

# **Central Nervous System Stimulants and Related Drugs**

Samar Hunaiti

# CNS Stimulants

- Drugs that stimulate a specific area of the brain or spinal cord
- Neurons contain receptors for excitatory neurotransmitters, including dopamine (dopaminergic drugs), norepinephrine (adrenergic drugs), and serotonin (serotonergic drugs)
- Sympathomimetic drugs

# Classification

- Classified according to
  - Chemical structural similarities: amphetamines, serotonin agonists, sympathomimetics, and xanthines
  - Site of therapeutic action in the central nervous system (CNS)
  - Major therapeutic uses: anti-attention deficit disorder, antinarcotic, anorexiant, antimigraine, and analeptic drugs

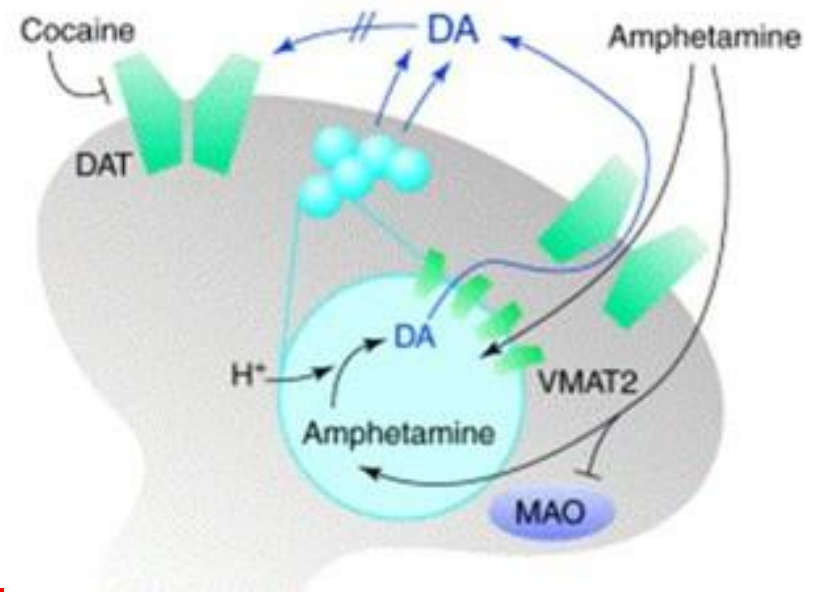
# Indirect-Acting Sympathomimetics

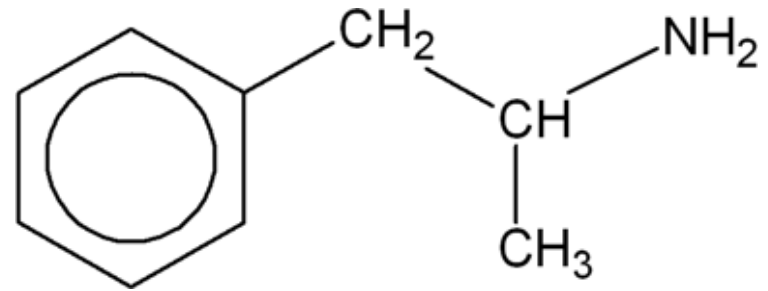
Indirect-acting sympathomimetics can have one of two different mechanisms:

- May enter the sympathetic nerve ending and **displace stored catecholamine** transmitter.

Such drugs have been called **amphetamine-like or "displacers."**

- May **inhibit the reuptake** of released NE by interfering with the action of the NE transporter e.g. Cocaine.





## Amphetamine-Like drugs

### Amphetamine

A racemic mixture that is important because of its use and misuse as a **CNS stimulant** .

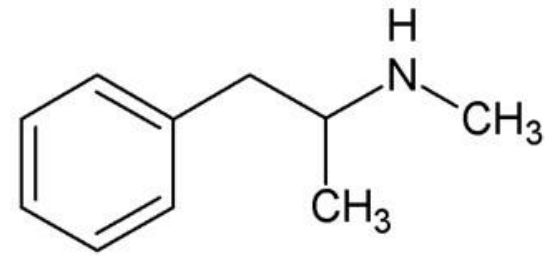
Readily enters the CNS, where it has marked stimulant effects on **mood and alertness and a depressant effect on appetite.**

Its **D-isomer** is more potent than the **L-isomer**.

Amphetamine's actions are mediated through the release of **NE** and **dopamine**.

# Methamphetamine

(*N*-methylamphetamine)



Very similar to amphetamine with an even higher ratio of central to peripheral actions.

# Methylphenidate

Its major pharmacologic effects and abuse potential are similar to those of amphetamine.

Methylphenidate may be effective in some children with **attention deficit hyperactivity disorder**.



# Catecholamine Reuptake Inhibitors

Many antidepressants, particularly **tricyclic antidepressants** inhibit **NE & serotonin** reuptake leading to orthostatic tachycardia as a side effect.

## Atomoxetine

A selective inhibitor of the NE reuptake transporter used in the **treatment of attention deficit disorders**

## Sibutramine

A **serotonin** and **NE** reuptake inhibitor and was used as **appetite suppressant for long-term treatment of obesity.**

# Modafinil

- A **psychostimulant**.
- Inhibits both NE & DA transporters
- Increases interstitial concentrations of NE, DA, serotonin and glutamate
- Decreases GABA levels
- It is used primarily to improve wakefulness in **narcolepsy**
- It is often associated with mild increases in BP & HR
- **Modafinil** may also be useful in **ADHD**



# Modafinil

- A new amphetamine substitute, with fewer side effects than amphetamine is used in this condition.
- Use: improvement of wakefulness in patients with excessive daytime sleepiness associated with narcolepsy and with *shift work sleep disorder*
- Less abuse potential than amphetamines and methylphenidate
- Schedule IV drug
- Armodafinil: similar to modafinil

# Tyramine

- Found in ↑ conc. in some fermented foods such as **cheese**.
- Metabolized by MAO in GIT & the liver so it is inactive orally.
- If administered parenterally, it has an **indirect sympathomimetic action caused by the release of stored catecholamines**
- In patients treated with **MAO inhibitors** , tyramine may cause **marked increases in blood pressure (Cheese reaction)**
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# Cocaine

A local anesthetic with a sympathomimetic action that results from inhibition of NE reuptake .

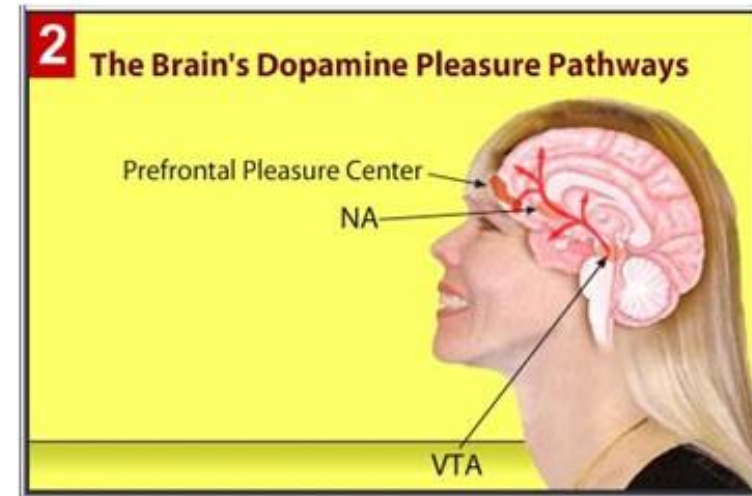
Readily enters CNS causing an **amphetamine-like psychological** effect that is **shorter** lasting and **more intense** than amphetamine.

Its major action in the CNS is to **inhibit dopamine reuptake** into neurons in the **pleasure centers**.

it can be smoked, snorted into the nose, or injected.

It is a **heavily abused drug**

- **Coca Cola** name refers to [kola nuts](#), a source of [caffeine](#), and [coca leaves](#) a source of cocaine.
- In 1903 cocaine was removed from coca cola drink.



# Attention Deficit Hyperactivity Disorder (ADHD)

- Most common psychiatric disorder in children, affecting 4% to 10% of school-age children
- Boys are affected from two to nine times more often than girls.
- Primary symptoms of ADHD are inappropriate ability to maintain attention span or the presence of hyperactivity and impulsivity.
- Drug therapy for both childhood and adult ADHD is the same.

# Narcolepsy

- Incurable neurologic condition in which patients unexpectedly fall asleep in the middle of normal daily activities. These “sleep attacks” are reported to cause car accidents or near-misses in 70% or more of patients.
- Cataplexy: sudden acute skeletal muscle weakness. Associated symptom in at least 70% of narcolepsy cases. It involves sudden acute skeletal muscle weakness.

# Obesity

- According to the National Institutes of Health and the Centers for Disease Control and Prevention, approximately 30% of Americans are obese, and nearly two thirds (64.5%) are overweight.
- More than 72 million obese adults
- Associated health risks

# Migraine

- Common type of recurring headache, usually lasting from 4 to 72 hours
- Typical features: pulsatile quality with pain that worsens with each pulse
- Most commonly unilateral but may occur on both sides of the head
- Associated symptoms: nausea, vomiting, *photophobia* (avoidance of light), and *phonophobia* (avoidance of sounds)
- Aura

# Analeptic-Responsive Respiratory Depression Syndromes

- Neonatal apnea
- Bronchopulmonary dysplasia
- Postanesthetic respiratory depression
- Drugs: analeptic drugs such as theophylline, aminophylline, caffeine, and doxapram



# Drugs for Attention Deficit Hyperactivity Disorder (ADHD) and Narcolepsy

- **Amphetamines:** methylphenidate
- **Nonamphetamine stimulants**
  - Pemoline and Modafinil
  - Atomoxetine: nonstimulant drug that is also used to treat ADHD
  - Lisdexamphetamine prodrug for dextroamphetamine

# Mechanism of Action and Drug Effects

- **Amphetamines**

- Stimulate areas of the brain associated with mental alertness

- **CNS effects**

- Mood elevation or euphoria
- Increased mental alertness and capacity for work
- Decreased fatigue and drowsiness
- Prolonged wakefulness

- **Respiratory effects**

- Relaxation of bronchial smooth muscle
- Increased respiration
- Dilation of

# Adverse Effects

- Wide therapeutic range
- Dose related
- Tend to “speed up” body systems
- Common adverse effects include:
  - palpitations, tachycardia, hypertension, angina and dysrhythmias
  - nervousness, restlessness, anxiety and insomnia
  - nausea, vomiting, diarrhea and dry mouth
  - increased urinary frequency
  - others

# Principal Drugs Used to Treat ADHD and Narcolepsy

- Amphetamines
- Nonamphetamine stimulants
- Atomoxetine: non stimulant drug also used for ADHD

# Amphetamines

- Dextroamphetamine sulfate
- Dextroamphetamine saccharate
- Amphetamine sulfate
- Amphetamine aspartate : one of the most commonly prescribed drugs for ADHD

# Atomoxetine

- Approved for treating ADHD in children older than 6 years of age and in adults
- In September 2005, the FDA issued a warning describing cases of suicidal thinking and behavior in small numbers of adolescent patients receiving this medication.

# Methylphenidate

- First prescription drug indicated for ADHD
- Also used for narcolepsy
- Extended-release dosage forms

# Anorexiant

- Used to treat obesity
- Anorexiant
  - phentermine
  - benzphetamine
  - methamphetamine
  - diethylpropion



# Other Drugs to Treat Obesity

- Orlistat (Xenical): related nonstimulant drug used to treat obesity
  - Mechanism of action: works locally in the small and large intestines, where it inhibits absorption of caloric intake from fatty foods.
- lorcaserin (Belviq)
- Qsymia (phentermine and topiramate)

# Mechanism of Action

- Suppress appetite control centers in the brain
- Increase the body's basal metabolic rate
- Mobilization of adipose tissue stores
- Enhanced cellular glucose uptake
- Reduce dietary fat absorption

# Adverse Effects

- Possible elevated blood pressure and heart palpitations
- Anxiety
- Agitation
- Dizziness
- Headache

# Antimigraine Drugs

- Antimigraine (serotonin agonists; also called triptans)
  - sumatriptan
  - almotriptan
  - eletriptan
  - naratriptan
  - rizatriptan
  - zolmitriptan
  - frovatriptan

# Sumatriptan

- Original prototype drug for this class
- Seven triptans
- Slight pharmacokinetic differences exist between some of these products.
- Effects are comparable overall.

# Natural and hydrogenated ergot alkaloids

- **Ergotamine and ergotoxine** from *ergot fungus*
- They are partial agonists and antagonists at  $\alpha$ , serotonergic and dopaminergic receptors
- They produce long-lasting vasoconstriction more than  $\alpha$  blockade
- Their principal use is in migraine
- Hydrogenation reduces vasoconstrictors and increases  $\alpha$  blocking activity
- Hydrogenated ergot alkaloids are used for symptoms of mental decline in elderly
- Dihydroergotamine has been used as a cognition enhancer
- The amine alkaloid **ergometrine** has no  $\alpha$  blocking activity

# Antimigraine Drugs-2

- **Ergot alkaloids**

- Were the mainstay of treatment of migraine headaches but have been replaced by the triptans for first-line therapy
- Their lack of selectivity leads to more adverse effects, making them second line compared to triptans
- they have been shown to prevent recurrence better than triptans
- Dihydroergotamine mesylate: injectable form and as a nasal spray
- Ergotamine tartrate with caffeine : tablet form

# Mechanism of Action and Drug Effects

- Triptans
  - Stimulate 5-HT receptors in cerebral arteries, causing vasoconstriction and reducing headache symptoms
  - Reduce the production of inflammatory neuropeptides
- Ergot alkaloids
  - Narrow or constrict blood vessels in the brain



# Adverse Effects

- Triptans
  - Vasoconstriction
  - Irritation at injection site
  - Tingling, flushing
- Ergot alkaloids
  - Nausea and vomiting
  - Cold or clammy hands and feet
  - Muscle pain
  - Dizziness
  - Others

# Analeptics

- Used less frequently
- Still used for neonatal apnea
- Examples
  - Doxapram
  - Methylxanthines, such as aminophylline, theophylline, and caffeine

# Analeptics-2

- Doxapram
  - Treatment of respiratory depression associated with anesthetic drugs and drugs of abuse, COPD-induced hypercapnia
  - Monitor deep tendon reflexes, in addition to vital signs and heart rhythm, to prevent overdose of this drug.

# Analeptics-3

- Caffeine
  - Found in:
    - Over-the-counter drugs
    - Combination prescription drugs
    - Foods and beverages
  - Use with caution in patients with a history of:
    - Peptic ulcer
    - Recent myocardial infarction
    - Dysrhythmias
  - Intravenous: caffeine citrate and caffeine sodium benzoate

# Mechanism of Action

- Stimulate areas of CNS that control respiration
- Methylxanthines
  - Inhibit phosphodiesterase, leading to buildup of cyclic adenosine monophosphate (cAMP)
- Caffeine
  - Antagonizes adenosine receptors

# Adverse Effects

- Vagal
  - Stimulation of gastric secretions, diarrhea, and reflex tachycardia
- Vasomotor
  - Flushing, sweating
- Respiratory
  - Elevated respiratory rate
- Musculoskeletal
  - Muscular tension and tremors

# Doxapram

- Used in conjunction with supportive measures in cases of respiratory depression that involve anesthetics, drugs of abuse and COPD-associated hypercapnia.
- To prevent overdose, monitor deep tendon reflexes, vital signs, and heart rhythm.

# CNS Applications

**Treatment of narcolepsy.**

**Modafinil**

**Attention-deficit hyperactivity disorder (ADHD)**

A behavioral syndrome of short attention span, hyperkinetic physical behavior, and learning problems.



THANK YOU