CNS STIMULANTS

CNS Stimulants

- Stimulants are a family of compounds chemically and pharmacologically dissimilar; when ingested in sufficient dosage they cause a **wide variety of effects related to central stimulation**
- **…….enhance the intensity of our reactions to external stimuli……**
- **"Heightened awareness, quick thinking, elevated mood"**

CNS Stimulants

- Specific stimulant concerned are:
  - Amphetamine-like drugs
  - Cocaine
  - Methylxanthines

Amphetamine-like drugs

- Numerous derivatives have been used over the years to modify a variety of medical conditions
  - Narcolepsy,
  - Hyperkinesis (Attention Deficit Hyperactivity Disorder (ADHD)),
  - Short-term treatment of obesity
- In **many states** are nowadays **banned**, so their clinical usage has declined significantly
- However, in many countries, despite the tight control, **amphetamine abuse**, is still ranked overall as a very significant medical problem

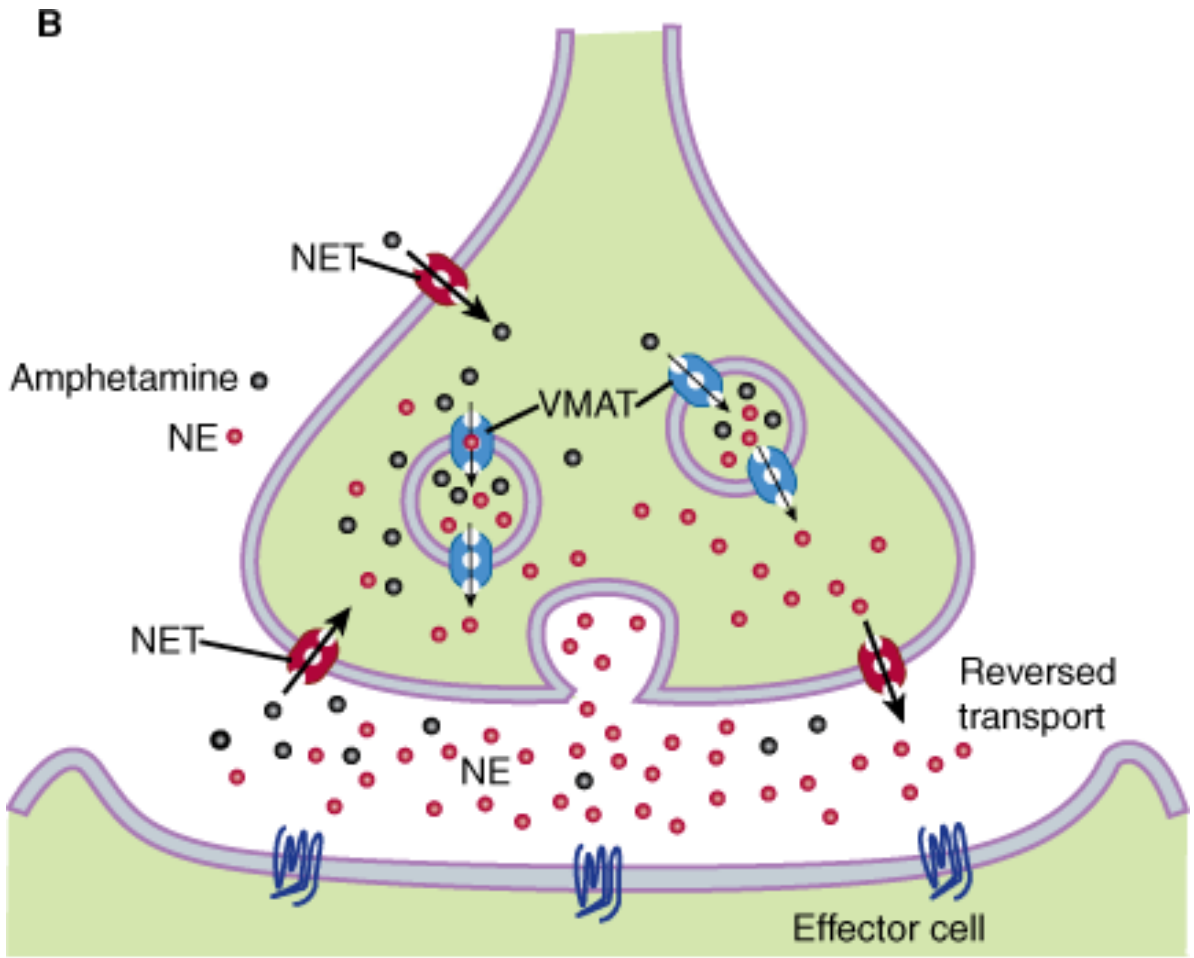
Amphetamines

- **Methylphenidate**
  - used to treat attention deficit disorder and hyperactivity disorders in children
- **Atomoxetine** ADHD
- **Phenmetrazine**
  - (no more used to treat obesity)

Mechanism of Toxicity

- **Amphetamine and related drugs** activate the sympathetic nervous system

1. Induce peripheral release of catecholamines
2. Inhibition of neuronal reuptake of catecholamines, and
3. Inhibition of monoamine oxidase
4. Some also cause serotonin release and block neuronal serotonin uptake.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Toxicokinetics

- All these drugs are well absorbed orally
- Have **large volumes of distribution** (Vd = 3–33 L/kg)
- They are generally **extensively metabolized** by the liver
- **Excretion** of most amphetamines is highly **dependent on urine pH**…….eliminated more rapidly in an **acidic urine**

TOXIC DOSES

- Low therapeutic index, with toxicity at levels only slightly above usual doses…**BUT high degree of tolerance**

- Acute ingestion of more than 1 mg/kg of dextroamphetamine is considered potentially life-threatening

Characteristics of amphetamine toxicity grouped by severity

S&S	Severity
Euphoria, restlessness, insomnia, tremor,, sweating, mydriasis	+1
Hyperactivity, confusion,, tachycardia, hypertension,	+2
Delirium, mania, arrhythmias,	+3
All above+ convulsion, coma, circulatory collapse, death	+4

CLINICAL PRESENTATION

- **Death** may be caused by ventricular arrhythmia, status epilepticus, intracranial hemorrhage or hyperthermia
- **Hyperthermia** results from seizures and muscular hyperactivity (cause rhabdomyolysis) and drug-induced vasoconstriction (especially in athletes abusers prior to race)
- The toxic lethal dose varies but has been reported as 20-25mg/kg

CHRONIC EFFECTS

- ***AMPETAMINE ABUSE INCLUDES:***
- Weight loss
- Cardiomyopathy
- Pulmonary hypertension
- psychosis
- **After cessation of habitual use, patients may experience fatigue, and depression lasting several days.**

Treatment

- ABC
- Treat agitation, seizures, coma, and hyperthermia if they occur
- Continuously monitor the temperature, other vital signs, and the ECG for a minimum of 6 hours
- **Agitation:** benzodiazepines usually satisfactory. Antipsychotics (haloperidol, olanzapine) may be needed
- **Hypertension** parenteral vasodilator (phentolamine or nitroprusside)

Treatment

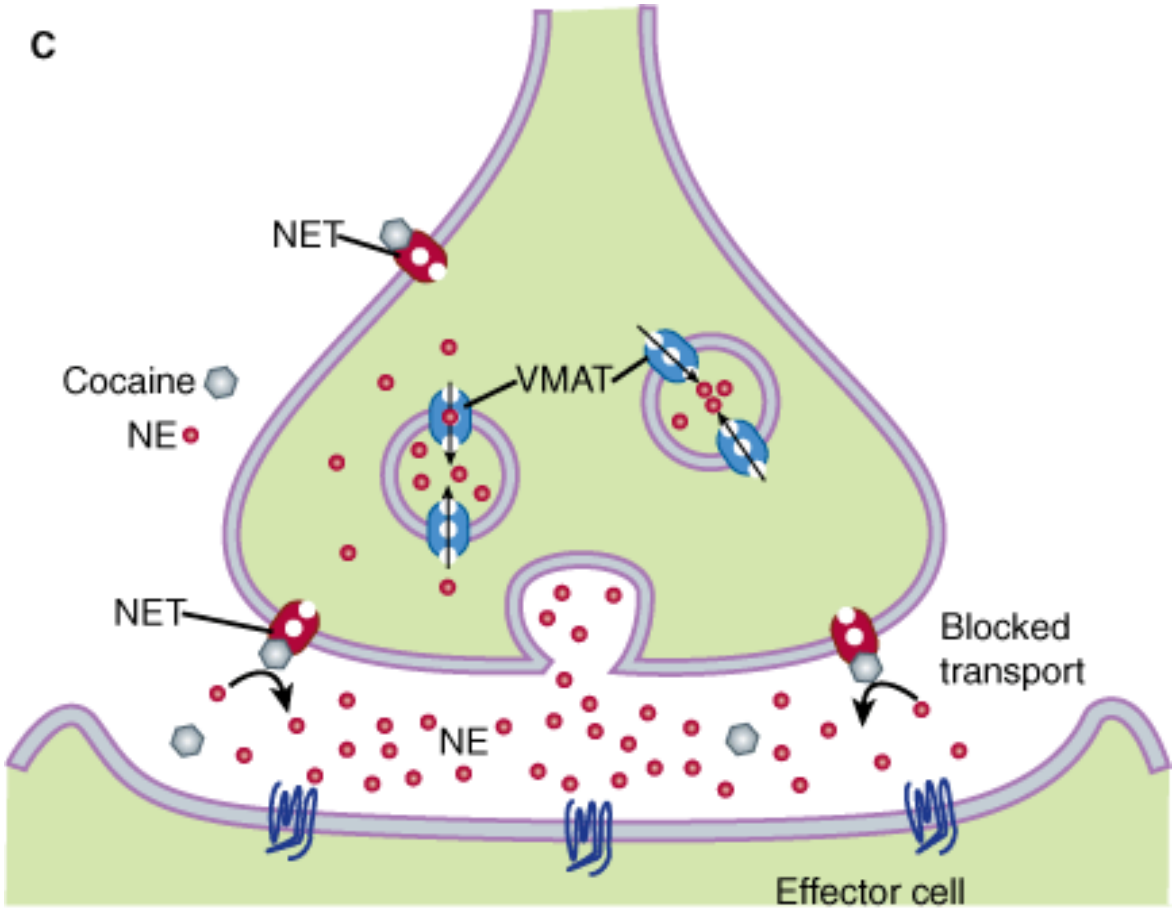
- Treat **tachyarrhythmias** with propranolol
- **Decontamination.** Administer activated charcoal orally if conditions are appropriate. Gastric lavage is not necessary after small to moderate ingestions
- **Dialysis and hemoperfusion** are not effective
- **Renal elimination** may be enhanced by urine acidification……BUT **not recommended....**may aggravate nephrotoxicity

Cocaine

- Cocaine is one of the most popular drugs of abuse
- May be **sniffed** (snorted), **smoked**, or **injected** IV
- Occasionally injected combined with **heroin** ("**speedball**“).

Mechanism of toxicity

- The primary actions are local anesthetic effects, CNS stimulation, and
- Inhibition of neuronal uptake of catecholamines
- Results in a state of generalized sympathetic stimulation very similar to that of amphetamine intoxication



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Toxicokinetics

- **Well absorbed from all routes**, local anesthetic toxicity after mucosal application
- Smoking and IV injection produce maximum effects within 1–2 minutes,
- Oral or mucosal absorption may take up to 20–30 minutes
- Elimination by metabolism and hydrolysis, $T_{1/2}$ ~60 minutes

Cocaine Toxicity

- ***Variety of S & S….***
- ✓ Euphoria followed by anxiety, agitation, delirium, psychosis, muscle rigidity or hyperactivity, and seizures
- ✓ Hyperthermia, intracranial hemorrhage, HTN and coma
- ✓ CV toxicity: tachycardia, hypertension with hemorrhagic stroke, **Most common cause of drug-induced stroke**

Cocaine Toxicity

- **Death** due to arrhythmia, status epilepticus, intracranial hemorrhage, or hyperthermia
- Hyperthermia is usually caused by seizures, muscular hyperactivity, or rigidity…..
- Following an initial period of HTN….blood pressure falls and cardiac depression ensues
- Respiratory system: initial stimulation resulting in tachypnea followed by respiratory arrest…..cause of death!

Management

- ✓ **ABC**
- ✓ **Treat** coma, agitation, seizures, hyperthermia, arrhythmias, Tachycardia, and Ventricular dysrhythmias, and hypotension if they occur
- ✓ **Benzodiazepines** are a good choice for initial management of hypertension and tachycardia associated with agitation
- ✓ **Hyperthermia** must be controlled
- ✓ **Cocaine-induced psychosis**: neuroleptic agents or lithium

Management

- **Decontamination**
  - **Activated charcoal**….if necessary gastric lavage
  - *Most cocaine use occurs by intravenous or by nasal routes……*
- **Acidification** of the urine not effective and may aggravate renal failure

Methylxanthines

- Three alkaloids present naturally
  - Caffeine
  - Theophylline
  - Theobromine

Theophylline

- Methylxanthine used for the treatment of asthma

- **Mechanism of toxicity:**
- Exact mechanism not known….BUT:

i. Antagonist of adenosine receptors, and

ii. Inhibits phosphodiesterase at high levels, increasing intracellular cAMP

iii. Also known to release endogenous catecholamines at therapeutic concentrations

Pharmacokinetics

- Absorption may be delayed with sustained-release preparations
- The normal elimination half-life is 4–6 hours
- May be doubled by illnesses (eg, liver disease, congestive heart failure) OR
- Interacting with drugs (eg, erythromycin, cimetidine) that slow hepatic metabolism

Toxic Levels

- Serum levels are essential for diagnosis and determination of emergency treatment
- After acute oral overdose, obtain repeated levels every 2–4 hours
- Levels <80–100 mg/L after **acute overdose** usually are not associated with severe symptoms (mild)
- With **chronic intoxication**, severe toxicity may occur with levels of 40–60 mg/L

Clinical Presentation

- **Acute single overdose:** due to suicidal attempt, or accidental childhood ingestion but also accidental or iatrogenic misuse :
  - Vomiting (sometimes hematemesis), tremor, anxiety, and tachycardia
  - Metabolic effects include pronounced hypokalemia, hypophosphatemia, hyperglycemia, and metabolic acidosis
  - Severe intoxication (levels > 90–100 mg/L): hypotension, ventricular arrhythmias, and seizures

Clinical Presentation

- **Chronic intoxication:** If doses administered over time or intercurrent illness or interacting drug interferes with the hepatic metabolism
  - **Vomiting** may occur but **not as common as** in acute overdose
  - Tachycardia is common, but hypotension is rare
  - No hypokalemia, no hyperglycemia
  - Seizures may occur with lower serum levels (eg, 40–60 mg/L)

Treatment

- Maintain an open airway and assist ventilation if necessary
- Treat seizures, arrhythmias, and hypotension if they occur
- Tachyarrhythmias and hypotension are best treated with propranolol or esmolol
- Hypokalemia due to intracellular movement of potassium (does not reflect total body deficit)….usually resolves spontaneously
- Monitor vital signs, ECG, and serial theophylline levels for at least 16–18 hours after a significant oral overdose

Treatment

- **Decontamination**. Administer activated charcoal orally if conditions are appropriate
- Consider repeated doses of activated charcoal and WBI after a large ingestion of a sustained-released formulation

- **Enhanced elimination**. Hemodialysis, or charcoal hemoperfusion are effective (small Vd 0.5 L/kg),
- It is protein-bound at therapeutic concentrations, BUT the free fraction dominates at higher levels

DEXTROMETHORPHAN (DXM)

Dextromethorphan

- Common antitussive agent found in many OTC cough and cold preparations
- Found in combination products containing antihistamines, decongestants, ethanol, or acetaminophen
- Structurally related to opioids (codeine), but no activity at mu or kappa receptors and not typical opioid syndrome in overdose

Mechanism of toxicity

- Metabolized in the liver by the cyt. P-450 to dextrorphan
- Antagonize *N*-methyl-d-aspartate (NMDA) glutamate receptors (dextrorphan is more potent and responsible for the psychoactive effects)
- Extensive metabolizers are more likely to experience the "desirable" psychoactive effects with recreational use….**hallucination and dissociation from reality**

Mechanism of toxicity

- Dextromethorphan inhibit reuptake of serotonin and may lead to **seratonin syndrome** …..especially with SSRI or MAOI
- Inhibits adrenergic neurotransmitter reuptake in the peripheral and central nervous system
- Serotoninergic effects, as well as NMDA glutamate receptor inhibition, may explain the acute and chronic abuse potential of dextromethorphan

Clinical presentation

- **Mild to moderate intoxication.** N, V, nystagmus, tachycardia, HTN, dizziness, lethargy, agitation, ataxia, euphoria, dysphoria, and auditory and visual hallucinations

- **Severe poisoning.** Disorientation, psychosis, seizures, coma, hyperthermia, respiratory depression, pulmonary and cerebral edema, and death can occur

Clinical presentation

- **Serotonin syndrome**. Severe hyperthermia, muscle rigidity, altered mental status, and hypertension

- **Withdrawal syndrome.** vomiting, diarrhea, tachycardia, hypertension, depression, tremor, restlessness, and drug craving have been reported

Treatment

- Most patients with mild symptoms (ie, restlessness, ataxia, or mild drowsiness) can be observed for 4–6 hours
- Maintain an open airway and assist ventilation if needed
- Treat seizures and coma if they occur
- Rarely, DXM poisoning is associated with coma and, respiratory depression may respond to **naloxone**
- **Decontamination**. Administer activated charcoal orally if conditions are appropriate
- **Enhanced elimination.** The Vd is very large, and there is no role for enhanced removal procedures