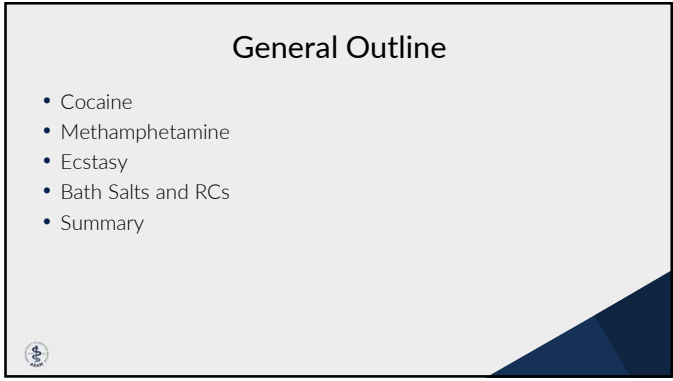


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3

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




4

Cocaine

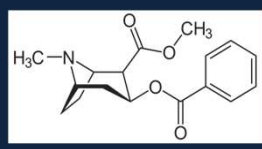


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Cocaine is a Plant Based Alkaloid

CN1[C@H]2CC[C@@H]1[C@@H](C(=O)OC)OC(=O)c3ccccc3

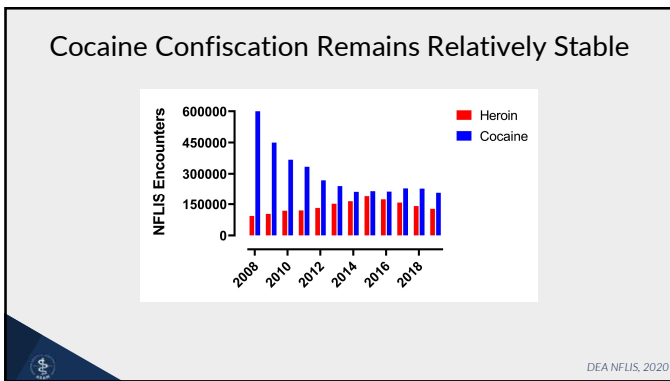
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9

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

10

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

11

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

12

Desired Effects


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



13

Adverse Effects

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




14

Tolerance- Blunted Effects

- Acute Tachyphylaxis or "First Dose" Effect
- Cardiovascular effects blunted
- Euphoria and sexual arousal diminished
- 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



16

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



18

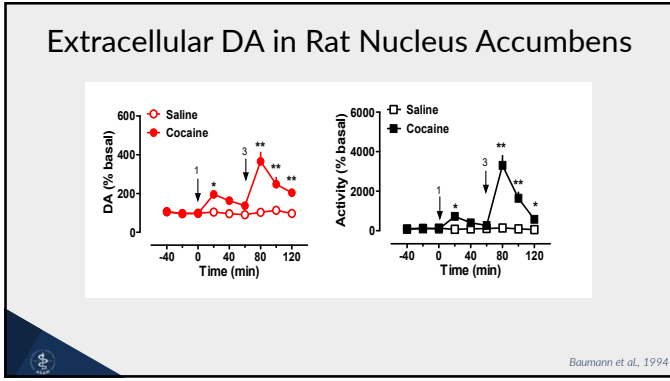
DATs Mediate DA Uptake

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

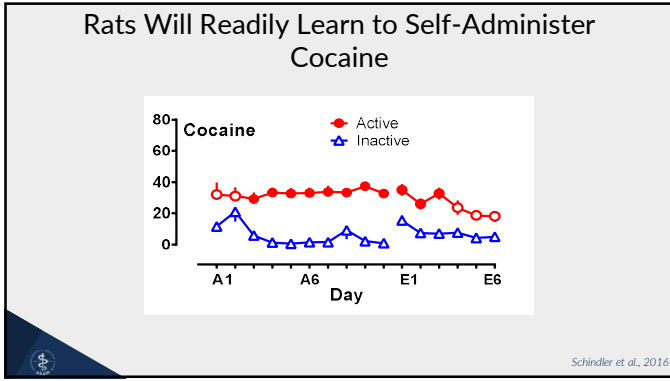
19

Cocaine is a DAT Blocker (DA Uptake Inhibitor)

20



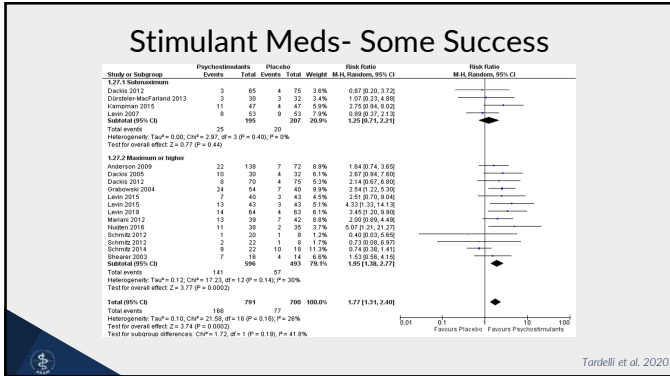
21



22

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

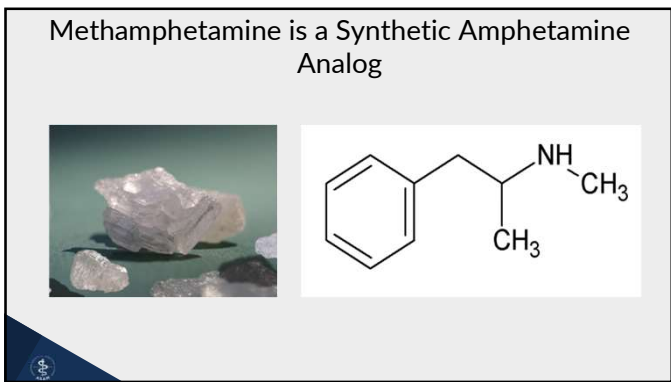
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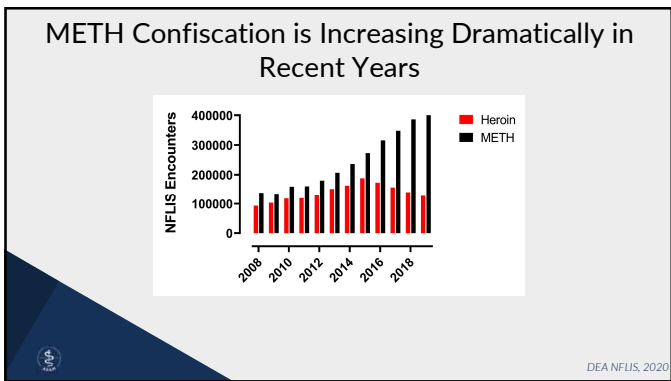
24



25



26



27

Most METH is Now Trafficked by Mexican Cartels



DEA/NFLIS, 2020

28

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

29

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

30

Desired Effects


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



31

Adverse Effects

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



32



33



34

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

35

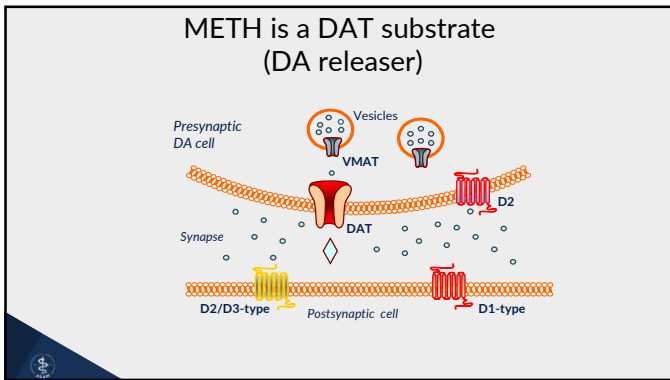
- Withdrawal Effects**
- Anhedonia and Depressed Mood
 - Increased Appetite
 - Anergia and Fatigue
 - Vivid or Unpleasant Dreams
 - Insomnia or Hypersomnia

36

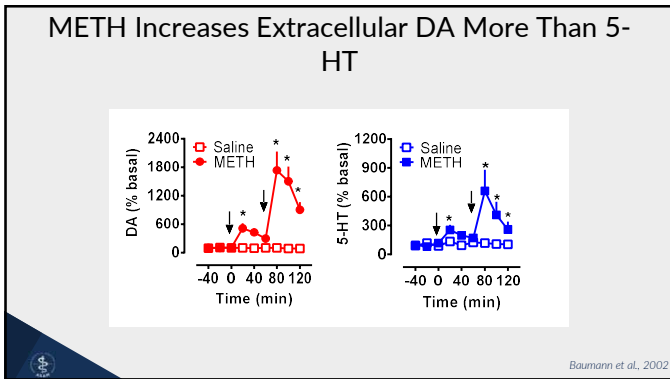
Molecular Sites of Action

- 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)

37



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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
---	---

40

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
---	--

41

METH decreases DAT sites in brain

The image shows four PET scan slices of a brain. The top row is labeled 'Normal Control' and shows high DAT binding (yellow/red). The bottom row is labeled 'Methamphetamine Abuser (1 month abstinent)' and shows significantly reduced DAT binding (blue). A color scale on the right indicates 'high' (yellow/red) and 'low' (blue). Source: Volkow et al., 2001.

42

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


43

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

44

Internet Websites Foster Risky Behaviors

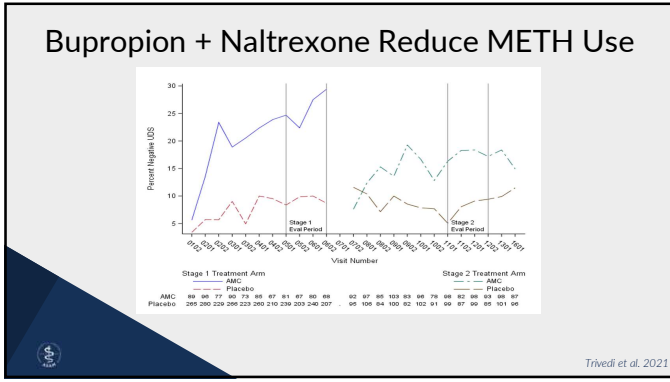


45

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

46



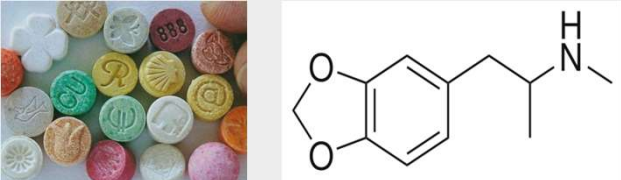
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Ecstasy

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Ecstasy (MDMA) is a Synthetic Club Drug

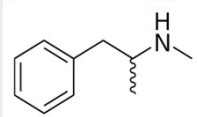


The image shows a collection of colorful, multi-colored pills on the left, and the chemical structure of MDMA (3,4-methylenedioxyamphetamine) on the right. The structure features a benzene ring with a methylenedioxy group at the 3 and 4 positions and a 2-(propylamino)ethyl side chain.

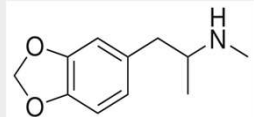
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MDMA is a Ring-Substituted Amphetamine Analog

Methamphetamine

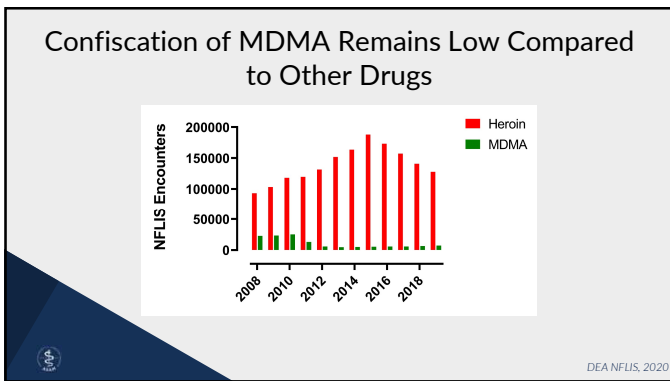


3,4-Methylenedioxy Methamphetamine (MDMA)



The slide compares the chemical structures of Methamphetamine and MDMA. Methamphetamine is shown as a benzene ring with a 2-(propylamino)ethyl side chain. MDMA is shown as a benzene ring with a methylenedioxy group at the 3 and 4 positions and a 2-(propylamino)ethyl side chain.

50



51

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-demethylation to form hydroxylated metabolites

de la Torre et al., 2004

53

MDMA Metabolism is Complex


The diagram illustrates the complex metabolism of MDMA. MDMA is converted to MDA via N-demethylation (enzymes: CYP1A). MDA is then converted to HHMA via O-demethylation (enzymes: CYP2D6, CYP2D1) and to HMA via O-methylation (enzyme: COMT). HHMA is converted to HMA via O-methylation (enzyme: COMT). Both HHMA and HMA are converted to HHA via O-demethylation (enzymes: CYP2D6, CYP2D1). Finally, both HHA and HMA are converted to glucuronide sulfate conjugates via O-methylation (enzyme: COMT).

Baumann et al., 2007

54

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



55

Adverse Effects


- Psychosis
- Sympathetic Stimulation
 - Palpitations and heart attack
 - Hypertension
- 5-HT Syndrome
 - Hyperthermia and dehydration
 - Treat with hydration, cooling, and sedation
 - Avoid b 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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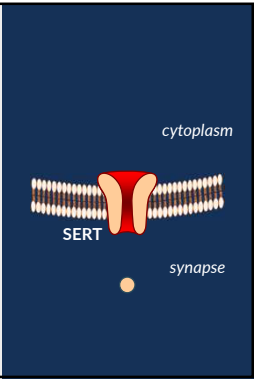
Molecular Sites of Action

- 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

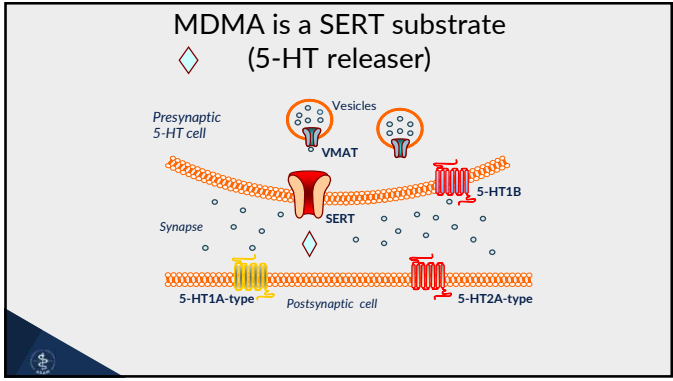
- SERTs are membrane proteins responsible for uptake of released 5-HT
- Drugs that disrupt SERT function increase synaptic 5-HT
- Increases in 5-HT are not rewarding (e.g., SSRIs)



The diagram shows a cross-section of a cell membrane. On the left side, labeled 'cytoplasm', a red SERT protein is embedded in the membrane. On the right side, labeled 'synapse', a small orange sphere representing 5-HT is shown near the membrane. The SERT protein has a red channel that opens towards the synapse, indicating its role in transporting 5-HT from the synapse back into the cytoplasm.

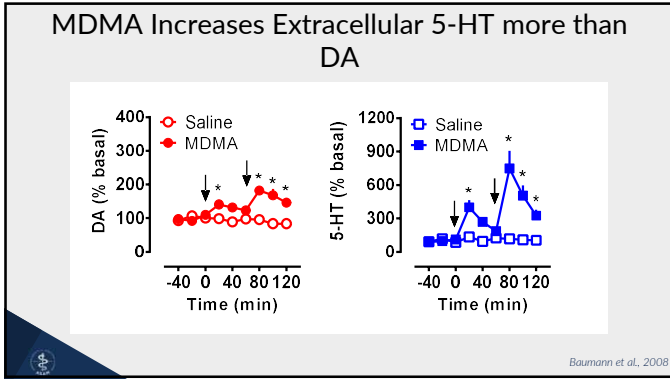
59

MDMA is a SERT substrate (5-HT releaser)



The diagram illustrates the transport and release of 5-HT in a synapse. At the top, a 'Presynaptic 5-HT cell' contains vesicles. One vesicle is shown fusing with the membrane, releasing 5-HT (small orange spheres) into the 'Synapse'. This process is mediated by 'VMAT' (Vesicular Monoamine Transporter) on the vesicle membrane. In the cytoplasm of the presynaptic cell, 'SERT' (Serotonin Transporter) is shown on the membrane, responsible for re-uptake of 5-HT. On the 'Postsynaptic cell' membrane, there are '5-HT1A-type' and '5-HT2A-type' receptors. Additionally, '5-HT1B' receptors are shown on the presynaptic membrane. MDMA is indicated as a substrate for SERT, shown as a red diamond shape near the transporter.

60



61

- ### 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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Bath Salts

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Cathinone is a Plant-Based Alkaloid



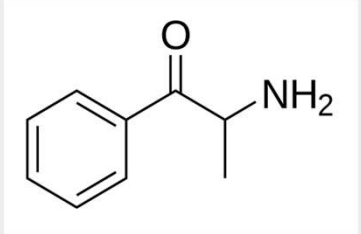
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Khat Plant *Catha edulis*



65

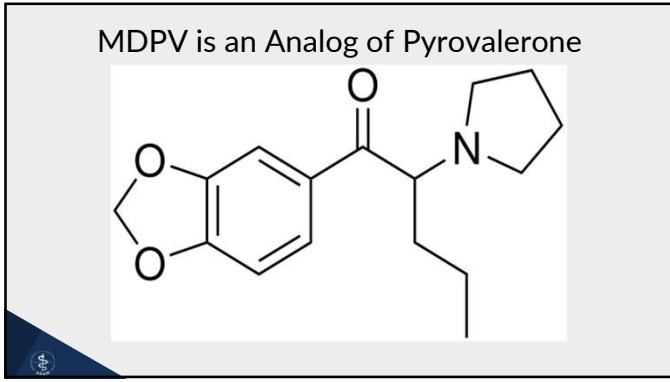
Cathinone is β -Keto Amphetamine



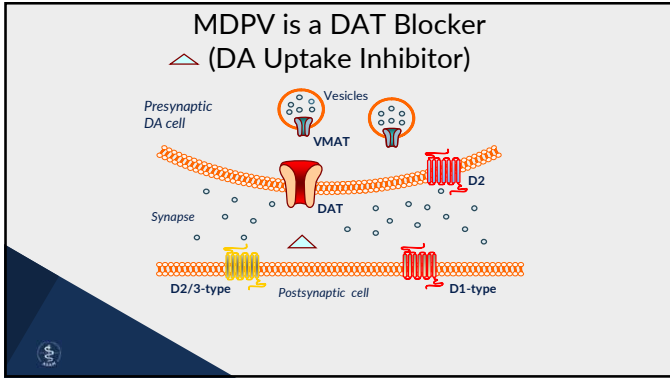
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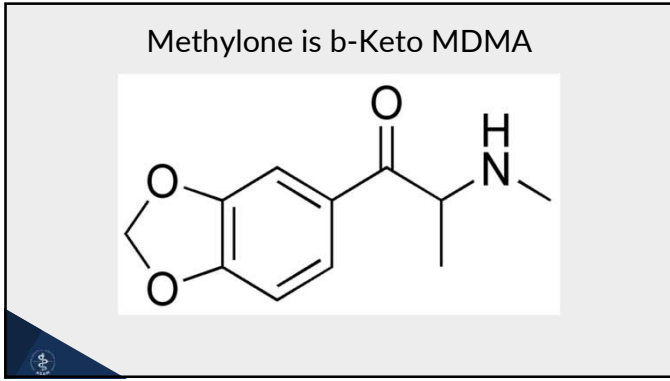
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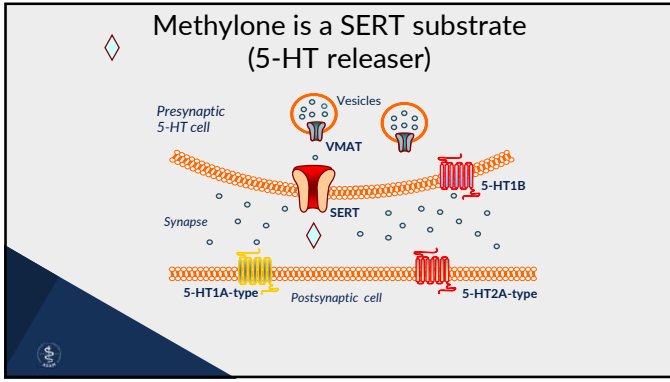
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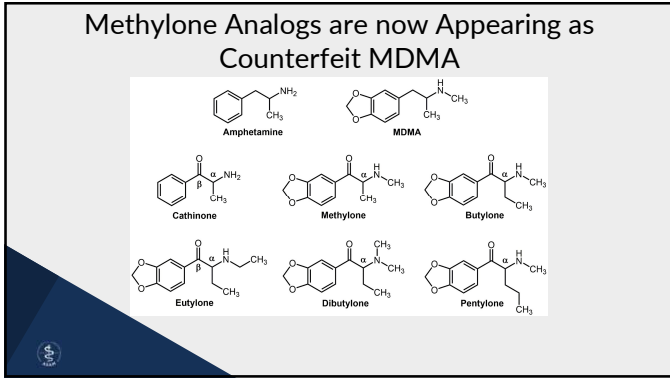
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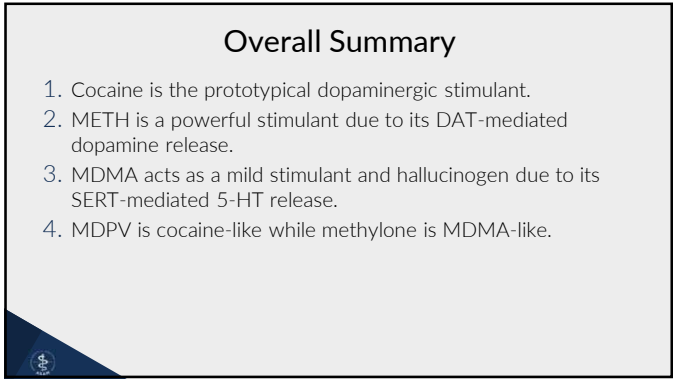
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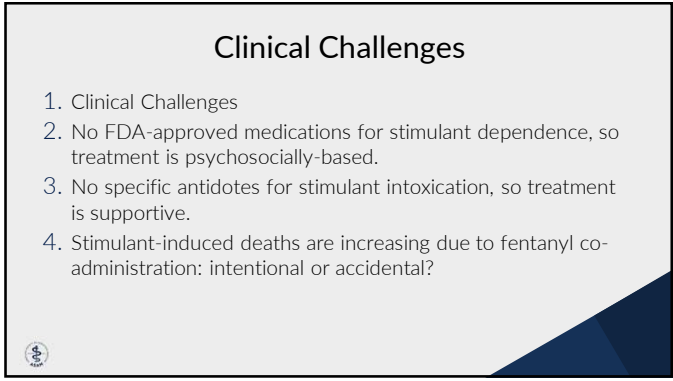
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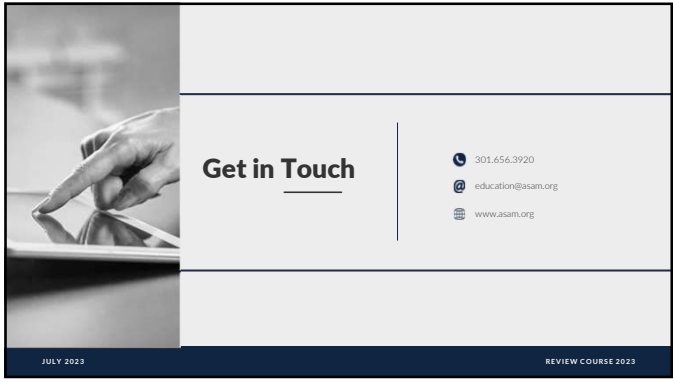
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