

Central Nervous System Stimulants and Related Drugs

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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

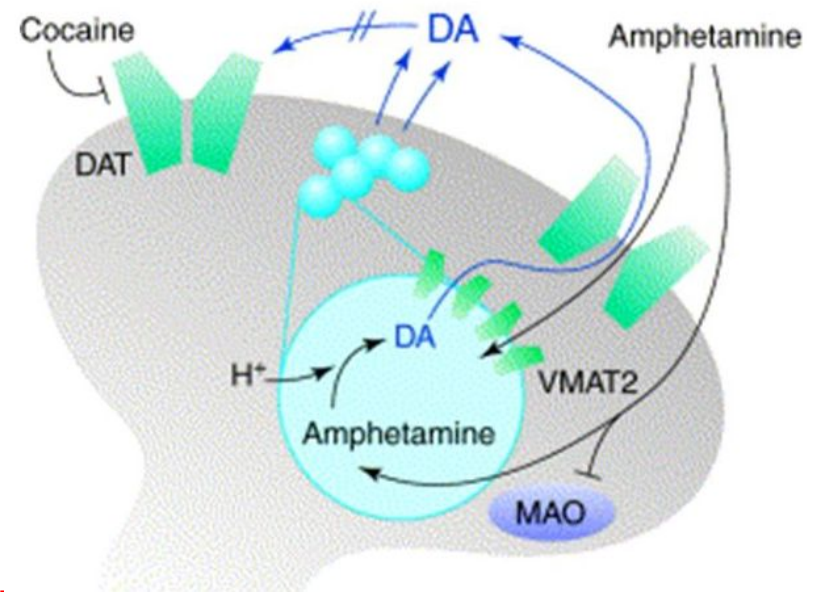
Indirect-acting sympathomimetics can have one of two different mechanisms:

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

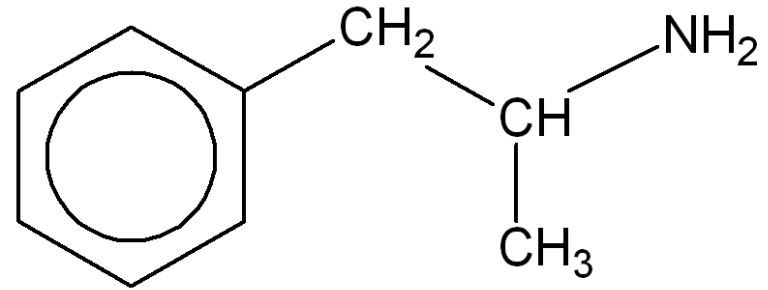
Such drugs have been

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.**

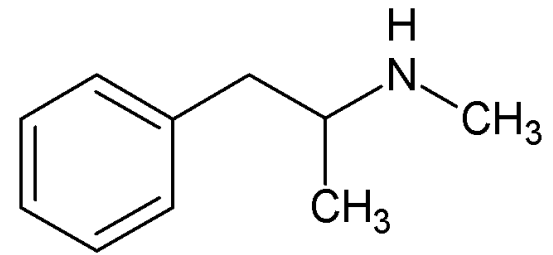
Its **D-isomer** is more potent than the **L-isomer**.

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 .

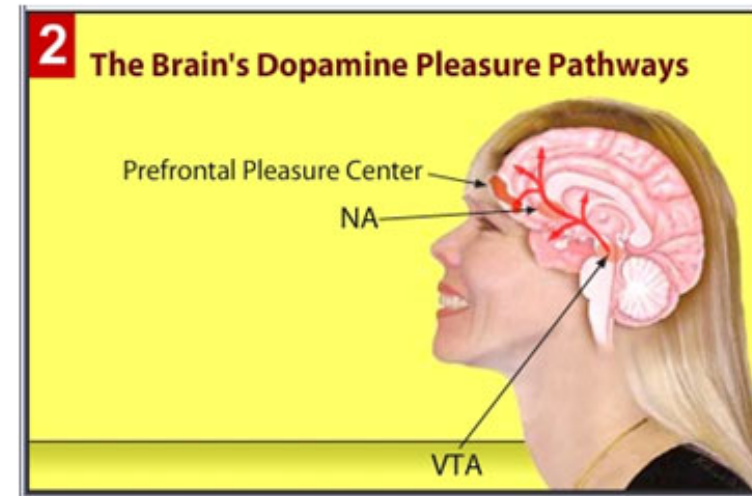
Readily enters CNS causing an **amphetamine-like psychological** effect that is **shorter** lasting and **more intense** than amphetamine.

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 α , serotonergic and dopaminergic receptors
- They produce long-lasting vasoconstriction more than α blockade
- Their principal use is in migraine
- Hydrogenation reduces vasoconstrictors and increases α 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 α 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.