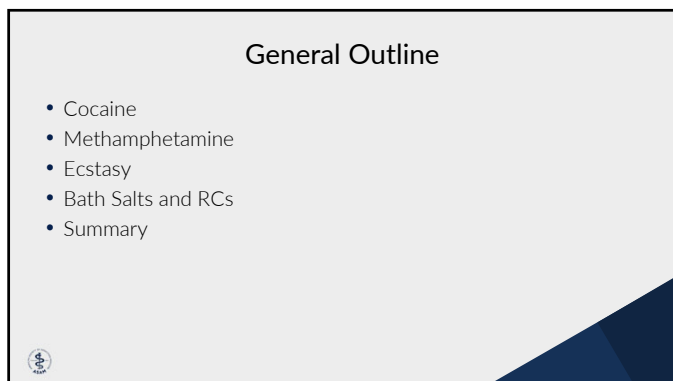




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3

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




4

Cocaine

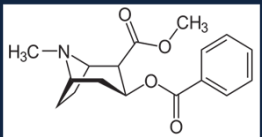


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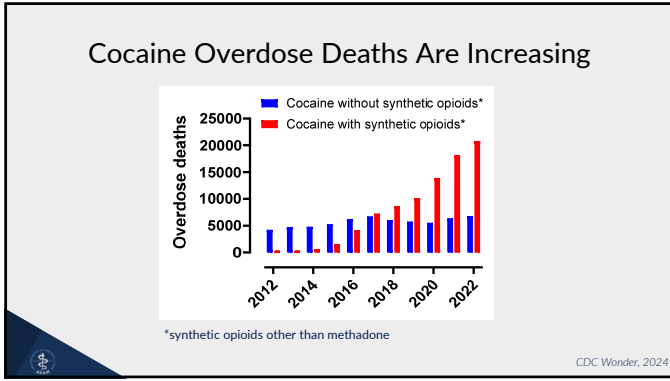
5



Cocaine is a Plant Based Alkaloid

CN1[C@H]2CC[C@@H]1[C@@H](C(=O)OC)c3ccccc3C(=O)O2

6



7

- ### 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


8

- ### 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

9

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



10

Desired Effects


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



11

Adverse Effects


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



12

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



13

Sensitization- Enhanced Effects


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



14

Withdrawal Effects

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



15

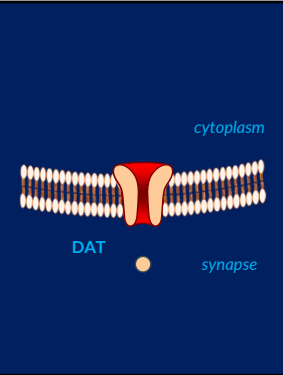
Molecular Sites of Action

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

16

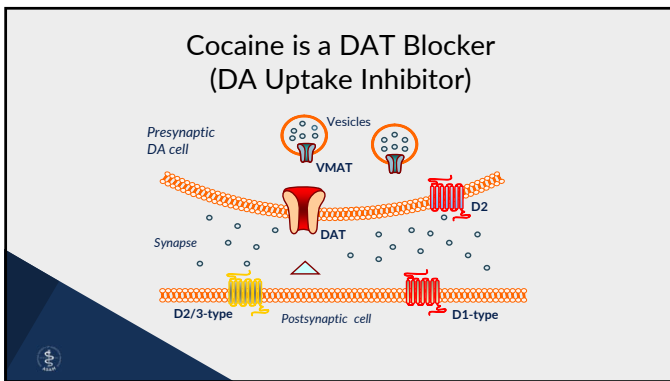
DATs Mediate DA Uptake

- 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

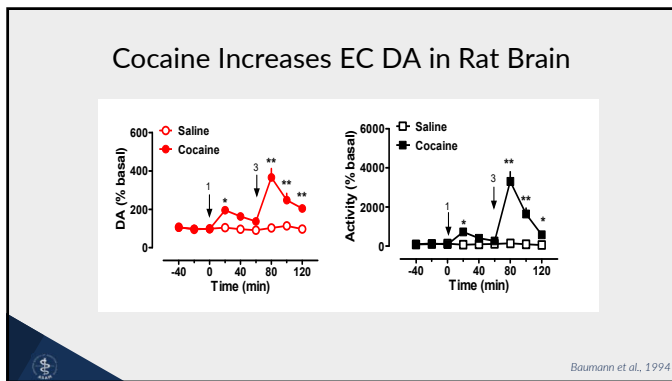


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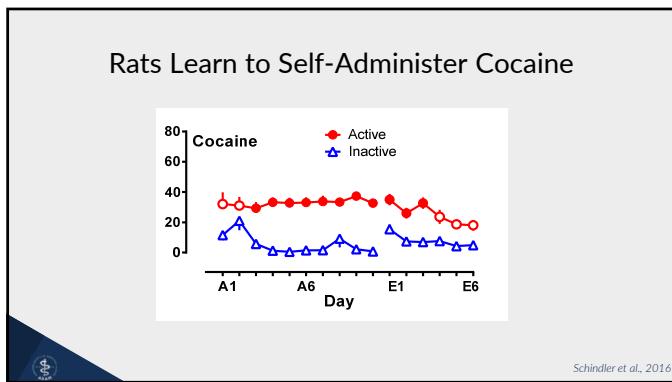
Cocaine is a DAT Blocker (DA Uptake Inhibitor)



18



19



20

- ### Treatment for Cocaine Use Disorder (CUD)
- Pharmacotherapy
 - No FDA-approved medication for CUD
 - Psychosocial Therapies
 - Contingency Management
 - Cognitive Behavioral Therapy
 - Group & Community Therapies

21

Experimental Pharmacotherapies for CUD

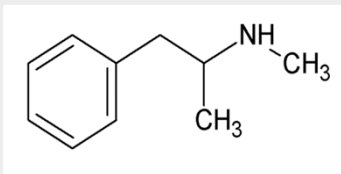

- Single agonist medications
 - Some positive results with stimulant medications, like mixed amphetamine salts (MAS) (*Tardelli et al., 2020*)
- Medication combinations
 - MAS + topiramate (*Levin et al., 2020*)

22

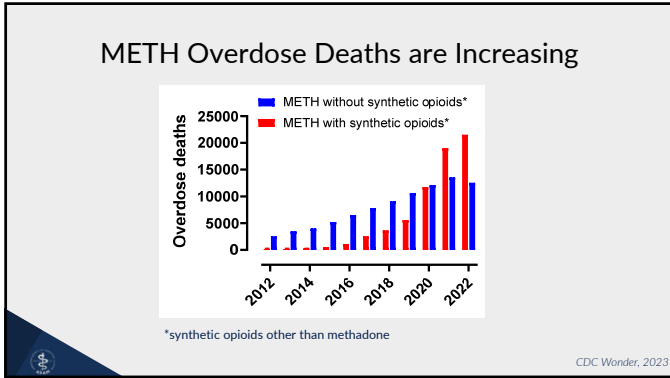
Methamphetamine

23

Methamphetamine (METH) is a Synthetic Amphetamine Derivative



24



25

- ### 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


26

- ### 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

27

Desired Effects


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



28

Adverse Effects

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



29

METH causes adverse health consequences



2005© "Faces of Meth" 1.5 Years



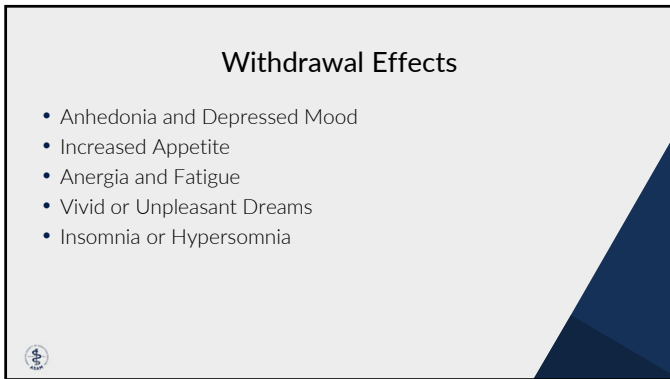
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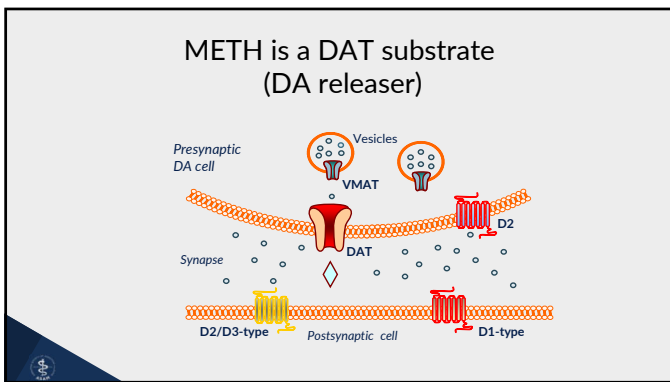


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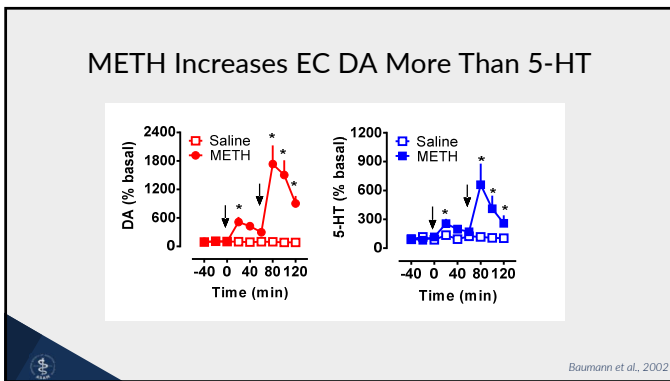
Molecular Sites of Action

- 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)

34



35



36

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
---	---

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Cocaine vs Methamphetamine

COCAINE <ul style="list-style-type: none">• Rapidly metabolized• Effects last 1-2 hours• Withdrawal lasts 1-2 days	METH <ul style="list-style-type: none">• Slowly metabolized• Effects last 10-20 hours• Withdrawal lasts many days
---	--

38

Chronic METH decreases DAT sites in brain

The image shows four PET scan slices of the brain. The top row, labeled 'Normal Control', shows two slices with high DAT site density, indicated by bright yellow and red colors. The bottom row, labeled 'Methamphetamine Abuser (1 month abstinent)', shows two slices with significantly lower DAT site density, indicated by mostly blue and green colors. A color scale legend on the right indicates 'high' (red) and 'low' (blue). The source 'Volkow et al., 2001' is noted in the bottom right corner.

39

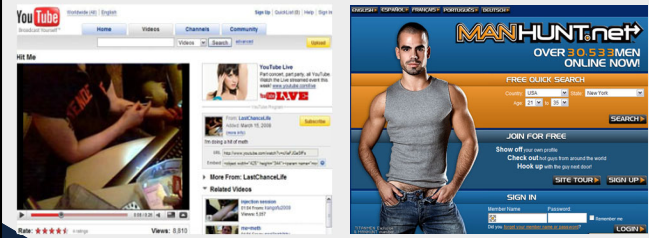
Role of METH in Gay Subculture

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

Lee & Rawson, 2008

40

Internet Websites Foster Risky Behaviors



The image shows two side-by-side screenshots. The left screenshot is a YouTube page for a video titled 'LIVE' with a view count of 8,912. The right screenshot is the homepage of Manhunt.net, featuring a search bar, a 'JOIN FOR FREE' button, and a 'SIGN IN' section.

41

Treatment for METH Use Disorder (MUD)

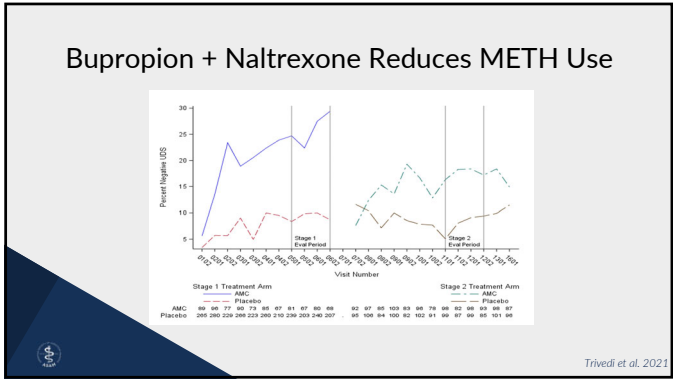
- Pharmacotherapy
 - No FDA-approved medication for MUD
- Psychosocial Therapies
 - Contingency Management
 - Cognitive Behavioral Therapy
 - Group and Community Therapies

42

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)

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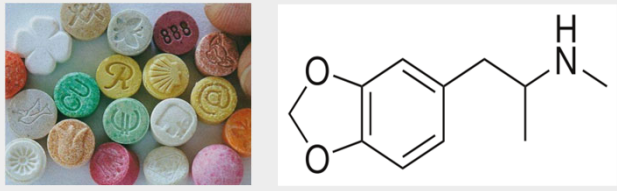
44

Ecstasy

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Ecstasy (MDMA) is a Synthetic Amphetamine Derivative

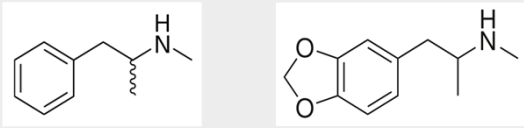


The image shows a collection of colorful pills in various shapes and colors (white, yellow, green, red, orange, pink) on the left. On the right is the chemical structure of MDMA, which consists of a benzene ring with a 1,3-dioxole ring fused to it, and a 2-(propylamino)ethyl group attached to the benzene ring.

46

MDMA is a Ring-Substituted Amphetamine

Methamphetamine 3,4-Methylenedioxy Methamphetamine (MDMA)



The image shows two chemical structures side-by-side. On the left is Methamphetamine, which has a benzene ring attached to a 2-(propylamino)ethyl group. On the right is MDMA, which has a benzene ring with a 1,3-dioxole ring fused to it, and a 2-(propylamino)ethyl group attached to the benzene ring.

47

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

48

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

de la Torre et al., 2004

49

MDMA Metabolism is Complex

The diagram illustrates the metabolic pathways of MDMA. MDMA is converted to MDA via N-demethylation (enzymes: CYP1A). MDA is then converted to HHMA via O-demethylation (enzymes: CYP2D6, CYP2D1). HHMA is further converted to HMMA via O-methylation (enzyme: COMT). MDA is also converted to HHA via O-demethylation (enzymes: CYP2D6, CYP2D1). HHA is converted to HMA via O-methylation (enzyme: COMT). Both HHMA and HMA are converted to glucuronide sulfate conjugates. The diagram includes chemical structures for MDMA, MDA, HHMA, HMMA, HHA, and HMA.

Baumann et al., 2007

50


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

51

Adverse Effects


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



52

Withdrawal


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



53

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



54

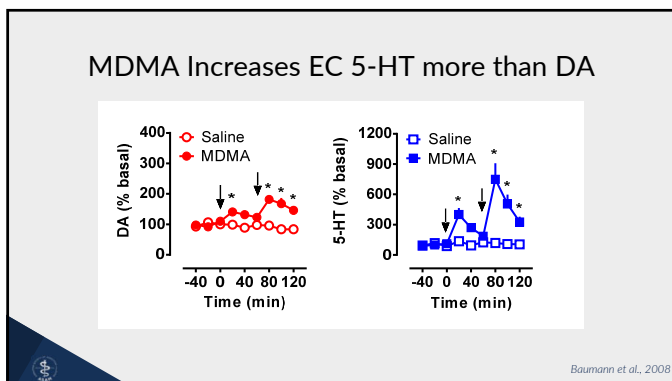
SERTs Mediate 5-HT Uptake

- 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)

55

MDMA is a SERT substrate (5-HT releaser)


56



57

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?



58


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



59

Bath Salts



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60

Cathinone is a Plant-Based Alkaloid



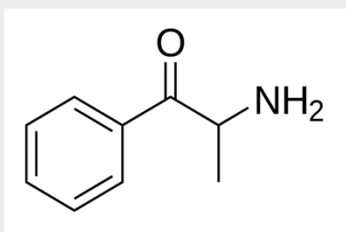
61

Khat Plant *Catha edulis*



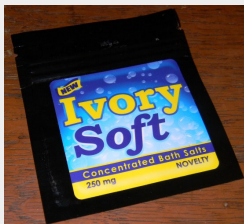
62

Cathinone is β -Keto Amphetamine



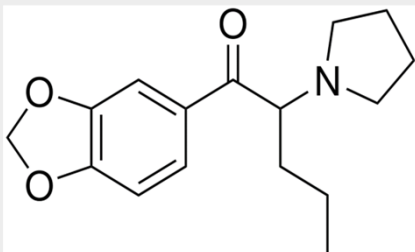
63

Psychoactive "Bath Salts" Products Contain
Synthetic Cathinones



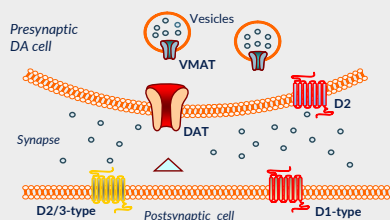
64

MDPV is an Analog of Pyrovalerone

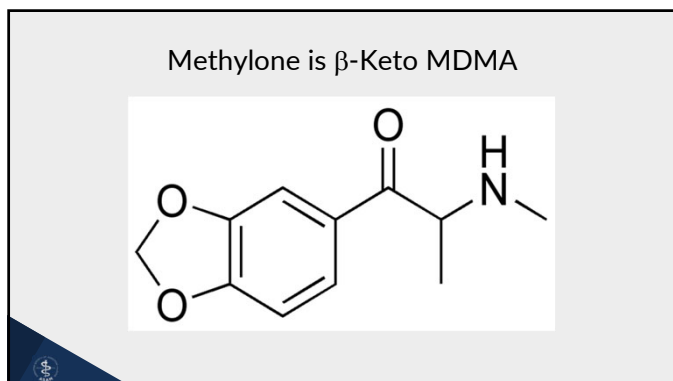


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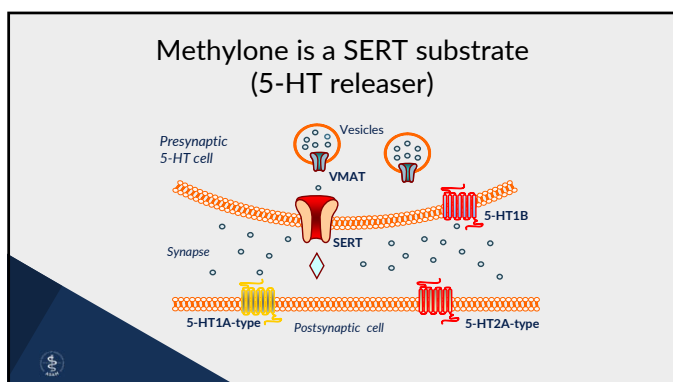
MDPV is a DAT Blocker
(DA Uptake Inhibitor)



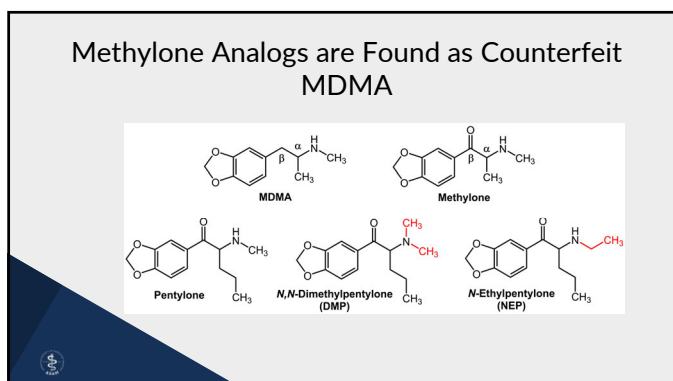
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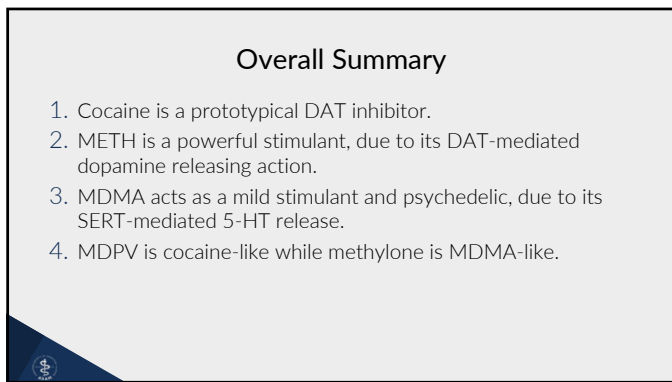
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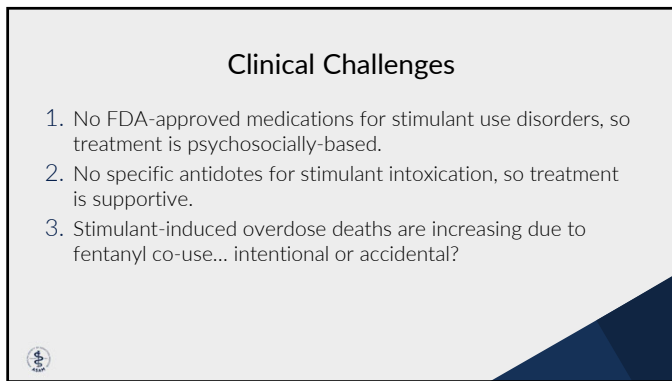
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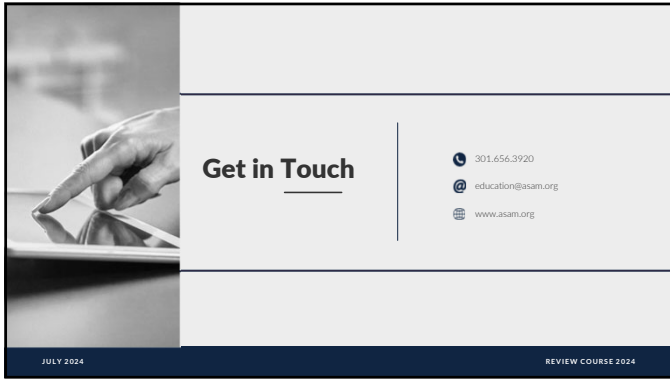
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