

Drugs of Abuse

Dr. Qutaiba Ghanim

Department of Pharmacology

College of Medicine, University of Diyala



Dugs of Abuse

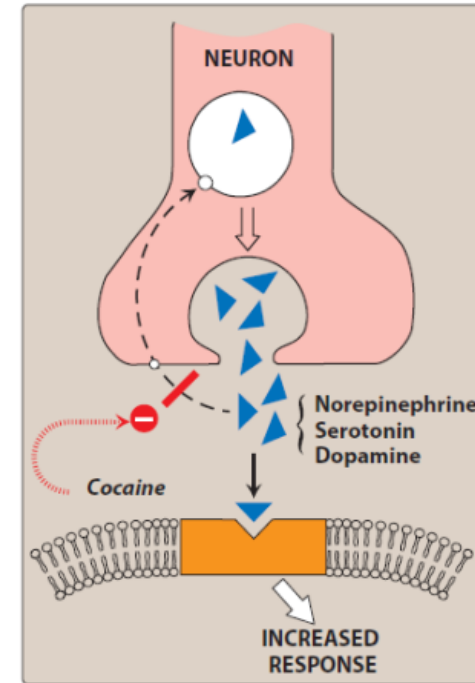
- Drug abuse is described as excessive use or misuse of drugs or alcohol for intoxicating or mind-altering effects.

1. Sympathomimetics

- Sympathomimetics are stimulants that mimic the sympathetic nervous system, producing “fight-or-flight” responses.
- Sympathomimetics cause tachycardia, hypertension, hyperthermia, and tachypnea.

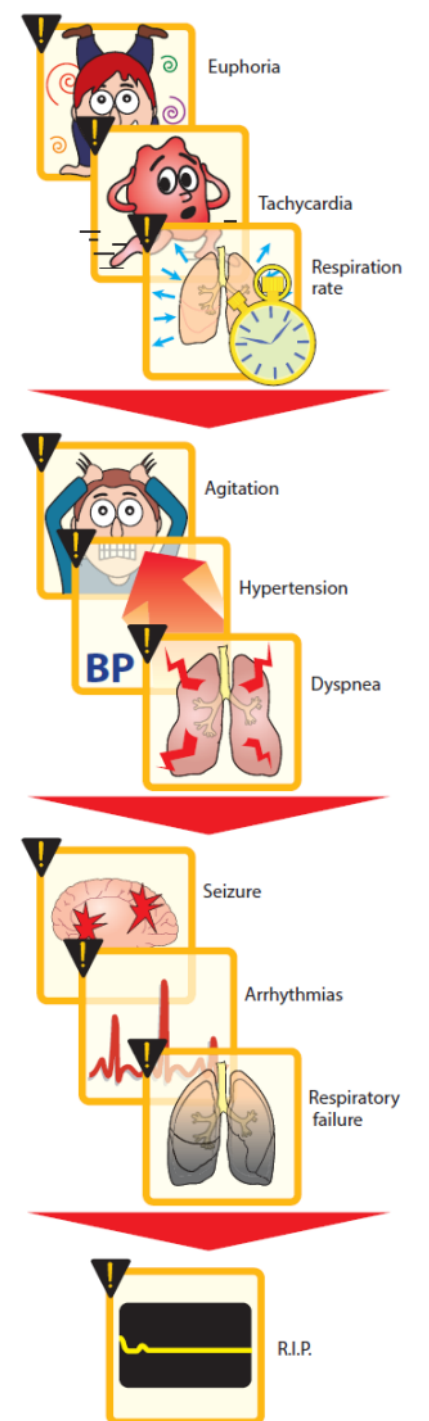
Cocaine

- Cocaine is derived from the erythroxylon coca shrub that grows in the foothills of the Andes Mountains in South America.
- It causes central nervous system (CNS) stimulation by inhibiting the reuptake of norepinephrine into the adrenergic neuron, thus increasing the amount of catecholamines available at the synapse.
- The profound ability of cocaine to stimulate the pleasure center of the human brain is thought to result from inhibition of reuptake of dopamine and serotonin.
- Cocaine has minimal bioavailability when taken by the oral route. Instead, the cocaine hydrochloride powder is snorted, or solubilized and injected.
- The cocaine powder cannot be effectively smoked, as it is destroyed upon heating. However, crack cocaine, an alkaloidal form, can be smoked.
- Cocaine causes an intense euphoria or “rush” that is followed rapidly by an intense dysphoria or “crash.” It is this immediate positive reinforcement, followed rapidly by the negative reinforcement, that makes the drug, particularly in this form, so addictive.



Cocaine

- A few of the more common reasons for cocaine users to come to the emergency department include psychiatric complaints (depression precipitated by cocaine dysphoria, agitation/paranoia), convulsions, hyperthermia, and chest pain.
- The hyperthermia is caused by cocaine-induced CNS stimulation that generates increased heat production, coupled with vasoconstrictive effects of cocaine that minimize the ability to dissipate the heat.
- Cocaine-related chest pain can be chest muscle pain or cardiac in nature, as cocaine causes vasoconstriction of the coronary arteries and accelerates the atherosclerotic process.
- Cocaine convulsions are a natural extension of the CNS stimulant effect. Cocaine toxicity is treated by calming and cooling the patient.
- Benzodiazepines, such as lorazepam, help to calm the agitated patient and can both treat and prevent convulsions.
- In addition, the calming effect helps cool the patient and manage the hyperthermia. This is an important effect, as hyperthermia is one of the major causes of cocaine fatalities.
- The remainder of cocaine toxicity is treated with short-acting antihypertensives, anticonvulsants, and symptomatic supportive care.

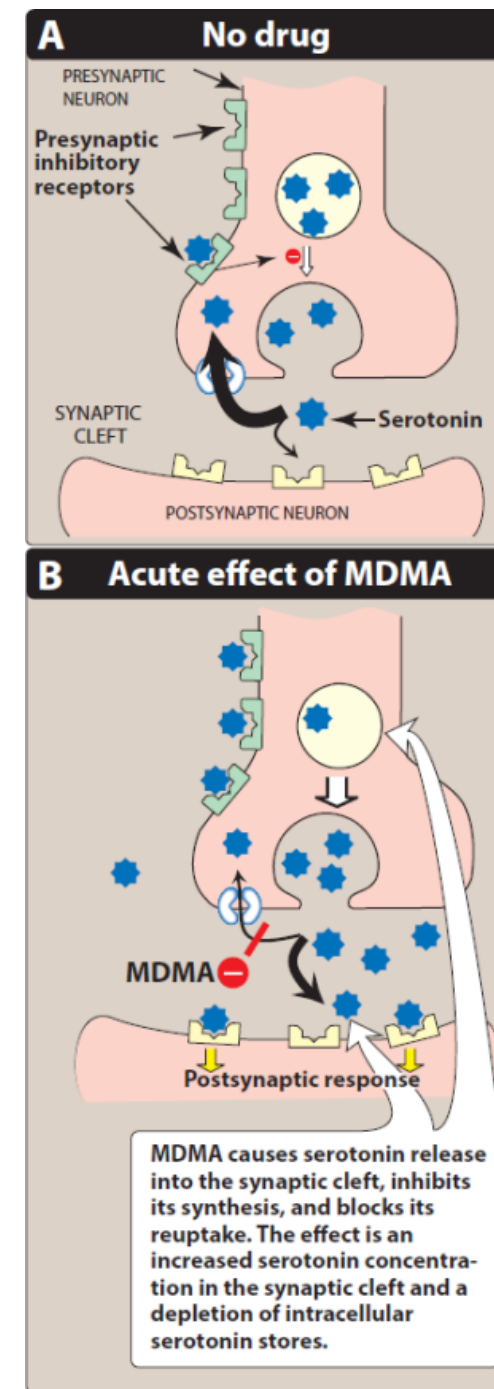


Amphetamines

- Amphetamines such as methamphetamine are sympathomimetics with clinical effects very similar to those of cocaine.
- In many cases, these effects may last longer and be associated with more stimulation and less euphoria when compared to cocaine.
- Treatment of amphetamine toxicity is similar to that of cocaine toxicity.

Methylenedioxymethamphetamine

- Methylenedioxymethamphetamine (MDMA), commonly known as ecstasy or Molly, is a hallucinogenic amphetamine with profound serotonin-releasing effects.
- Like many amphetamines, MDMA can cause bruxism (teeth grinding) and trismus (jaw clenching), profound hyperthermia, altered mental status, and movement disorders known as the serotonin syndrome.
- Benzodiazepines help to calm and cool the patient.
- Life-threatening hyperthermia has been treated with neuromuscular blockers and endotracheal intubation to control excessive movement and heat generation.
- **Cyproheptadine** is a serotonin antagonist that has been used to treat serotonin syndrome.



Synthetic Cathinones

- Cathinone is the psychoactive component in an evergreen shrub called Khat native to East Africa and the Arabian Peninsula.
- Synthetic cathinones include **methcathinone, butylone, methylene dioxypyrovalerone, and naphyrone**.
- These drugs increase the release and inhibit the reuptake of catecholamines (norepinephrine, epinephrine, and dopamine) in a manner very similar to cocaine and amphetamines.
- A rapid onset of amphetamine-like stimulation with psychotomimetic effects of variable duration is common with synthetic cathinones.
- Treatment is similar to the emergent treatment of amphetamines and cocaine.

Hallucinogens

Lysergic acid diethylamide (LSD), marijuana, and synthetic cannabinoids

A. Lysergic acid diethylamide

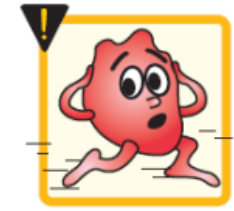
- LSD is the most commonly considered drug in the hallucinogen class.
- LSD produces its psychedelic effects through serving as a potent partial agonist at 5-HT_{2A} receptors.
- Aside from the very colorful hallucinations, the drug is also responsible for mood alterations, sleep disturbances, and anxiety.
- Although physical side effects are typically minimal, LSD may cause tachycardia, increased blood pressure and body temperature, dizziness, decreased appetite, and sweating.
- Perhaps, the most troubling side effects are the loss of judgment and impaired reasoning associated with use of LSD.

Hallucinogens

Lysergic acid diethylamide (LSD), marijuana, and synthetic cannabinoids

B. Marijuana

- Cannabis is a plant that is thought to have been used by humans for over 10,000 years.
- The main psychoactive alkaloid contained in marijuana is Δ^9 -tetrahydrocannabinol (THC).
- Specific receptors in the brain, cannabinoid or CB1 receptors, were found to be reactive to THC. When CB1 receptors are activated by marijuana, the effects produced include physical relaxation, hyperphagia (increased appetite), increased heart rate, decreased muscle coordination, conjunctivitis, and minor pain control.
- Although hallucinations are typically not as robust as those observed with LSD use, marijuana is often used for the hallucinogenic effects that it produces.
- The effects of marijuana on γ -aminobutyric acid (GABA) in the hippocampus diminish the capacity for short-term memory in users, and this affect seems to be more pronounced in adolescents.
- In addition to adversely affecting short-term memory and mental activity, THC decreases muscle strength and impairs highly skilled motor activity such as that required to drive a car. The effects of THC appear immediately after the drug is smoked, but maximum effects take about 20 minutes. By 3 hours, the effects largely disappear.



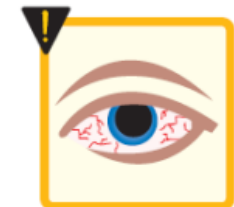
Tachycardia



Impaired memc



Hallucinations



Conjunctivitis



Increased appetite



Impaired coordination

Hallucinogens

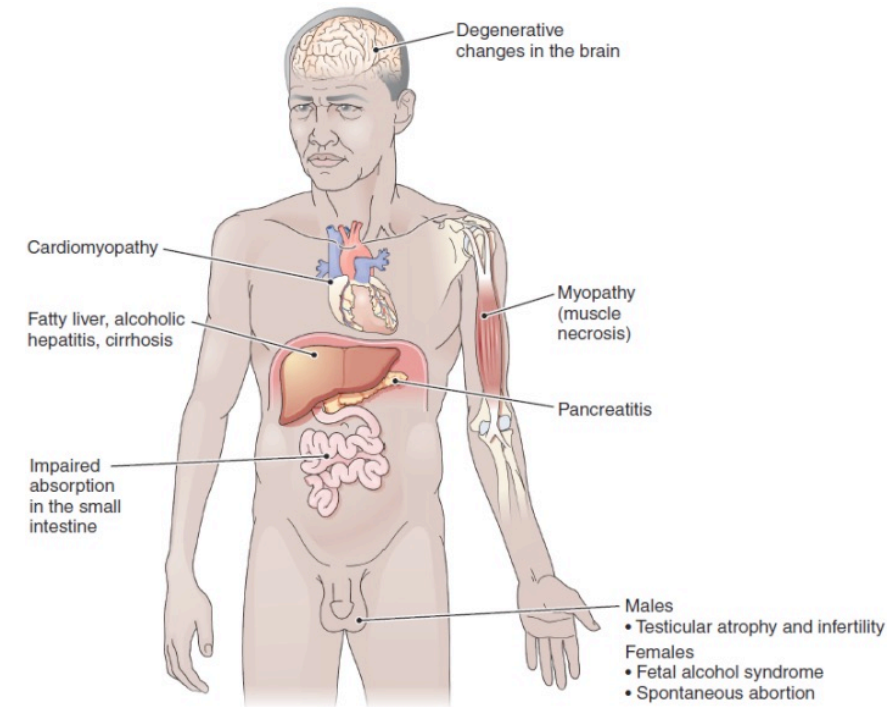
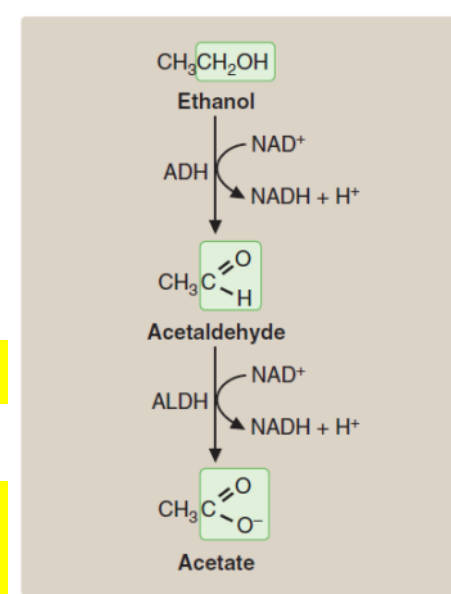
Lysergic acid diethylamide (LSD), marijuana, and synthetic cannabinoids

C. Synthetic Cannabinoids

- The effects of synthetic THC-containing compounds may be up to 800 times greater than the effects observed with cannabis.
- Sympathomimetic effects may also be seen in users, including tachycardia and hypertension.
- Possibly the greatest danger includes extreme hallucinations that have been reported with the use of these agents.

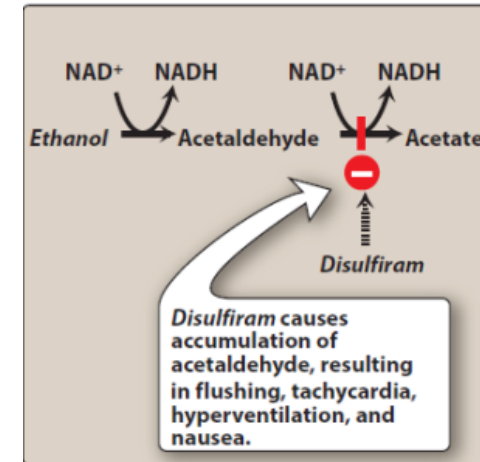
Ethanol

- Alcohol is the most commonly abused substance in modern society.
- Alcoholism decreases life expectancy by 10 to 15 years and impacts one in three families.
- It is thought that ethanol exerts its desired and toxic effects through several mechanisms, including enhancing the effects of the inhibitory neurotransmitter GABA, inducing the release of endogenous opioids, and altering levels of serotonin and dopamine.
- Medical management of acute ethanol toxicity includes symptomatic supportive care and the administration of thiamine and folic acid to prevent/treat Wernicke encephalopathy and macrocytic anemia.
- Chronic ethanol abuse can cause profound hepatic, cardiovascular, pulmonary, hematologic, endocrine, metabolic, and CNS damage.
- Sudden cessation of ethanol ingestion in a heavy drinker can precipitate withdrawal manifested by tachycardia, sweating, tremor, anxiety, agitation, hallucinations, and convulsions.
- Alcohol withdrawal is a life-threatening situation that should be medically managed with symptomatic/supportive care, benzodiazepines, and long-term addiction treatment.
- The following are drugs used in the treatment of alcohol dependence:



A. Disulfiram

- Disulfiram blocks the oxidation of acetaldehyde to acetic acid by inhibiting aldehyde dehydrogenase. This results in the accumulation of acetaldehyde in the blood, causing flushing, tachycardia, hyperventilation, and nausea.
- Disulfiram has found some use in the patient seriously desiring to stop alcohol ingestion.
- A conditioned avoidance response is induced so that the patient abstains from alcohol to prevent the unpleasant effects of disulfiram-induced acetaldehyde accumulation.



B. Naltrexone

- Naltrexone is a long-acting opioid antagonist that should be used in conjunction with supportive psychotherapy.
- Naltrexone is better tolerated than disulfiram and does not produce the aversive reaction that disulfiram does.

C. Acamprosate

- Acamprosate is an agent used in alcohol dependence treatment programs with an as-yet poorly understood mechanism of action.
- This agent should also be used in conjunction with supportive psychotherapy.

CNS Stimulants



CNS Stimulants

- **Psychomotor stimulants and hallucinogens** are two groups of drugs that act primarily to stimulate the central nervous system (CNS).
- The psychomotor stimulants cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity.
- The hallucinogens produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord.
- As a group, the CNS stimulants have diverse clinical uses and are important as drugs of abuse, as are the CNS depressants and the opioids.

Psychomotor Stimulants

- 1. Methylxanthines:** include theophylline (found in tea), theobromine (found in cocoa), and caffeine.

Mechanism of action: include translocation of extracellular calcium, increase in cyclic adenosine monophosphate and cyclic guanosine monophosphate caused by inhibition of phosphodiesterase, and blockade of adenosine receptors. The latter most likely accounts for the actions achieved by the usual consumption of caffeine-containing beverages.

Therapeutic uses:

- Caffeine and its derivatives relax the smooth muscles of the bronchioles.
- Caffeine is also used in combination with the analgesics acetaminophen and aspirin for the management of headaches in both prescription and over-the-counter products.

Psychomotor Stimulants

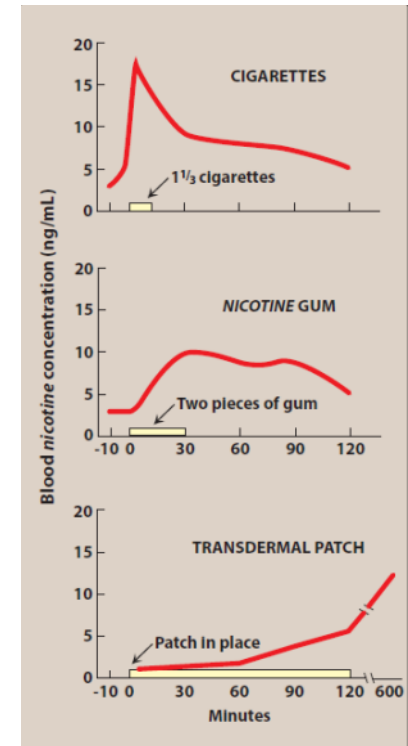
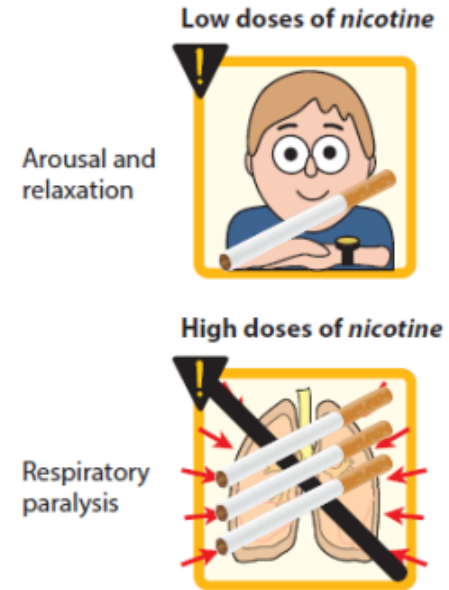
2. Nicotine: is the active ingredient in tobacco. Although this drug is not currently used therapeutically (except in smoking cessation therapy), nicotine remains important because it is second only to caffeine as the most widely used CNS stimulant, and it is second only to alcohol as the most abused drug.

Mechanism of action:

- In low doses, nicotine causes ganglionic stimulation by depolarization.
- At high doses, nicotine causes ganglionic blockade. Nicotine receptors exist at a number of sites in the CNS, which participate in the stimulant attributes of the drug.

Withdrawal syndrome: Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia. Appetite is affected, and GI upset often occurs.

- The transdermal patch and chewing gum containing nicotine have been shown to reduce nicotine withdrawal symptoms and to help smokers stop smoking.
- Other forms of nicotine replacement include the inhaler, nasal spray, and lozenges.
- **Bupropion**, an antidepressant, can reduce the craving for cigarettes.



Psychomotor Stimulants

3. Varenicline

- Varenicline is a partial agonist at neuronal nicotinic acetylcholine receptors in the CNS.
- Because varenicline is only a partial agonist at these receptors, it produces less euphoric effects than nicotine (nicotine is a full agonist at these receptors). Thus, it is useful as an adjunct in the management of smoking cessation in patients with nicotine withdrawal symptoms.
- Additionally, varenicline tends to attenuate the rewarding effects of nicotine if a person relapses and uses tobacco.

4. Cocaine

- Cocaine is a widely available and highly addictive drug.
- The primary mechanism of action underlying the effects of cocaine is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals.
- Chronic intake of cocaine depletes dopamine. This depletion triggers the vicious cycle of craving for cocaine that temporarily relieves severe depression.

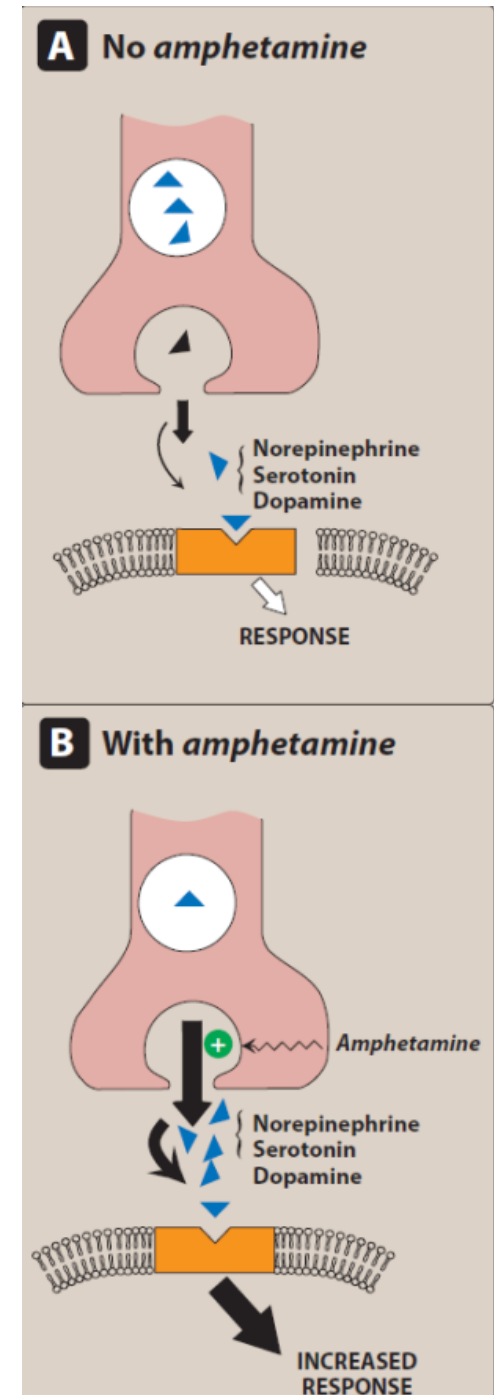
Psychomotor Stimulants

5. Amphetamine

- Amphetamine is a sympathetic amine that shows neurologic and clinical effects quite similar to those of cocaine.
- **Dextroamphetamine** is the major member of this class of compounds.
- **Methamphetamine** is a derivative of amphetamine available for prescription use.
- **3,4-Methylenedioxymethamphetamine (also known as MDMA, or Ecstasy)** is a synthetic derivative of methamphetamine with both stimulant and hallucinogenic properties.

Mechanism of action: it elevates of the level of catecholamine neurotransmitters in synaptic spaces by releasing intracellular stores of catecholamines.

- Because amphetamine also inhibits monoamine oxidase (MAO) and is a weak reuptake transport inhibitor, high levels of catecholamines are readily released into synaptic spaces.



Psychomotor Stimulants

Therapeutic uses:

- 1. Attention deficit hyperactivity disorder (ADHD):** Some young children are hyperkinetic and lack the ability to be involved in any one activity for longer than a few minutes.
 - **Dextroamphetamine, methamphetamine, the mixed amphetamine salts, and methylphenidate** can help improve attention span and alleviate many of the behavioral problems associated with this syndrome, in addition to reducing hyperkinesia.
 - **Atomoxetine** is a nonstimulant drug approved for ADHD in children and adults.
- 2. Narcolepsy:** Narcolepsy is a relatively rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day.
 - **Modafinil and its R-enantiomer derivative, armodafinil,** are considered first-line agents for the treatment of narcolepsy.
 - Modafinil promotes wakefulness, but it produces fewer psychoactive and euphoric effects and fewer alterations in mood, perception, thinking, and feelings typical of other CNS stimulants.
 - **The mechanism of action remains unclear, but may involve the adrenergic and dopaminergic systems.**
- 3. Appetite suppression:** Phentermine and diethylpropion are sympathomimetic amines that are related structurally to amphetamine.
 - These agents are used for their appetite-suppressant effects in the management of obesity.

Psychomotor Stimulants

6. Methylphenidate

- Methylphenidate has CNS-stimulant properties similar to those of amphetamine and may also lead to abuse, although its addictive potential is controversial.
- Methylphenidate is presently one of the most prescribed medications in children for ADHD.

Mechanism of action: Children with ADHD may produce weak dopamine signals, which suggests that once-interesting activities provide fewer rewards to these children.

- Methylphenidate is a dopamine and norepinephrine transport inhibitor and may act by increasing both dopamine and norepinephrine in the synaptic space.

Therapeutic uses: Methylphenidate has been used in the treatment of ADHD.

- It is also effective in the treatment of narcolepsy.



Vertigo



Hypertension



Insomnia



Confusion



Potential for addiction



Nausea



Diarrhea

