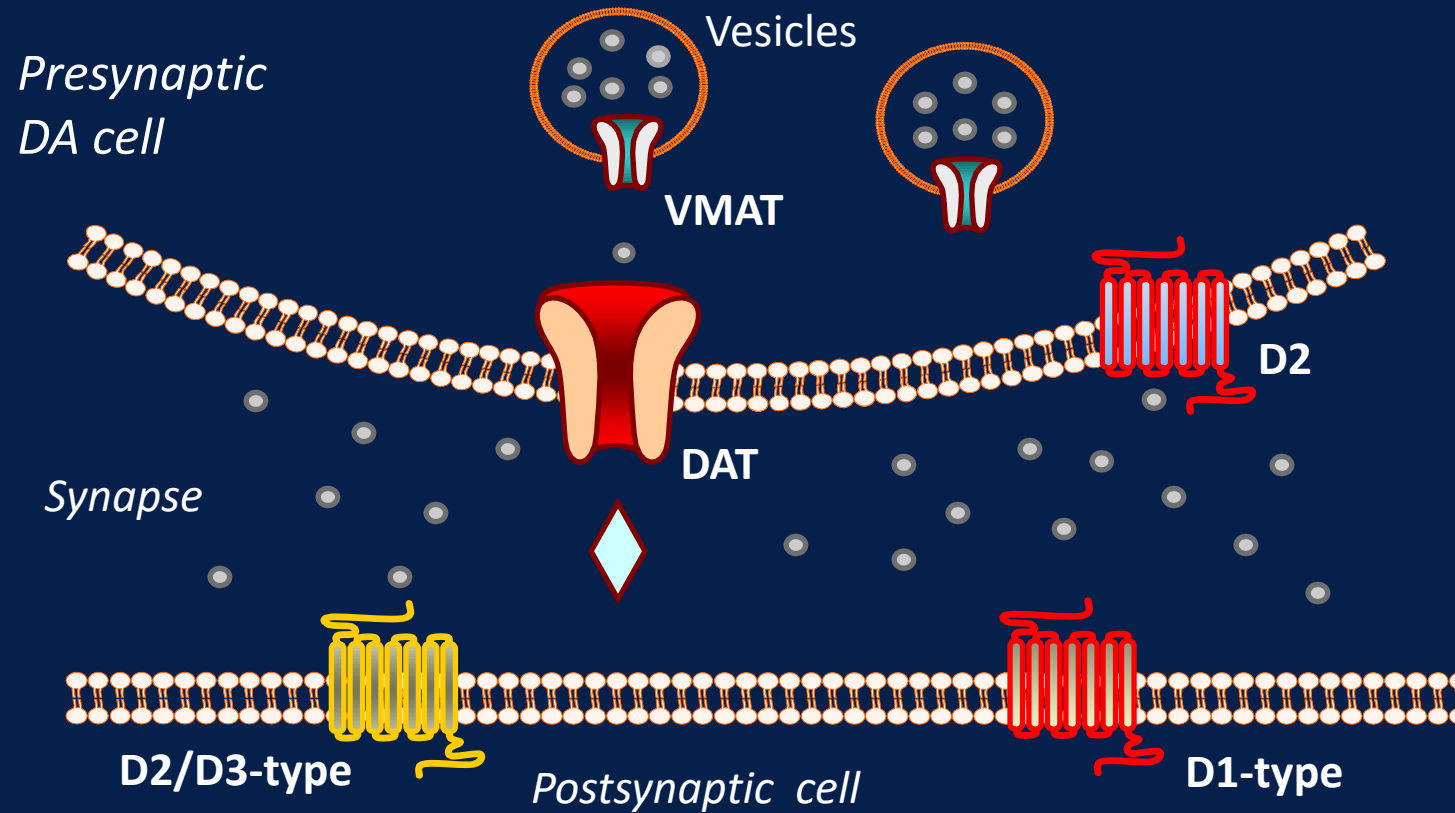
Withdrawal Effects

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

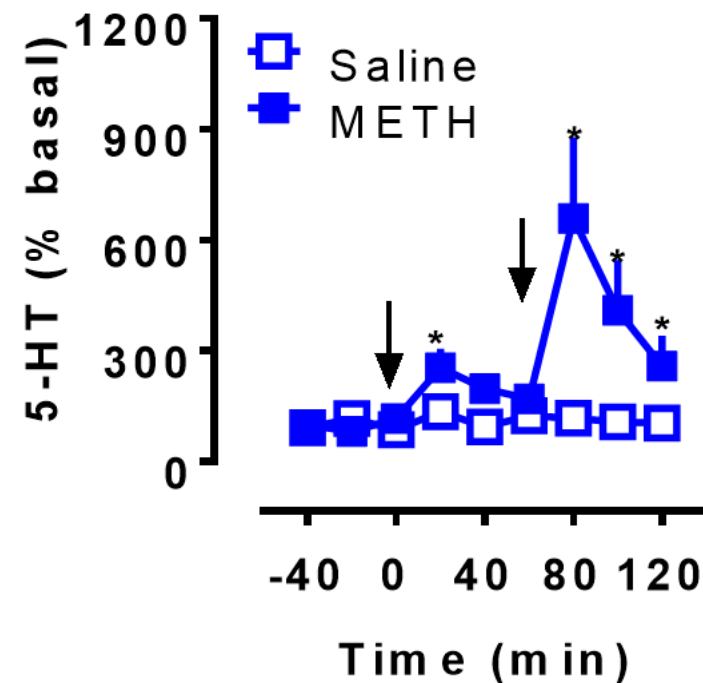
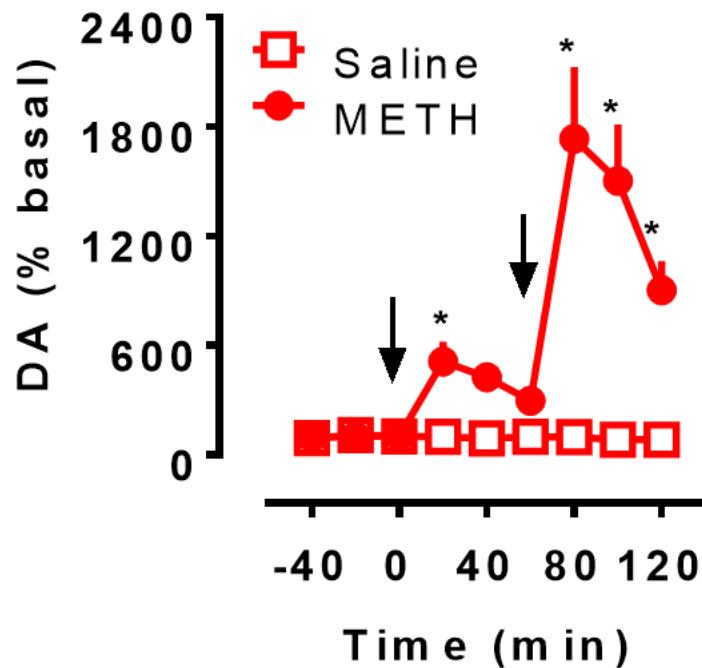
Molecular Sites of Action

- 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 Extracellular DA More Than 5-HT



Cocaine vs Methamphetamine

COCAINE

Inhibits DAT-mediated
reuptake of synaptic
dopamine

METH

Inhibits DAT-mediated
reuptake of synaptic
dopamine

Evokes DAT-mediated
release of dopamine

Cocaine vs Methamphetamine

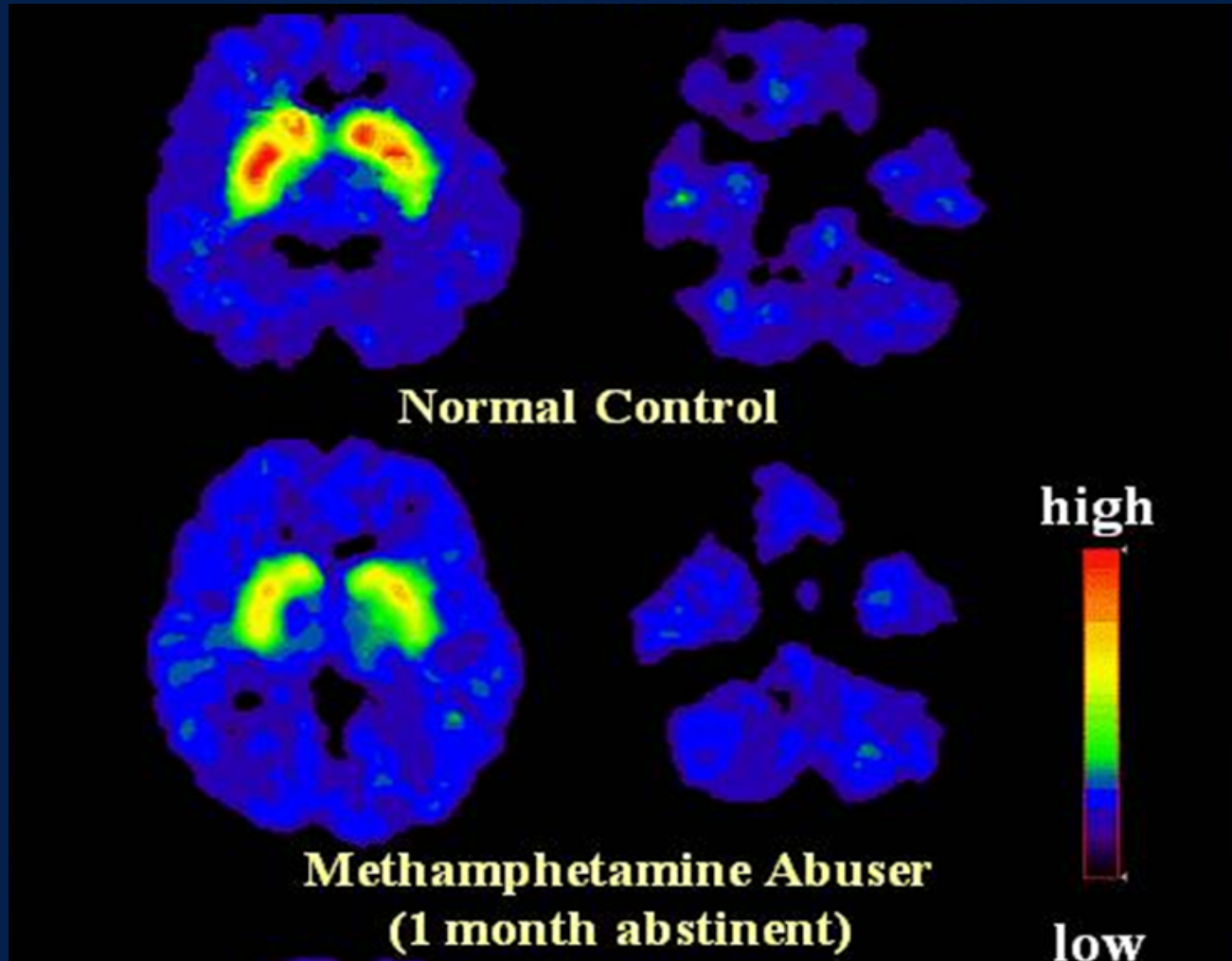
COCAINE

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

METH

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

METH decreases DAT sites in brain



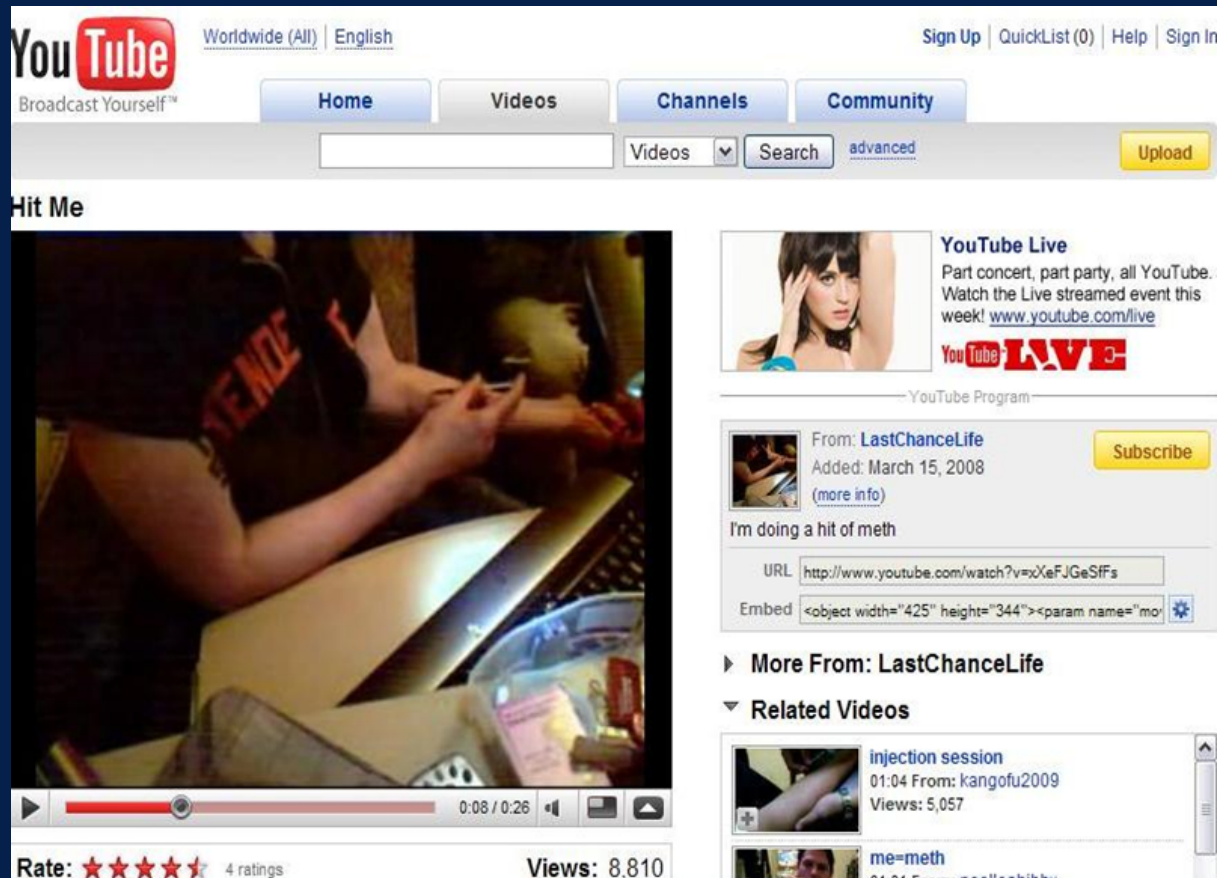
Role of METH in Gay Subculture

1. METH intoxication
2. Decreased inhibitions and judgment
3. Increased sensation seeking and sexual arousal
4. Unsafe sexual practices
5. HIV transmission

METH, Sex, and the Internet

- The Perfect Storm
- Sex, both virtual and real, both safe and unsafe, is only a click away
- Variable Intermittent Reinforcement

Internet Websites Foster Risky Behaviors



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YouTube LIVE

YouTube Program

From: LastChanceLife
Added: March 15, 2008
(more info)

I'm doing a hit of meth

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

Embed: `<object width="425" height="344"><param name="mo`

More From: LastChanceLife

Related Videos

injection session
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Views: 5,057

me=meth
0:04 From: ...

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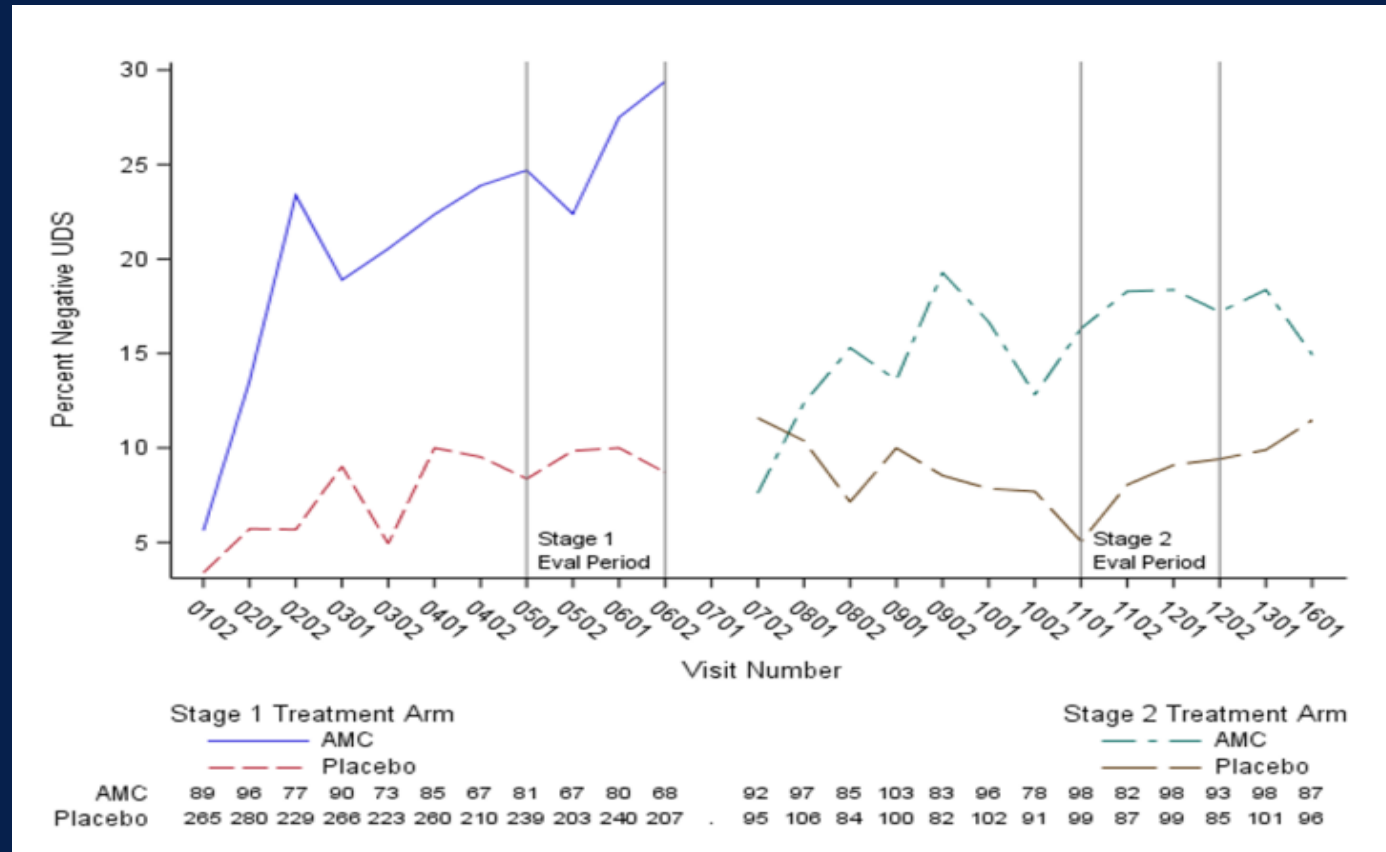
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Treatment for METH Dependence

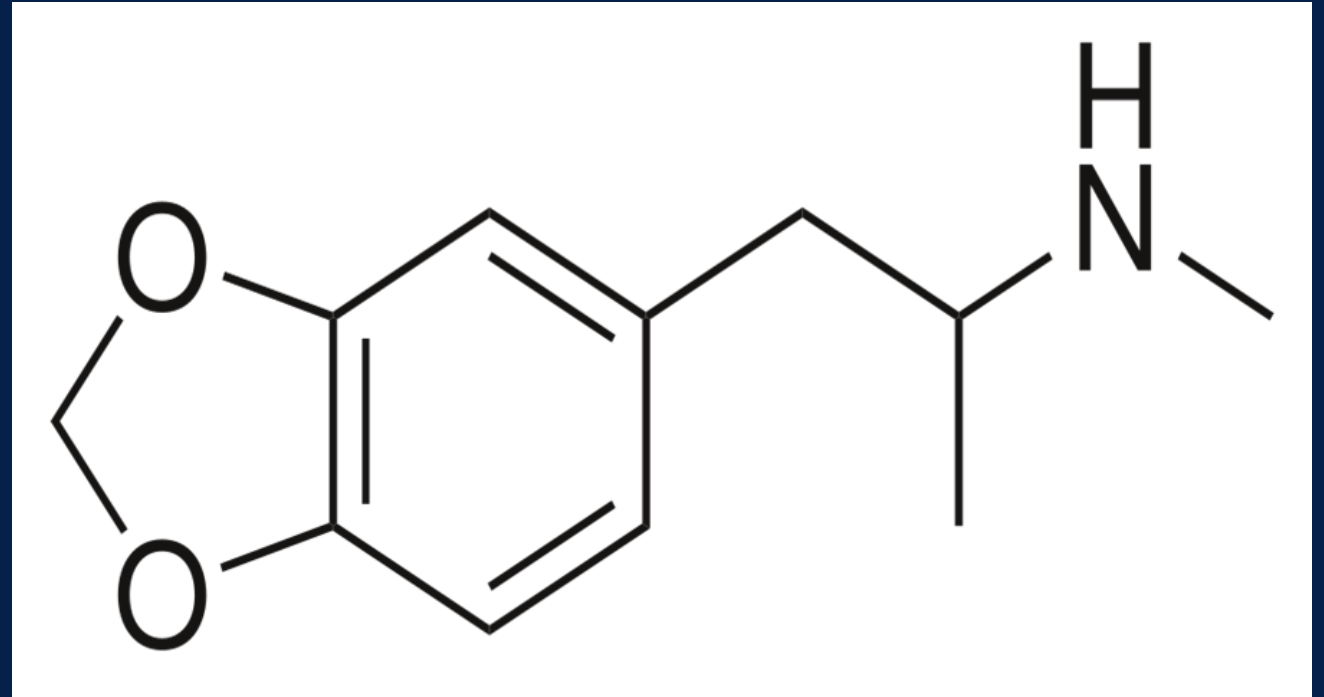
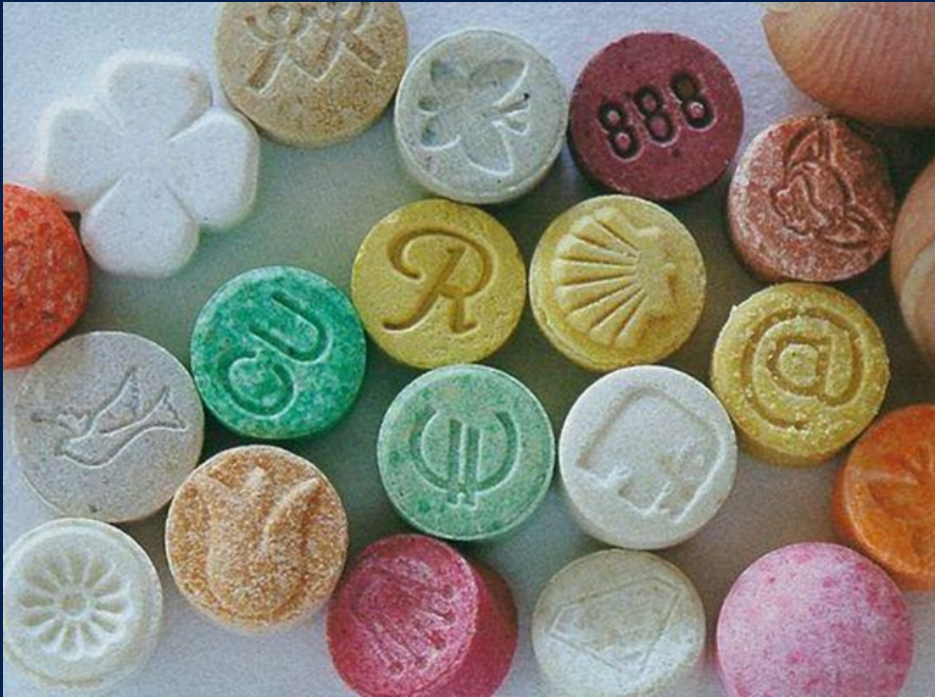
- Pharmacotherapy
 - No FDA-approved medication for METH dependence
- Psychologically-Based Therapies
 - Cognitive Behavioral Therapy
 - Group and Community Therapies
 - Twelve Step Programs

Bupropion + Naltrexone Reduce METH Use



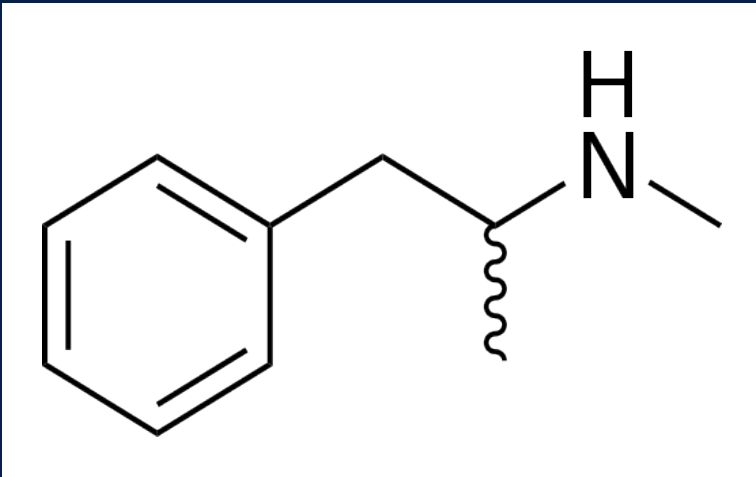
Ecstasy

Ecstasy (MDMA) is a Synthetic Club Drug

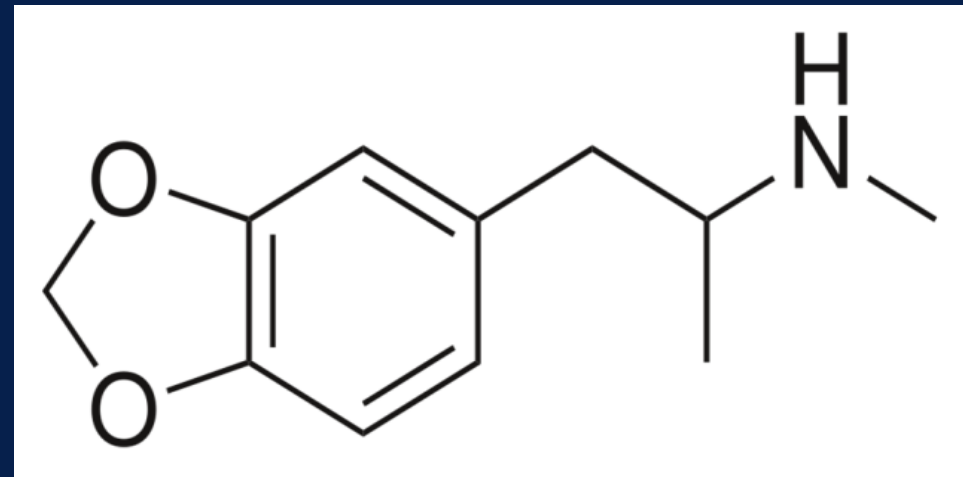


MDMA is a Ring-Substituted Amphetamine Analog

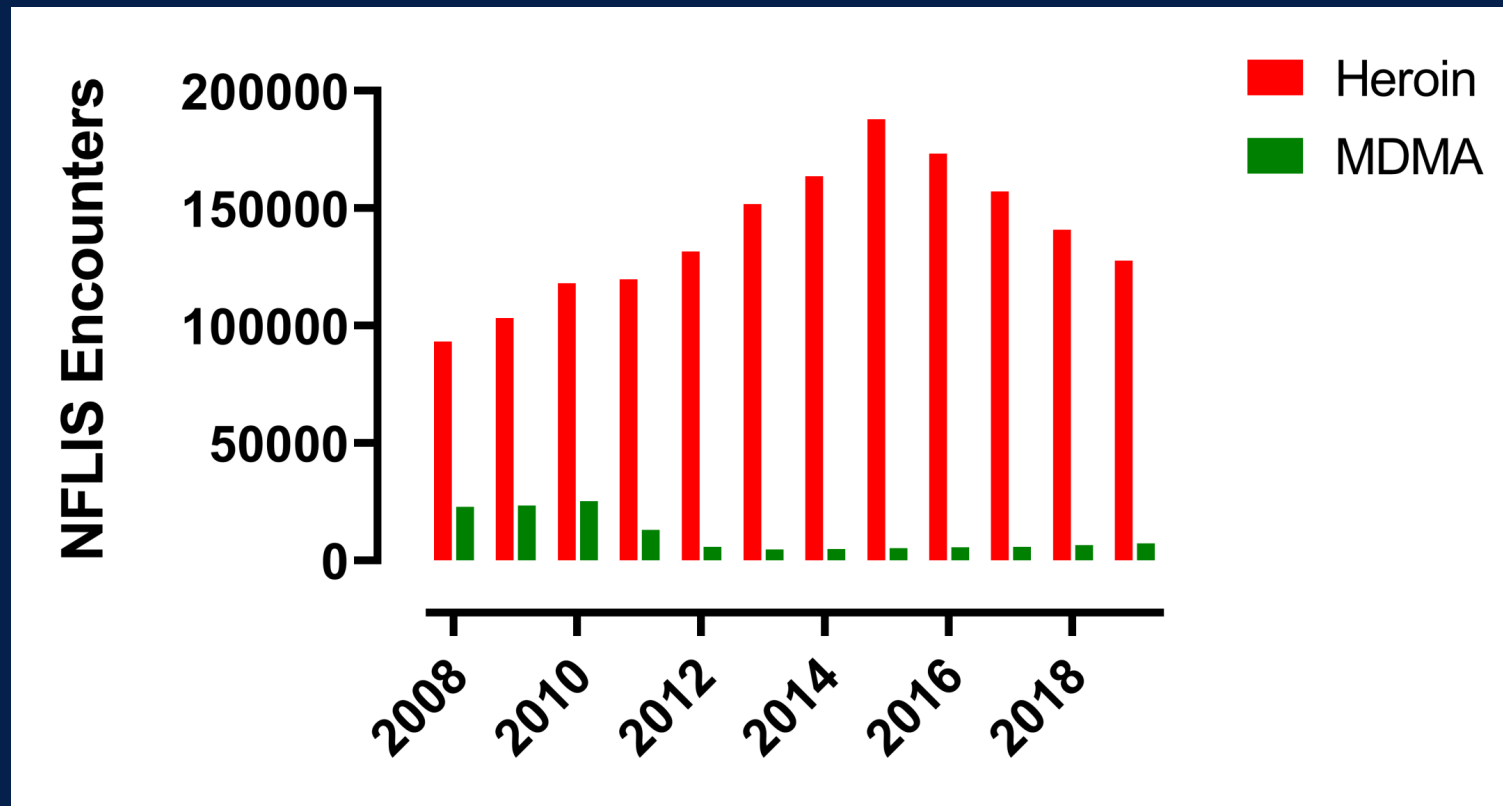
Methamphetamine



3,4-Methylenedioxy
Methamphetamine (MDMA)



Confiscation of MDMA Remains Low Compared to Other Drugs



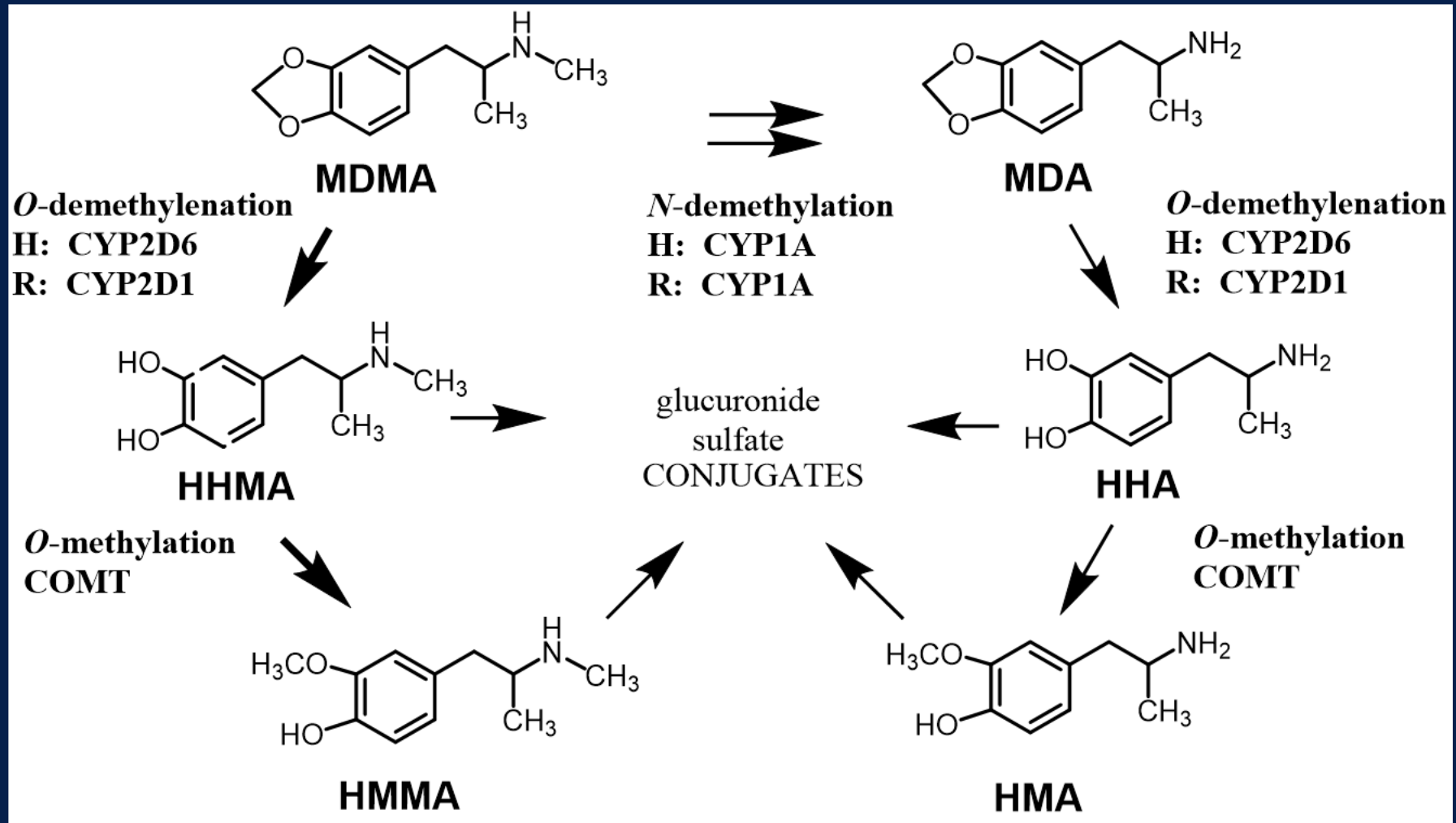
Formulations and Methods of Use

- 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
 - Cmax 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 hallucinogen
 - 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
 - Avoid β blockers, which could exacerbate hypertension

Withdrawal

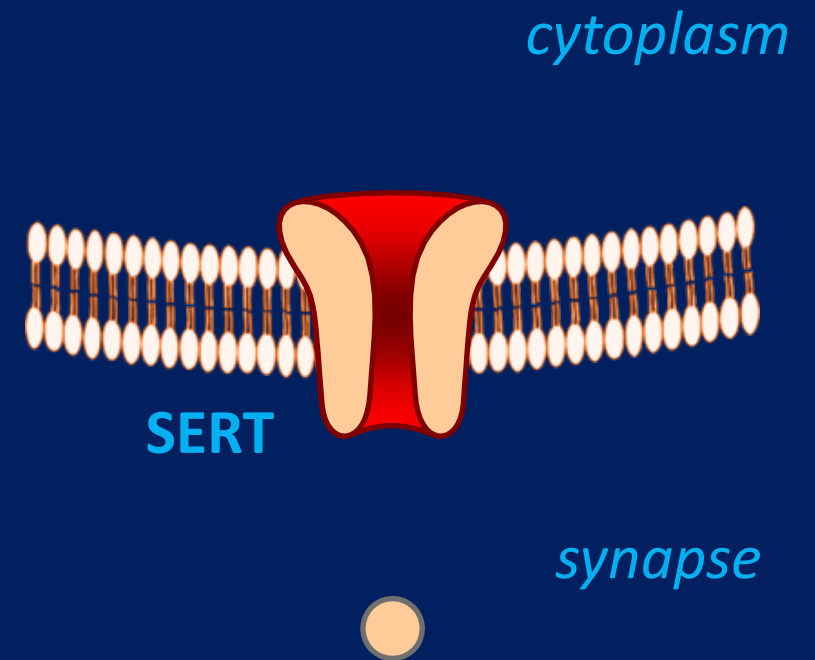
- Anhedonia and depressed mood
- Lethargy and fatigue for several days
- Sleep disturbances
- No indication for treatment

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_{2A} receptors

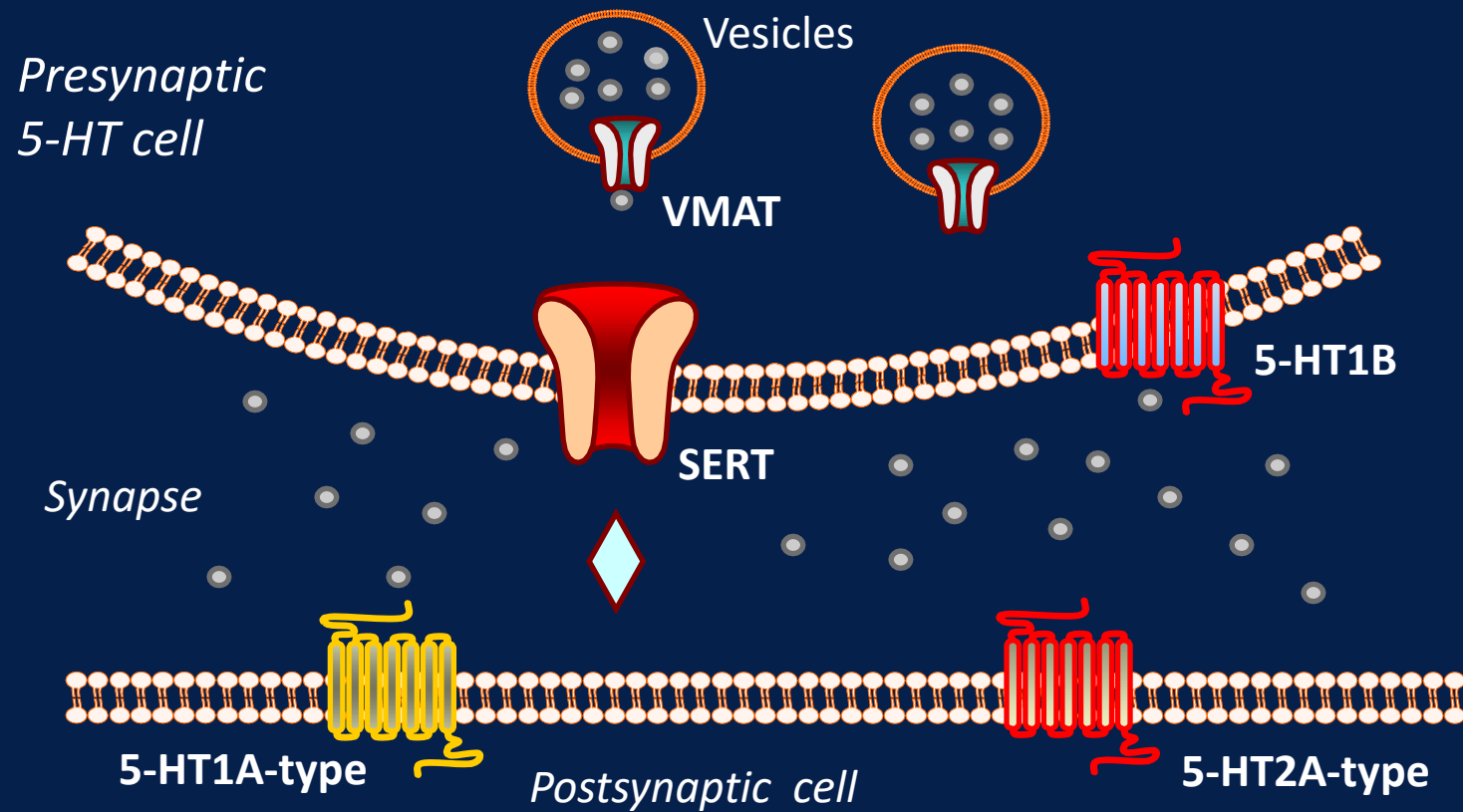
SERTs Mediate 5-HT Uptake

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

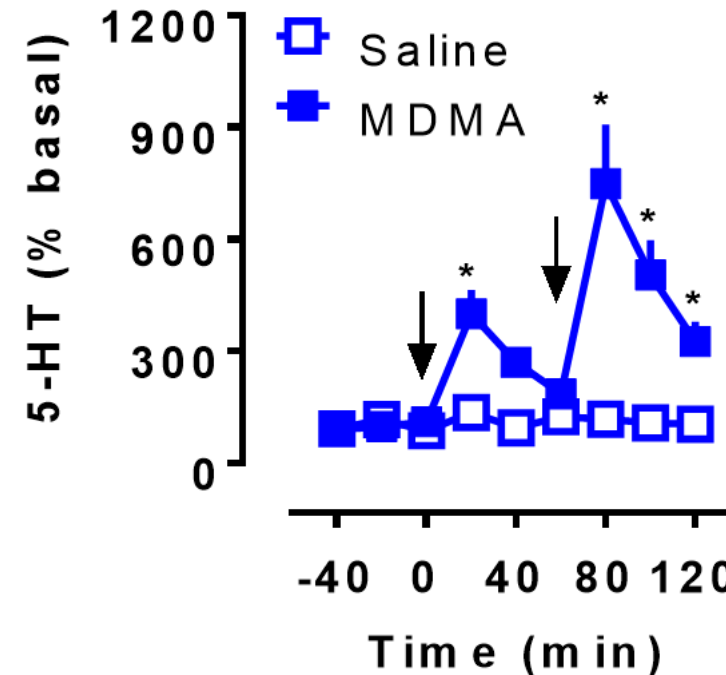
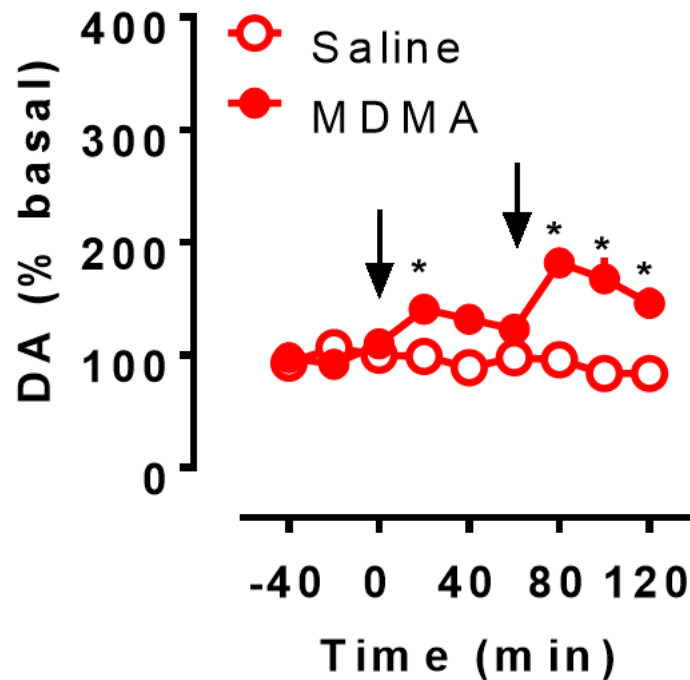




MDMA is a SERT substrate (5-HT releaser)



MDMA Increases Extracellular 5-HT more than DA



Neurotoxic Potential

- MDMA acutely increases synaptic 5-HT
 - SERT-mediated 5-HT release (i.e., reverse transport)
- MDMA chronically impairs 5-HT neurons
 - Depletion of 5-HT stores
 - Inhibition of 5-HT synthesis
 - Loss of SERT sites in brain
- Neurotoxicity?

Bath Salts

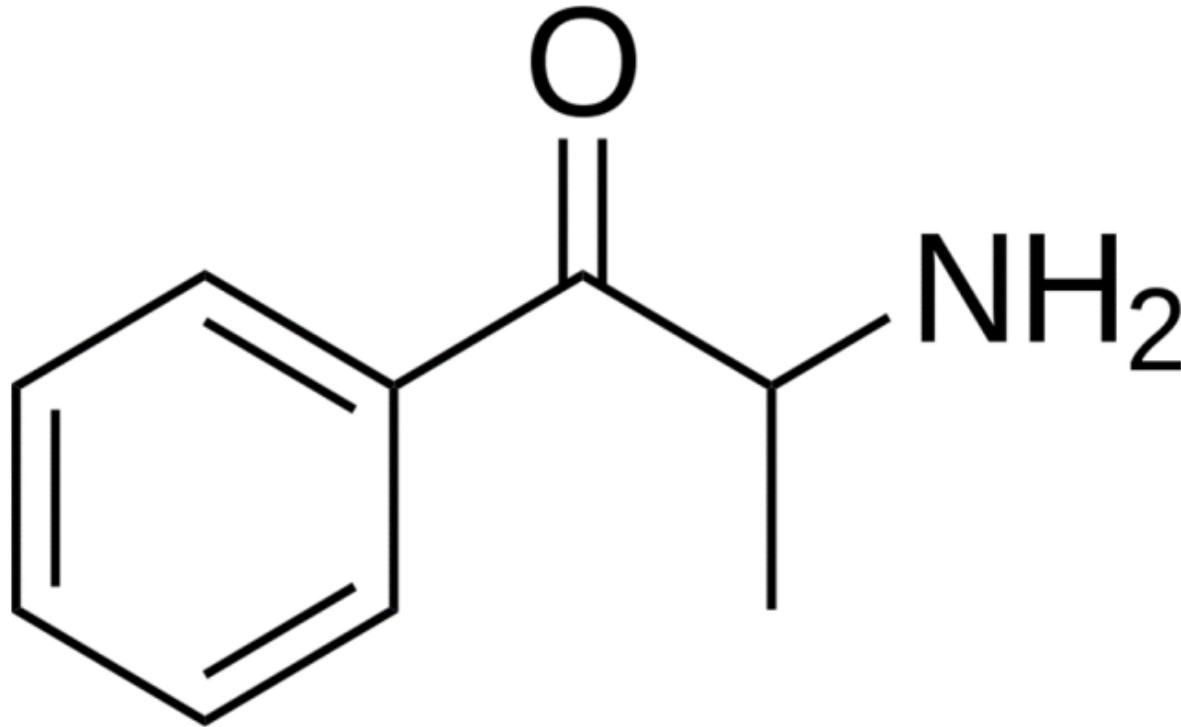
Cathinone is a Plant-Based Alkaloid



Khat Plant *Catha edulis*



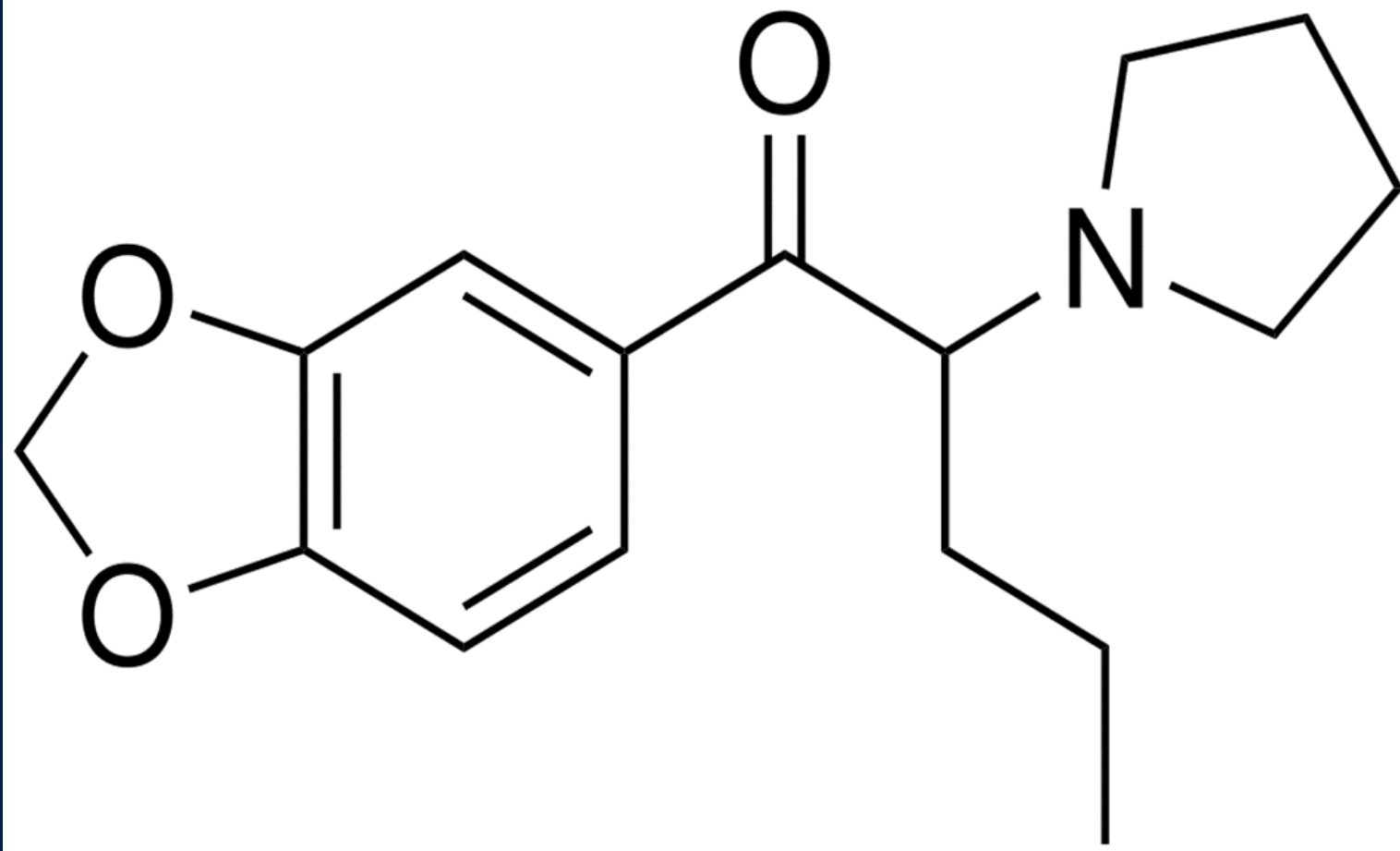
Cathinone is β -Keto Amphetamine



“Bath Salts” Products Contain Synthetic Cathinones

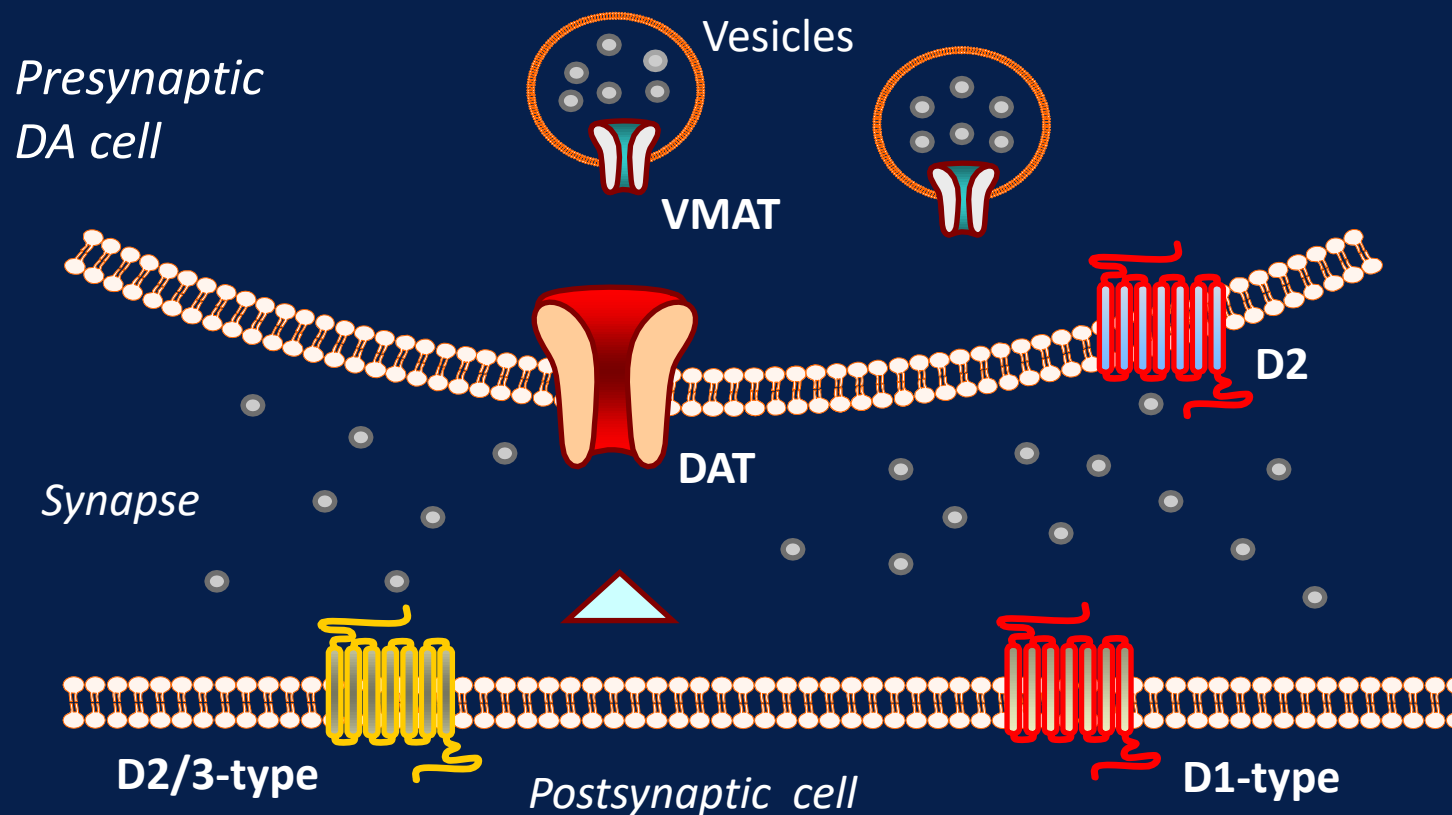


MDPV is an Analog of Pyrovalerone

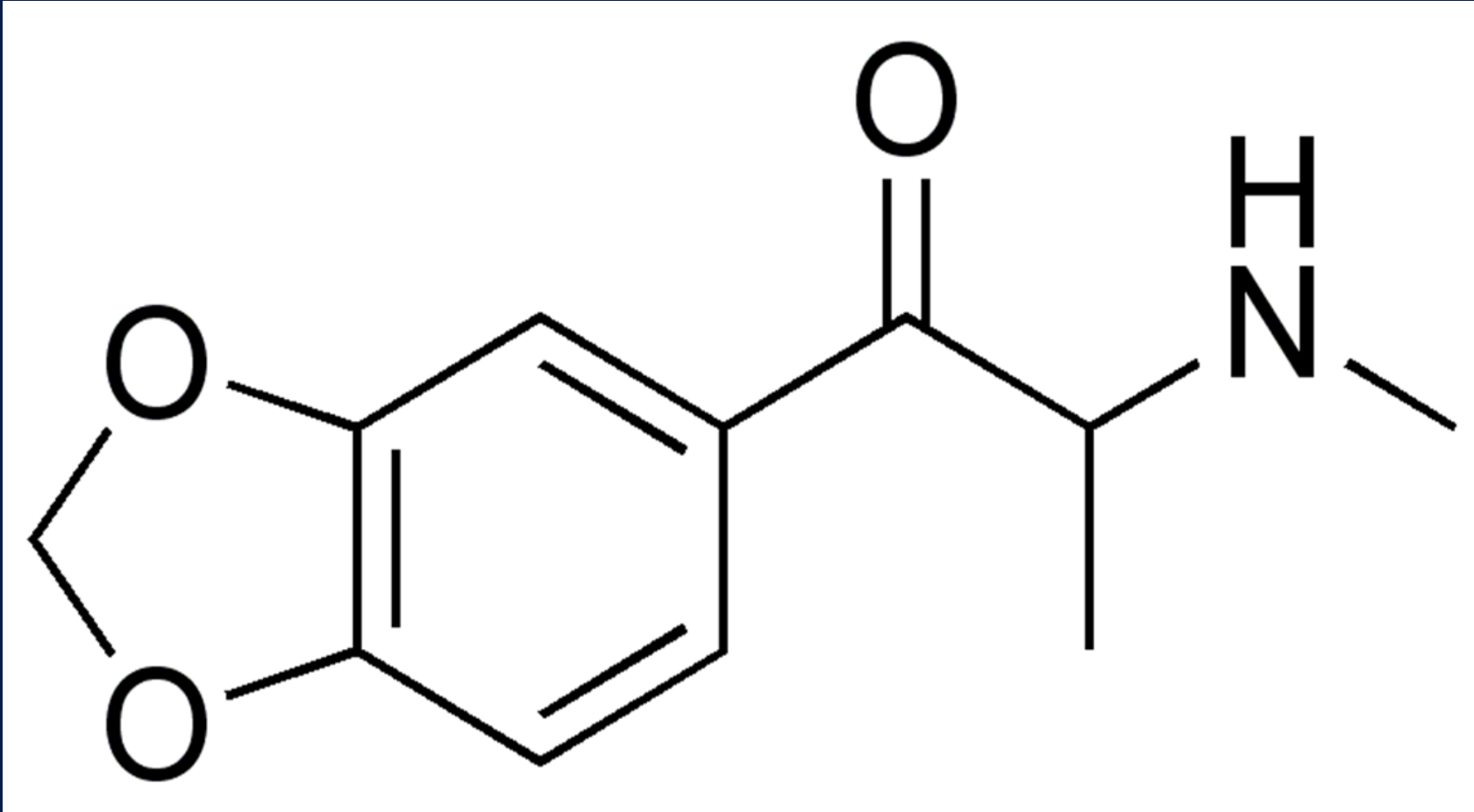




MDPV is a DAT Blocker (DA Uptake Inhibitor)

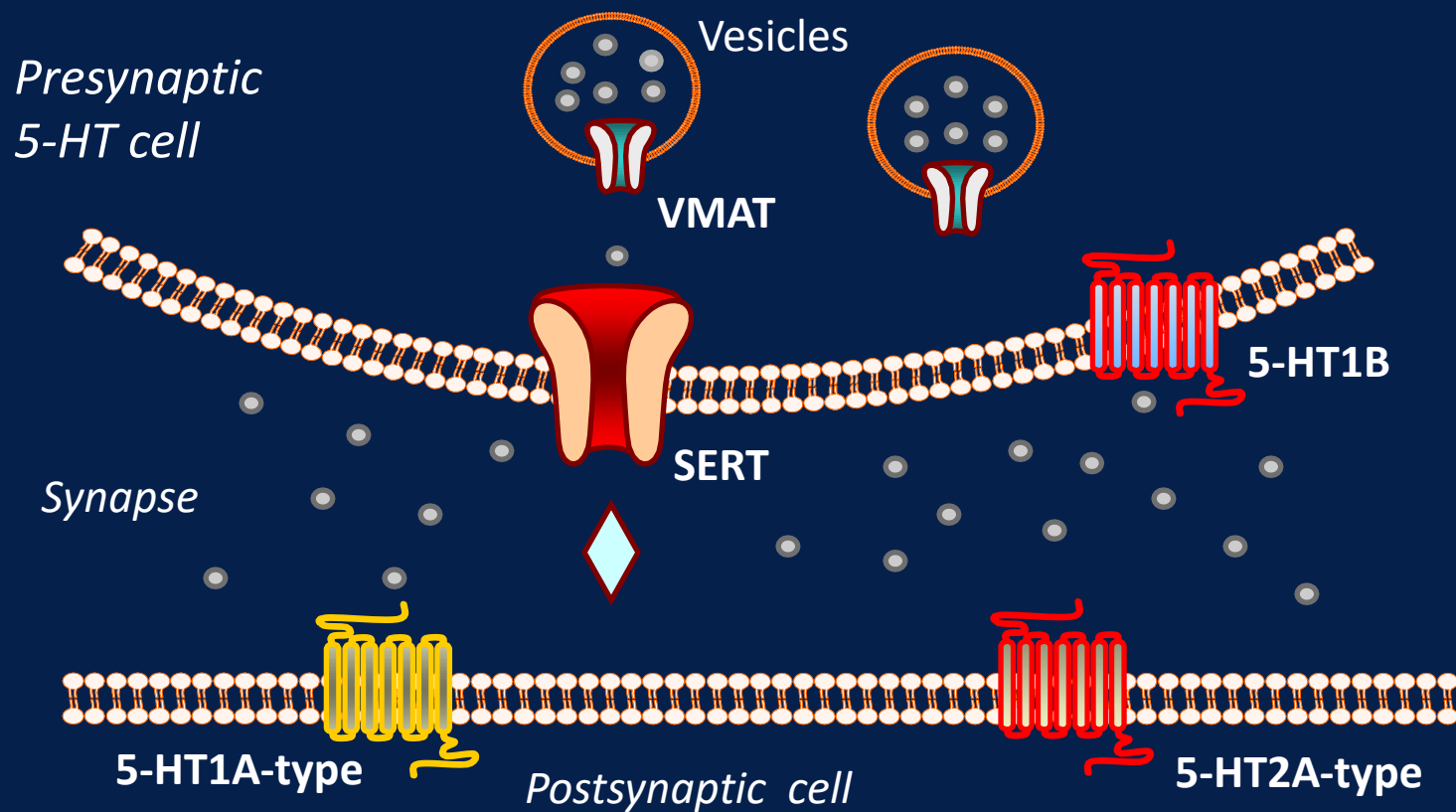


Methylone is β -Keto MDMA

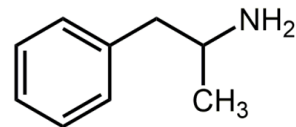




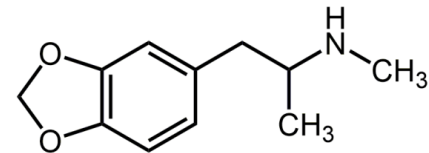
Methylone is a SERT substrate (5-HT releaser)



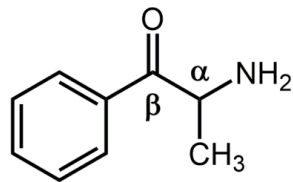
Methylone Analogs are now Appearing as Counterfeit MDMA



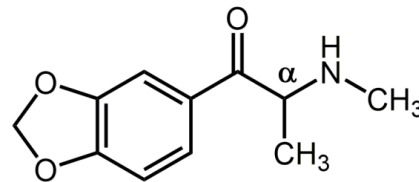
Amphetamine



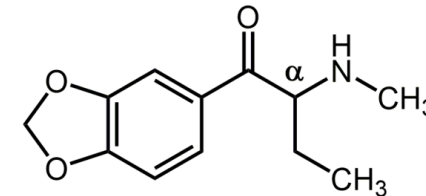
MDMA



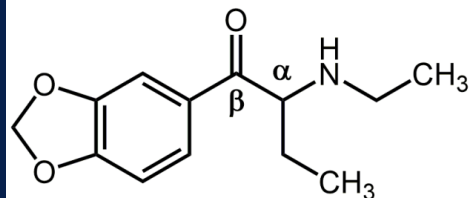
Cathinone



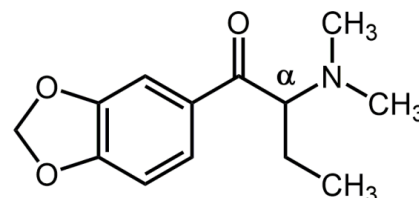
Methylone



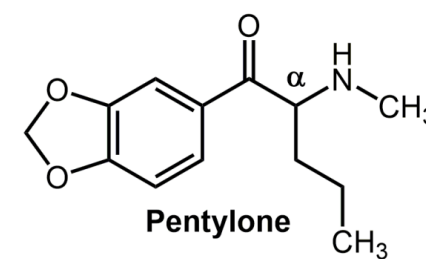
Butylone



Eutylone



Dibutylone



Pentylone

Summary

Overall Summary

1. Cocaine is the prototypical dopaminergic stimulant.
2. METH is a powerful stimulant due to its DAT-mediated dopamine release.
3. MDMA acts as a mild stimulant and hallucinogen 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 dependence, so treatment is psychosocially-based.
2. No specific antidotes for stimulant intoxication, so treatment is supportive.
3. Stimulant-induced deaths are increasing due to fentanyl co-administration: intentional or accidental?

Thank You

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Up Next: *Other Classes of Drugs* – Annie Levesque, MD, MSc