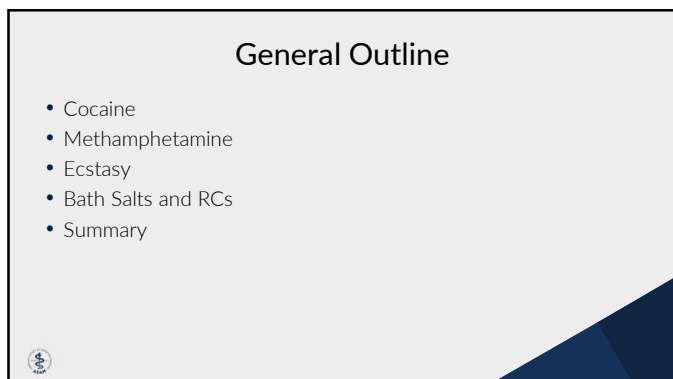




1




2



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

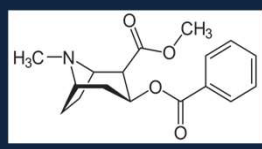


REVIEW COURSE 2023

5



Cocaine is a Plant Based Alkaloid

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

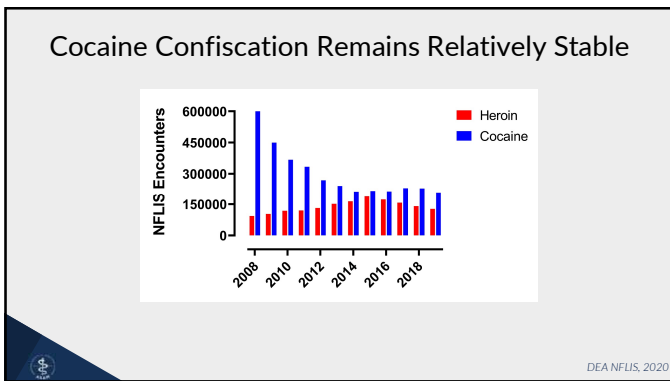
6



7



8



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



15

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



17

Molecular Sites of Action

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



18

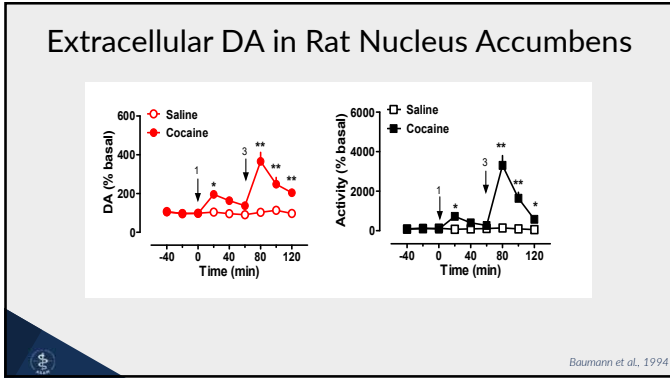
DATs Mediate DA Uptake

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

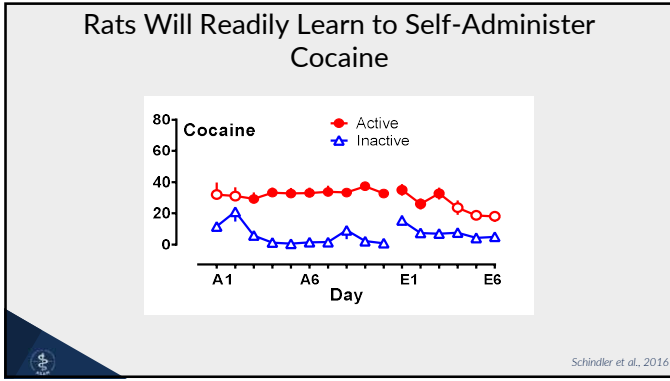
19

Cocaine is a DAT Blocker (DA Uptake Inhibitor)

20



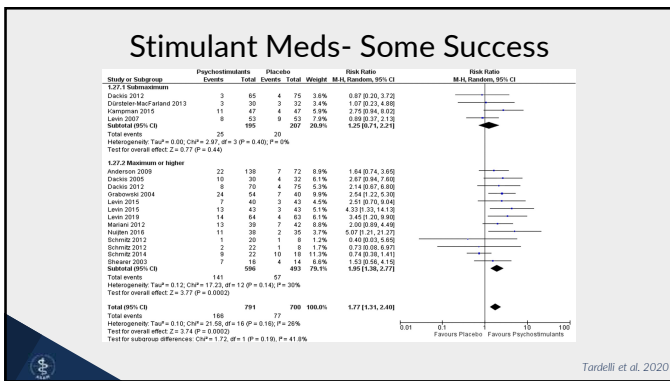
21



22

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

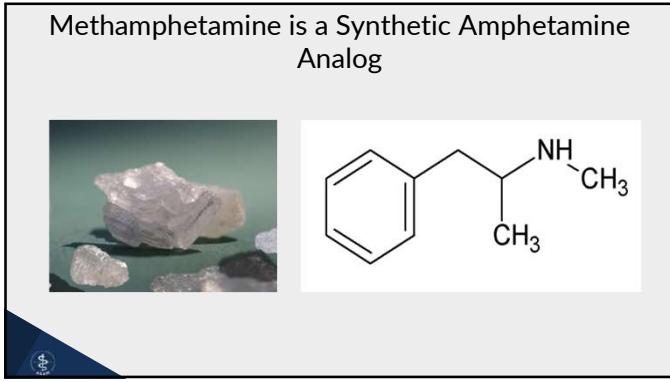
23



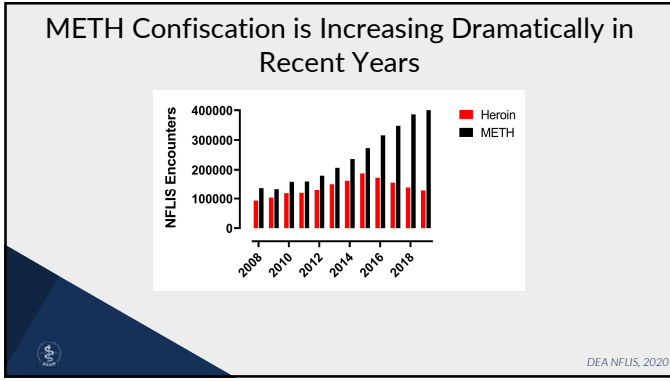
24



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

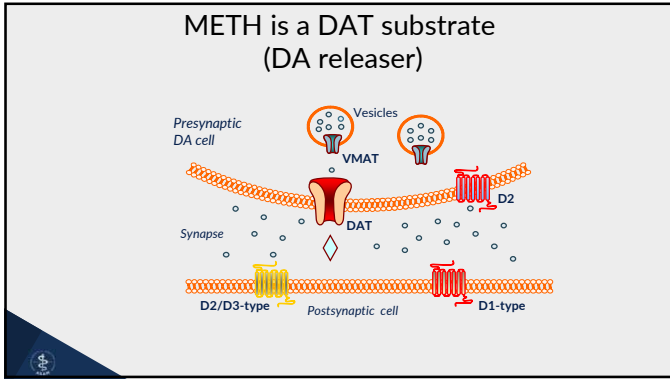
- Anhedonia and Depressed Mood
- Increased Appetite
- Anergia and Fatigue
- Vivid or Unpleasant Dreams
- Insomnia or Hypersomnia

36

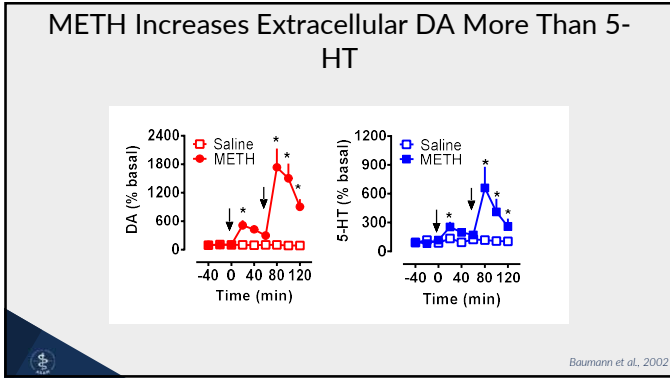
Molecular Sites of Action

- 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



38



39

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

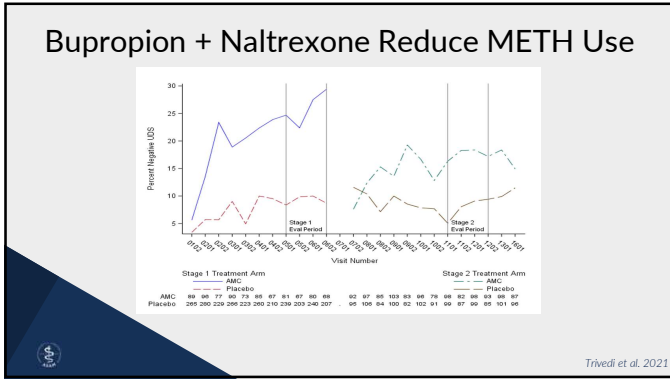


45

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



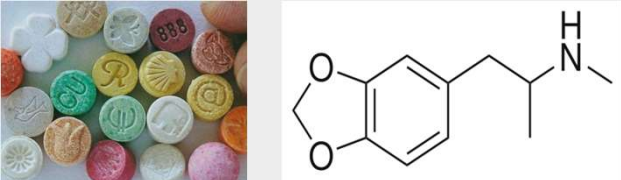
47

Ecstasy

REVIEW COURSE 2023

48

Ecstasy (MDMA) is a Synthetic Club Drug

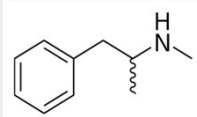


The image shows a collection of colorful, multi-colored pills on the left, and the chemical structure of MDMA (3,4-methylenedioxyamphetamine) on the right. The structure features a benzene ring with a methylenedioxy group at the 3 and 4 positions and a 2-(isopropylamino)ethyl side chain.

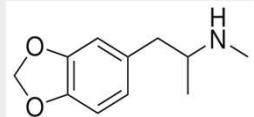
49

MDMA is a Ring-Substituted Amphetamine Analog

Methamphetamine

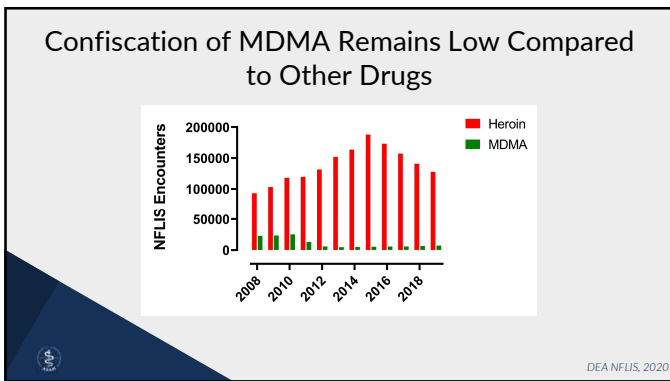


3,4-Methylenedioxy Methamphetamine (MDMA)



The image compares the chemical structures of Methamphetamine and MDMA. Methamphetamine has a benzene ring with a 2-(isopropylamino)ethyl side chain. MDMA has a benzene ring with a methylenedioxy group at the 3 and 4 positions and a 2-(isopropylamino)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

52

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



56

Withdrawal

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



57

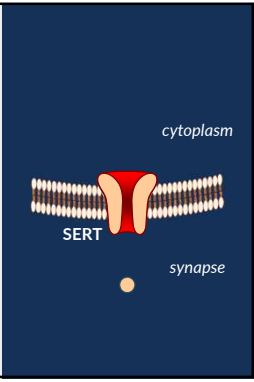
Molecular Sites of Action

- SLC6 Monoamine Transporters
 - 5-HT transporter (SERT)
 - Dopamine transporter (DAT)
 - Norepinephrine transporter (NET)
- Other sites
 - Vesicular Monoamine Transporter 2 (VMAT2)
 - 5-HT2A receptors

58

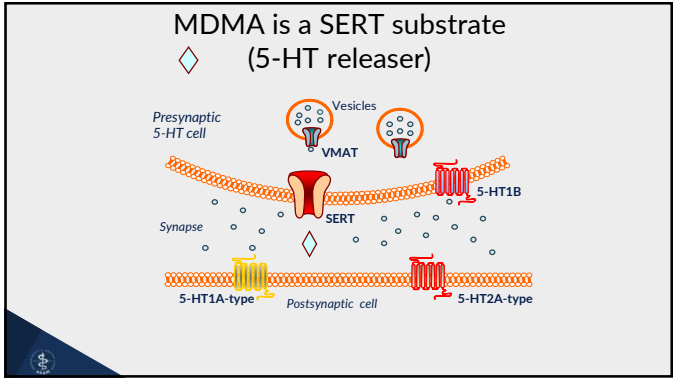
SERTs Mediate 5-HT Uptake

- 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)

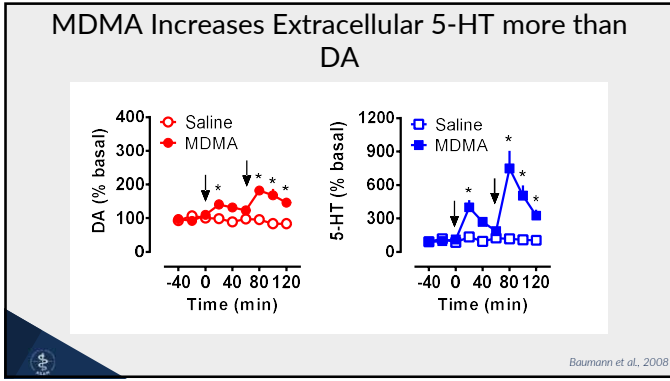


59

MDMA is a SERT substrate (5-HT releaser)



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?

62

Bath Salts

REVIEW COURSE 2023

63

Cathinone is a Plant-Based Alkaloid



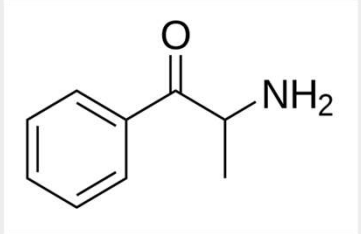
64

Khat Plant *Catha edulis*



65

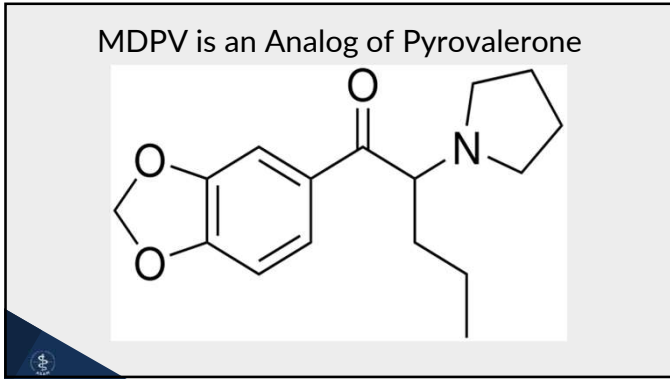
Cathinone is β -Keto Amphetamine



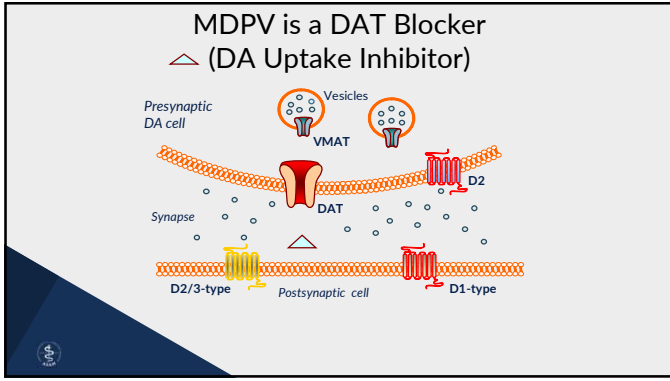
66



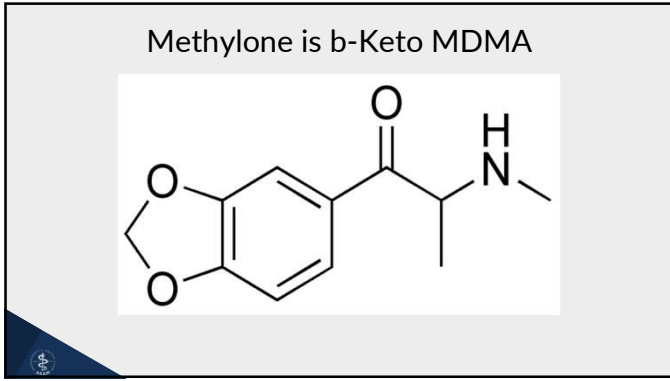
67



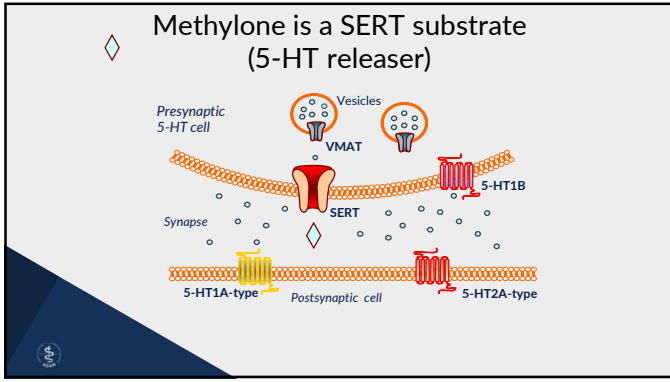
68



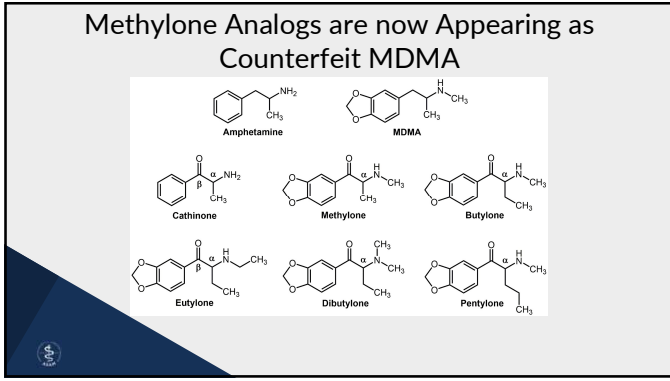
69



70



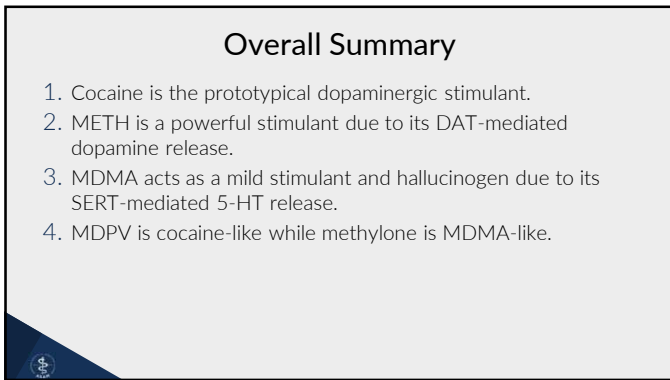
71



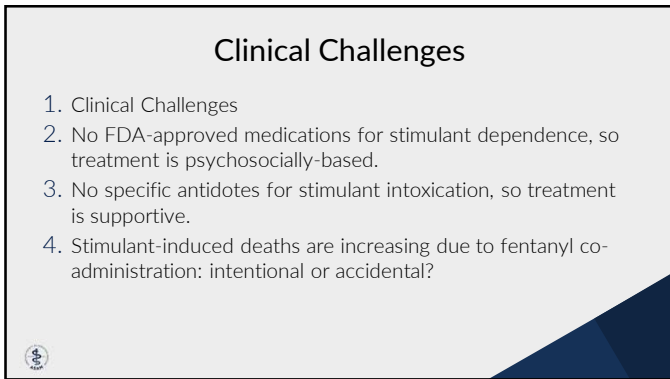
72



73



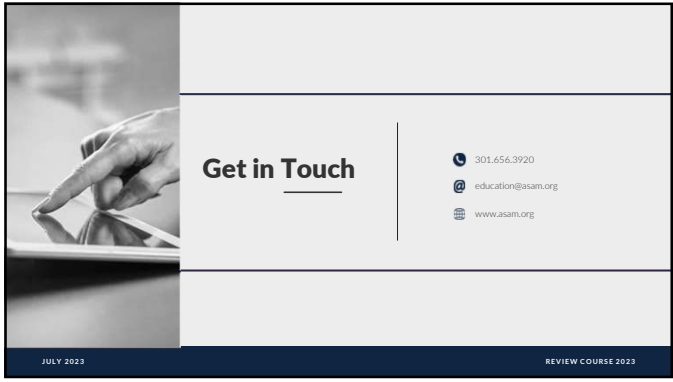
74



75



76



77
