STIMULANTS

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The ASAM Review Course of Addiction Medicine
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Financial Disclosures

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No Disclosures

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General Outline

- 1980s: Cocaine
- 1990s: Ecstasy
- 2000s: Methamphetamine
- 2010s: Bath Salts and RCs
- Summary

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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

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1980s: Cocaine

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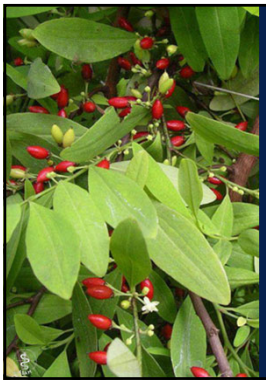
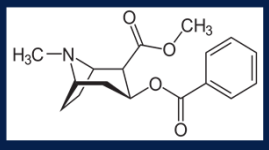


Cocaine, a Plant Based Alkaloid



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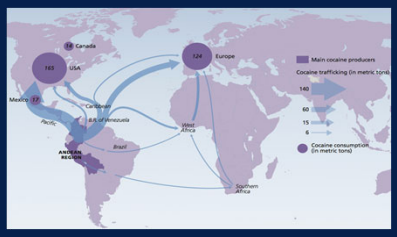
Andean Cocaine is Trafficked on a Global Scale



UNODC World Drug Report, 2018

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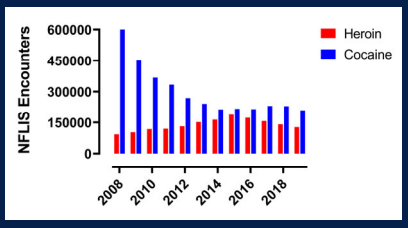
8

Cocaine Confiscation Remains Relatively Stable



DEA NFLIS, 2020

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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

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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

Cone, 1995

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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

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Desired Effects

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

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Adverse Effects

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

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Tolerance- Blunted Effects

- Acute Tachyphylaxis or "First Dose" Effect
  - Cardiovascular Effects
  - Euphoria and sexual arousal
  - But no longer-term tolerance
- Anorexia

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Sensitization- Enhanced Effects

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

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Withdrawal Effects

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

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Molecular Sites of Action

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

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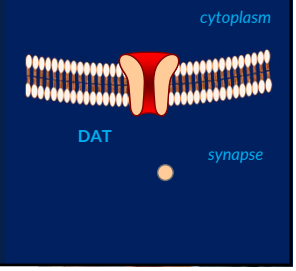
DATs mediate DA uptake

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



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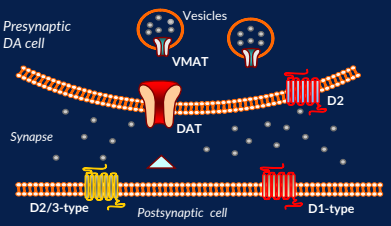
Cocaine is a DAT Blocker (DA Uptake Inhibitor)



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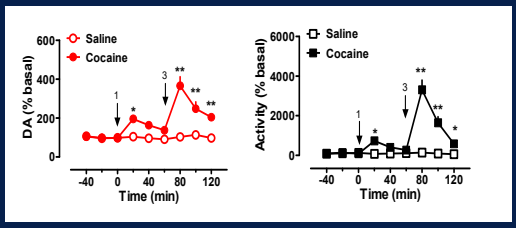
Cocaine Increases Synaptic DA in Rat Nucleus Accumbens



Baumann et al., 1994

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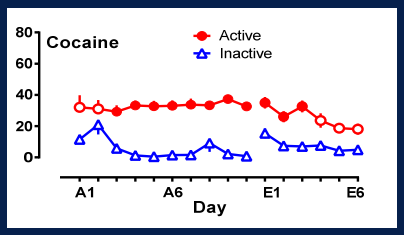
Rats Will Readily Learn to Self-Administer Cocaine



Schindler et al., 2016

22

Treatment for Cocaine Dependence

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

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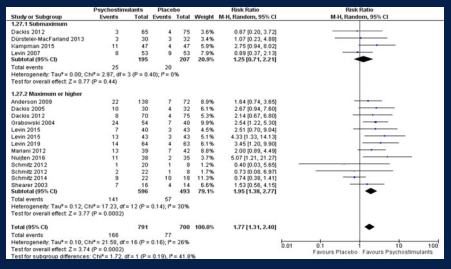
Stimulant Meds- Some Success



Tardelli et al. 2020

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1990s: Ecstasy

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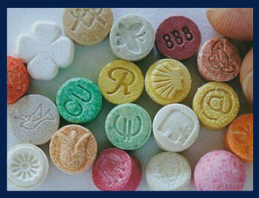
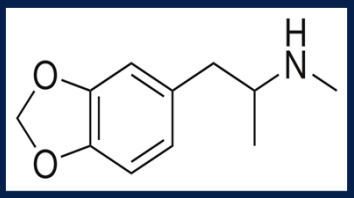
Ecstasy (MDMA), a synthetic club drug





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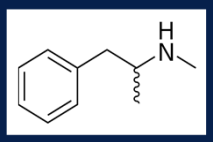
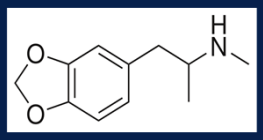
MDMA is a ring-substituted amphetamine analog

Methamphetamine



3,4-Methylenedioxy Methamphetamine (MDMA)



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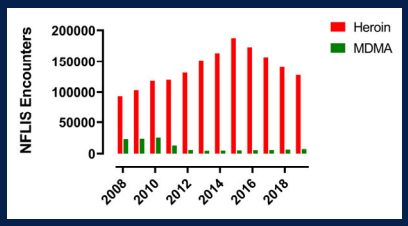
Confiscation of MDMA Remains Very Low



DEA NFLIS, 2020

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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

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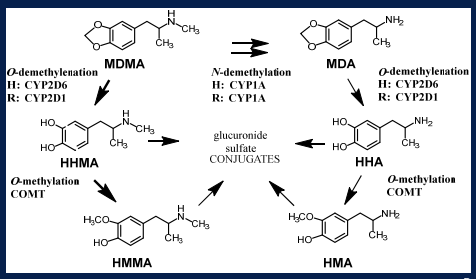
Pharmacokinetics And Metabolism

- 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*-demethylenation to form hydroxylated metabolites

de la Torre et al., 2004

30

MDMA metabolism is complex



Baumann et al., 2007

31

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

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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

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Withdrawal

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

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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-HT2A receptors

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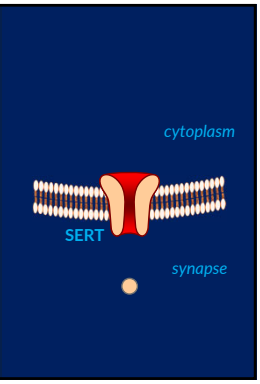
SERTs mediate 5-HT uptake

- 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)



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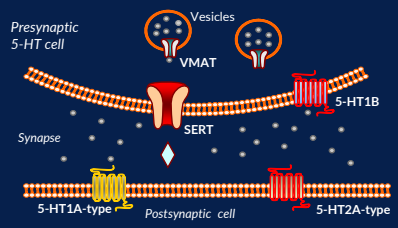
MDMA is a SERT substrate (5-HT releaser)



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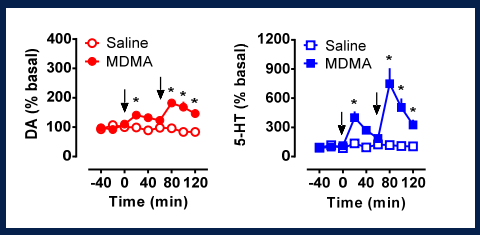
MDMA Increases Synaptic 5-HT more than DA



Baumann et al., 2008

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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?

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2000s: Methamphetamine

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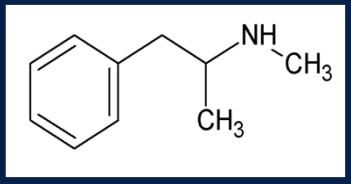
Methamphetamine, a synthetic amphetamine analog



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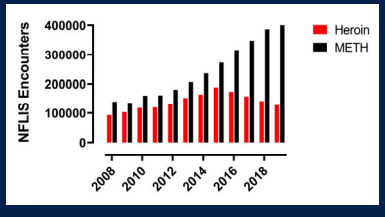
METH Confiscation is Increasing Dramatically in Recent Years



DEA NFLIS, 2020

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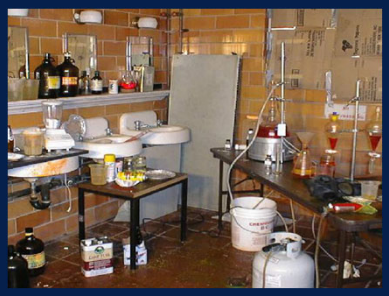

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Formulations and Methods of Use

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

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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

45

Desired Effects

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

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Adverse Effects

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

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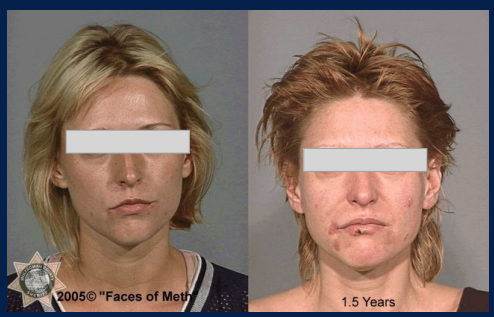

www.facesofmeth.us

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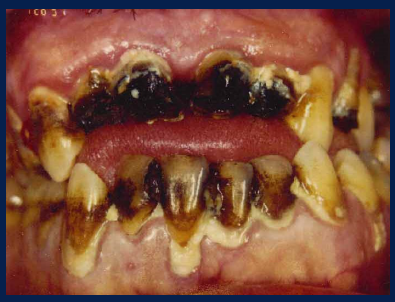
"METH Mouth"



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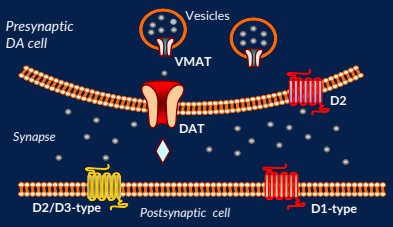
Molecular Sites of Action

- 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)

50

METH is a DAT substrate (DA releaser)



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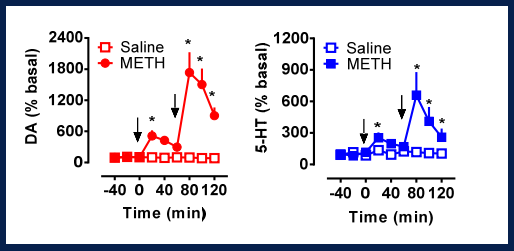
METH Increases DA more than 5-HT



Baumann et al., 2002

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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

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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

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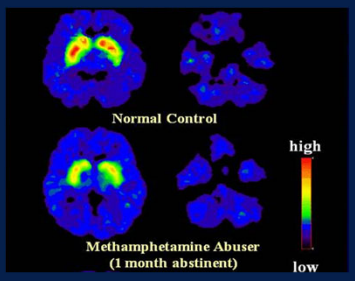
METH decreases DAT sites in brain



Volkow et al., 2001

55

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

Lee & Rawson, 2008

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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

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Internet websites foster risky behaviors

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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

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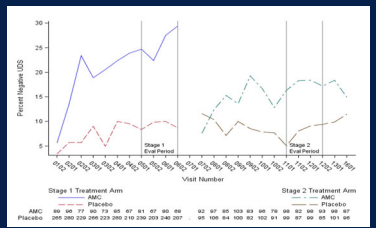
Bupropion + Naltrexone reduced METH use



Trivedi et al. 2021

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2010s: Bath Salts

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Cathinone, a Plant-Based Alkaloid

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Khat plant *Catha edulis*

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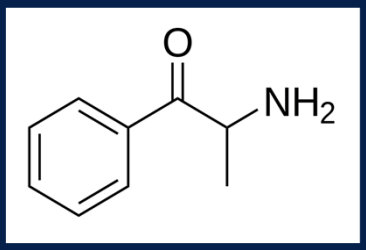
Cathinone is β-keto amphetamine



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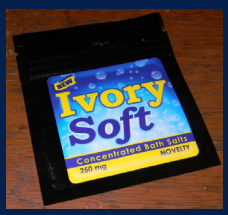
"Bath Salts" products contain synthetic cathinones



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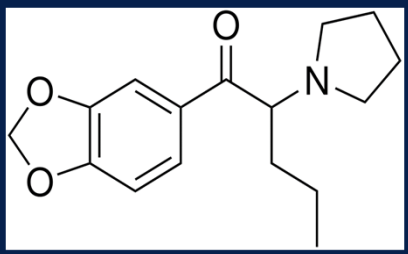
MDPV is an analog of pyrovalerone



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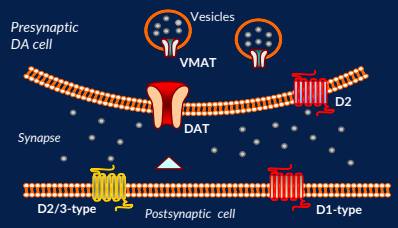
MDPV is a DAT Blocker (DA Uptake Inhibitor)



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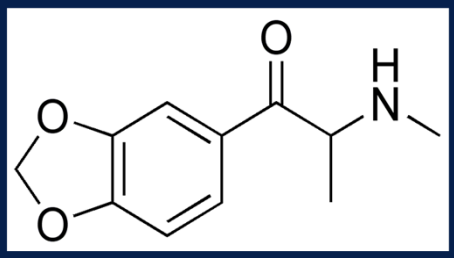
Methylone is β-keto MDMA



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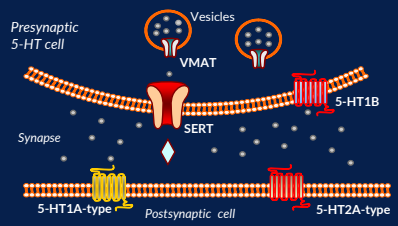
Methylone is a SERT substrate (5-HT releaser)



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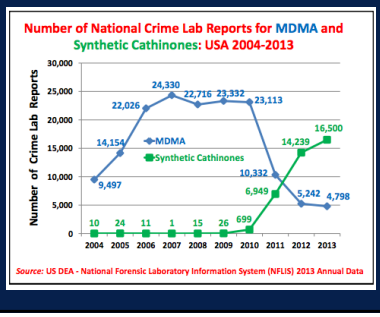
Cathinones replaced MDMA



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Summary

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Overall Summary

1. Cocaine is the prototypical dopaminergic stimulant
2. MDMA acts as a mild stimulant and hallucinogen due to its SERT-mediated 5-HT release
3. METH is a powerful stimulant due to its DAT-mediated dopamine release
4. MDPV is cocaine-like whereas methylone is MDMA-like

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Clinical Challenges

1. No FDA-approved medications for stimulant dependence, so treatment is psychologically-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?

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Thank you

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