CNS Stimulants

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Introduction

- Psychomotor stimulants
  - Cause excitement and euphoria
  - Decrease feeling of fatigue
  - Increase motor activity
- Hallucinogens (psychomimetic drugs)
  - Produce changes in thought patterns and mood

Introduction

- **Psychomotor stimulants**
  - Amphetamine
  - Dextroamephetamine
  - Methylphenidate
  - Caffeine
  - Theophylline
  - Nicotine
  - Cocaine
  - Varenicline
- **Hallucinogens**
  - Lysergic acid diethylamide (LSD)
  - Tetrahydrocannabinol
  - Phencyclidine
- **Nonstimulant drugs for ADHD**
  - Atomoxetine
  - Clonidine
  - Guanafacine
  - Viloxazine

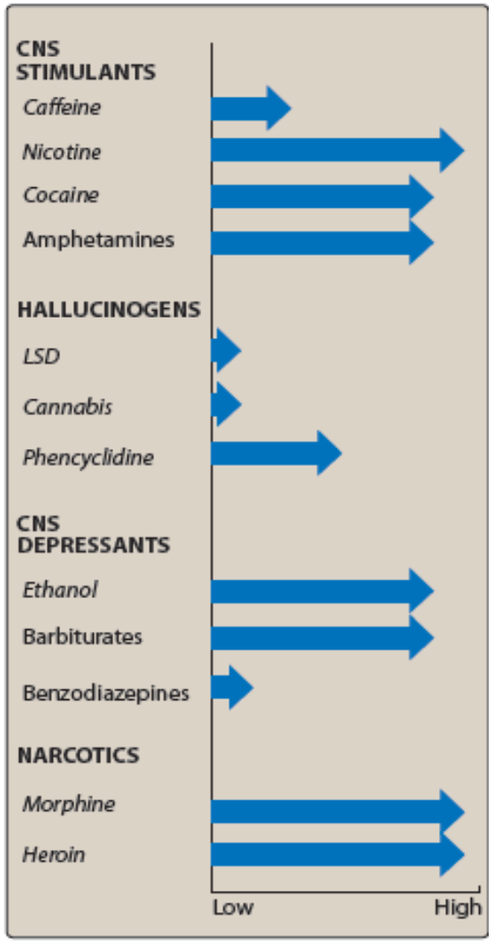


Figure 10.2
Relative potential for physical dependence on commonly abused substances. LSD = lysergic acid diethylamide.

Methylxanthines

- Include **theophylline** (tea); **theobromine** (cocoa); and **caffeine** (coffee, tea, cocoa, chocolates, cola drinks)

- **Mechanism of action**
  - Translocation of extracellular calcium
  - Increase in cAMP and cGMP caused by inhibition of phosphodiesterase
  - Blockade of adenosine receptors

Methylxanthines

- **Actions**
  - **CNS stimulants**
    - Reduces fatigue ad increase mental alertness due to stimulation of the cortex and other areas of the brain
    - At very high doses, can produce anxiety and tremor
    - Tolerance to caffeine can develop and withdrawal consists of feelings of fatigue and sedation
  - At high doses, has positive inotropic and chronotropic effects on the heart, can be harmful to angina patients and can trigger premature ventricular contractions
  - Caffeine has a mild diuretic effect increasing urinary output of Na, K, and Cl
  - Methylxanthines stimulate secretion of hydrochloric acid from gastric mucosa, should be avoided in peptic ulcer

Methylxanthines

- Therapeutic uses
  - All methylxanthines relax the smooth muscles of the bronchioles
  - Theophylline was used for asthma but it is being replaced by β2-agonists and corticosteroids

- Adverse effects
  - Insomnia
  - Anxiety
  - Agitation

Nicotine

- CNS stimulant
- Not used therapeutically (except in smoking cessation therapy)
- Stimulation of sympathetic ganglia increases blood pressure and heart rate
- Particularly harmful in hypertensive patients
- Nicotine induced vasoconstriction can decrease coronary blood flow, adversely affecting a patient with angina
- High doses of nicotine result in central respiratory paralysis and severe hypotension caused by medullary paralysis
- Along with other components of cigarettes like tars and carbon monoxide, nicotine is a risk factor for lung and cardiovascular diseases and cancer

Nicotine

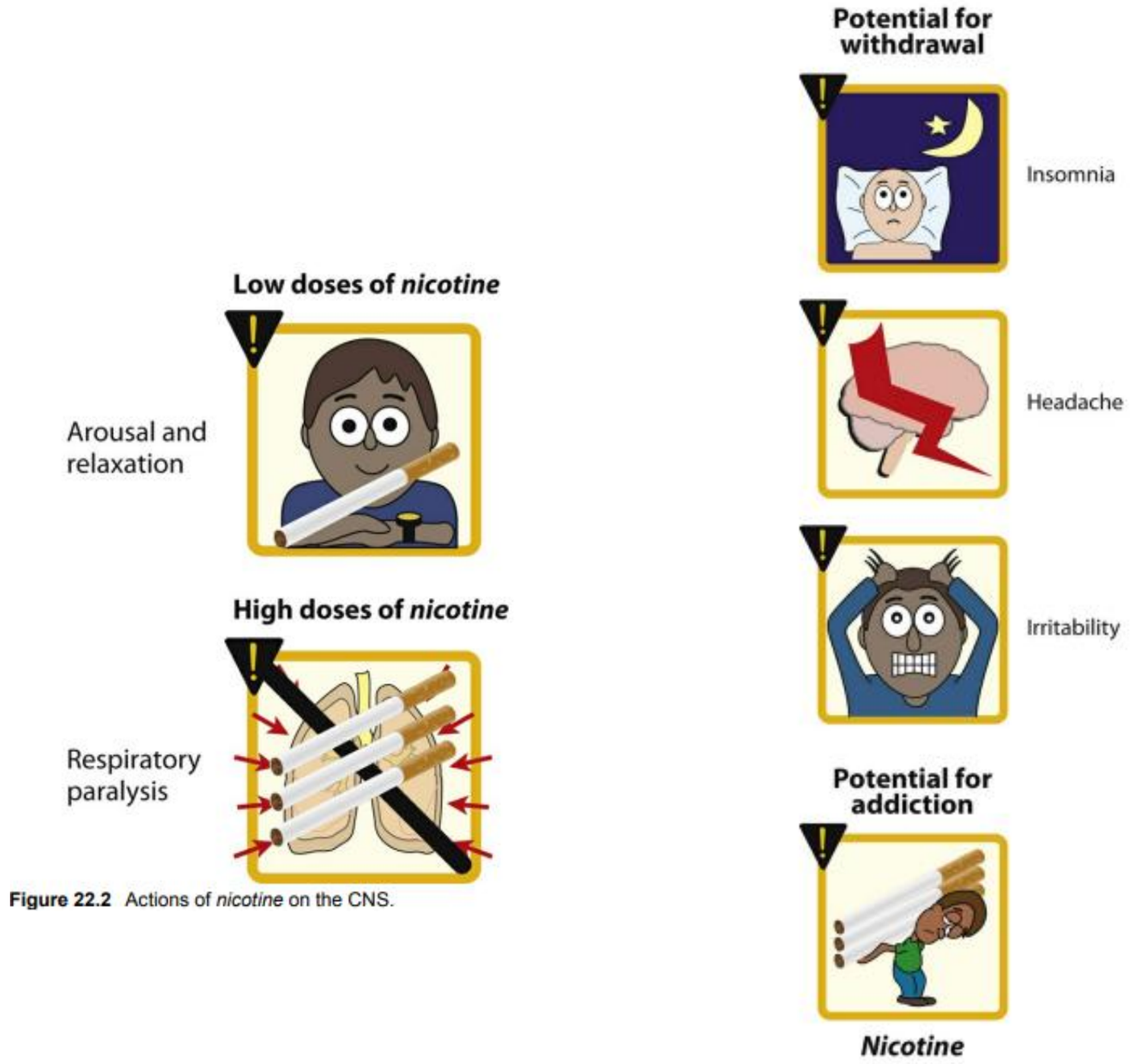
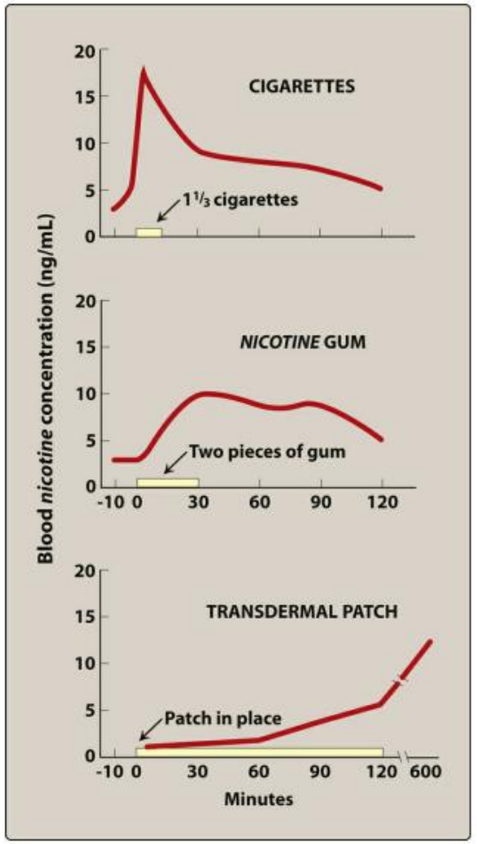


Figure 22.2 Actions of *nicotine* on the CNS.

Nicotine

- Causes dependence that is not easily overcome
- Withdrawal symptoms include irritability, anxiety, restlessness, headaches and insomnia
- Smoking cessation programs that combine pharmacologic and behavioral therapy are the most successful in helping individuals to stop smoking
- Transdermal nicotine patch and nicotine chewing gum can reduce withdrawal symptoms

- Bupropion (Wellbutrin®, Zyban®)
  - An antidepressant, can reduce the craving for cigarettes



Nicotine

- Varenicline (Champix®)
  - Partial agonist at neuronal nicotinic acetylcholine receptors in the CNS
  - Produces less euphoric effects than nicotine
  - Useful as an adjunct in the management of smoking cessation in patients with nicotine withdrawal symptoms
  - Varenicline tends to attenuate the rewarding effects of nicotine if a person relapses and uses tobacco
  - Patients should be monitored for suicidal thoughts and mood changes

Cocaine

- Highly addictive
- Drug of abuse

- Classified as schedule II by the US Drug Enforcement agency

Figure 22.5 *Cocaine* and *amphetamine* have potential for addiction.

Cocaine

- **Mechanism:**
  - Inhibit reuptake of norepinephrine, serotonin and dopamine into the presynaptic terminals
  - Binds to the monoaminergic reuptake transporters
  - Potentiates and prolongs the CNS and peripheral actions of these monoamines
  - Prolongation of dopaminergic effects in the brain's pleasure system (limbic system) produces the intense euphoria initially
  - Chronic intake of cocaine depletes dopamine causing craving for cocaine that temporarily relieves severe depression

Cocaine

- **Actions:**
  - CNS stimulant, produces euphoria, increases mental awareness, can cause hallucinations
  - At high doses, it causes convulsions, followed by respiratory depression
  - Activates sympathetic nervous system causing tachycardia and hypertension, ability of baroreceptor reflexes to buffer the hypertensive effect may be impaired
  - Hyperthermia: Cocaine is unique among illicit drugs in that death can result also from the drug's ability to cause hyperthermia. Even a small dose of intranasal cocaine impairs sweating and cutaneous vasodilation, perception of thermal discomfort is also decreased

Cocaine

- **Therapeutic uses:**
  - Cocaine has a local anesthetic action that represents its only current therapeutic use
  - Cocaine is applied topically as a local anesthetic during eye, ear, nose, and throat surgery
  - The local anesthetic action of cocaine is due to a block of voltage-activated sodium channels

Cocaine

- **Adverse effects**
  - Anxiety
  - Depression
  - Agitation
  - Seizures
  - Fatal arrhythmias

Amphetamines

- Releases intracellular stores of catecholamines (norepinephrine, serotonin, dopamine)
- Inhibits MAO

- **Dextroamphetamine (similar to amphetamine)**
- **Methamphetamine**

- **Actions**
  - CNS stimulant, increase alertness, reduce fatigue, depress appetite
  - Activate the sympathetic nervous system

- Can cause dependence (limit their use)

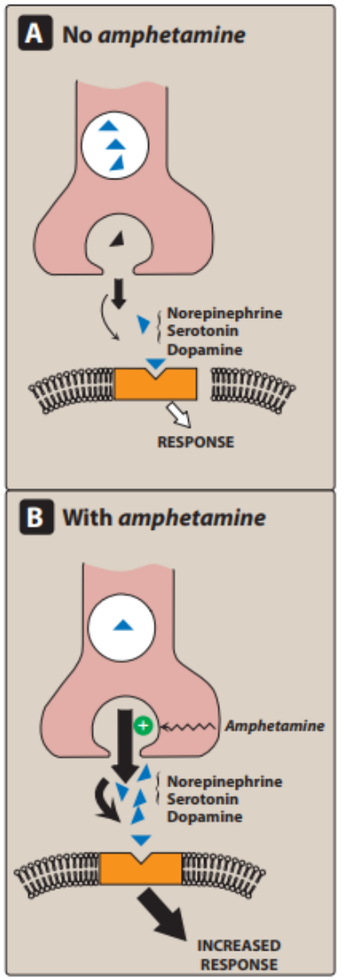


Figure 15.6
Mechanism of action of *amphetamine*.

Amphetamines

- **Therapeutic use:**
- Treatment of hyperactivity in children, attention deficit hyperactivity disorder (ADHD)
- Appetite control
- Narcolepsy (uncontrollable sleepiness during the day)
  - Amphetamine
  - Methylphenidate

Amphetamines

- **Adverse effects**
  - Insomnia
  - Irritability
  - Weakness
  - Palpitations, arrhythmias and hypertension
  - Nausea vomiting, diarrhea

- Contraindicated in hypertension, cardiovascular disease, hyperthyroidism or anyone taking MAO inhibitors

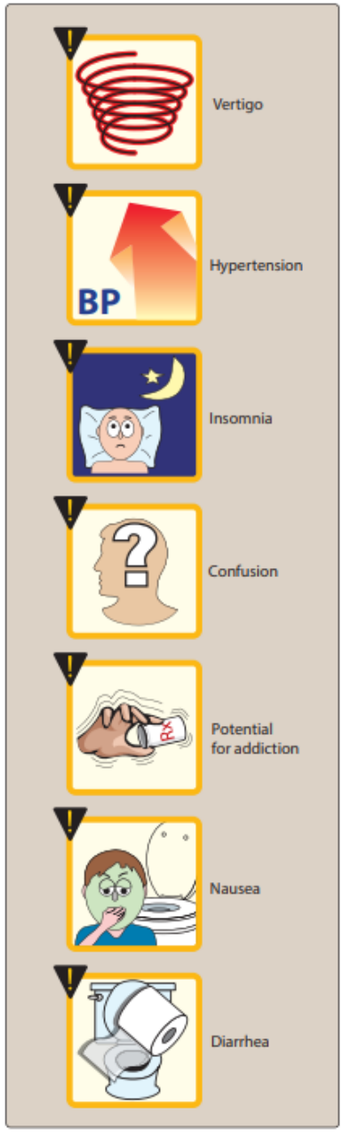


Figure 15.7
Adverse effects of amphetamines and *methylphenidate*.

Methylphenidate

- CNS stimulant

- **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 transport inhibitor and may act by increasing dopamine in the synaptic space.

- Used for ADHD in children
- Can cause dependence

Methylphenidate

- **Adverse reactions**
  - Abdominal pain and nausea
  - Anorexia
  - Insomnia, nervousness, and fever

- Methylphenidate can interfere in the metabolism of warfarin, phenytoin, phenobarbital, primidone, and the tricyclic antidepressants

Hallucinogens

- Psychomimetics, drugs that induce altered perceptual states accompanied by visions of bright, colorful changes in the environment and by a plasticity of constantly changing shapes and color

- These drugs impair normal decision-making because they interfere with rational thought

Hallucinogens

- **Lysergic acid diethylamide (LSD)**
  - Serotonin agonist
  - Activation of the sympathetic nervous system occurs causing pupillary dilation, increased blood pressure, piloerection, and increased body temperature
  - Taken orally, low doses of LSD can induce hallucinations with brilliant colors
  - Haloperidol and other neuroleptics can block the hallucinatory action of LSD and quickly abort the syndrome.

  - **Adverse effects**
    - Hyperreflexia, nausea, and muscular weakness
    - High doses may produce long-lasting psychotic changes in susceptible individuals

Hallucinogens

- **Tetrahydrocannabinol**
  - Found in marijuana
  - Produce euphoria followed by drowsiness and relaxation
  - Cause hallucinations

Hallucinogens

- Effects include
  - Appetite stimulation
  - Xerostomia
  - Visual hallucinations, delusions

- Adverse effects
  - Adversely affects short-term memory and mental activity
  - Deceases muscle strength and impairs highly skilled motor activity
  - Increased heart rate
  - Decreased blood pressure, and reddening of the conjunctiva
  - At high doses, a toxic psychosis develops

Hallucinogens

- **Phencyclidine**
  - Illegal drug
  - Also known as PCP or angel's dust
  - Inhibits the reuptake of dopamine, 5-HT, and norepinephrine
  - Causes dissociative anesthesia (insensitivity to pain without loss of consciousness) and analgesia
  - Produces numbness of extremities, staggered gait, slurred speech, and muscular rigidity
  - At increased dosages, anesthesia, stupor and coma may result
  - Increased sensitivity to external stimuli results, and the CNS actions may persist for a week
  - Tolerance often develops with continued use
  - No therapeutic applications

Table 1.2. DEA Schedule of Controlled Substances

SCHEDULE	DESCRIPTION	EXAMPLES
I	High abuse potential (++++) No accepted medical use	heroin, LSD, MDMA (ecstasy), *marijuana*
II	High abuse potential (++++) Accepted medical use	morphine, oxycodone (OxyContin®), methamphetamine, fentanyl, Adderall®
III	Moderate abuse potential (+++) Accepted medical use	ketamine, testosterone, anabolic steroids
IV	Low abuse potential (++) Accepted medical use	Xanax®, Valium®, Ambien®, tramadol
V	Low abuse potential (+) Accepted medical use	Lyrica®, Lomotil®, many codeine-containing cough syrups

Drugs for Obesity

Obesity

- Obesity: BMI ≥ 30 kg/m2 or greater
- Obesity is due in part to an energy imbalance
- Calorie consumption exceeds calorie expenditure.

- Who is a candidate for pharmacological intervention for obesity
  - BMI > 30
  - BMI > 27 with at least two comorbidities (e.g. hypertension and diabetes

- The majority of drugs approved to treat obesity have short-term indications

Drugs for Obesity

- Anorexiants
  - Diethylpropion
  - Phentermine

- Lipase inhibitor
  - Orlistat

- GLP receptor agonists
  - Liraglutide
  - Semaglutide

- Combination products
  - Phentermine/Topiramate
  - Bupropion/naltrexone

Anorexiants

- Phentermine
- Diethylpropion

- **Mechanism of action:**
  - Phentermine increases the release of norepinephrine and dopamine and inhibits their reuptake
  - Diethylpropion has similar effects on norepinephrine

- Tolerance to the weight loss effect of these agents develops within weeks, and weight loss plateaus
- Discontinuation is usually recommended once plateau is reached

Anorexiants

- Phentermine
- Diethylpropion

- Phentermine and diethylpropion are primarly excreted via **kidneys**
- Diethylpropion undergoes extensive first-pass metabolism, many of the metabolites are active

Anorexiants

- Adverse effects:
  - All anorexiants are classified as controlled substances due to the potential for dependence or abuse.
  - Dry mouth, headache, insomnia, and constipation
  - Heart rate and blood pressure may be increased with these agents.

- Should be avoided in uncontrolled hypertension, cardiovascular disease, arrhythmias, heart failure, or stroke

- Concomitant use of anorexiants with MAOIs or other sympathomimetics should be avoided

Orlistat

- Lipase inhibitors
- Use is limited by gastrointestinal adverse effects.

- Mechanism of action:
  - Orlistat inhibits gastric and pancreatic lipases, thus decreasing the breakdown of dietary fat into smaller molecules that can be absorbed.
  - Administration of orlistat decreases fat absorption by about 30%
  - The loss of calories from decreased absorption of fat is the main cause of weight loss.

- Administered orally with each meal that contains fat
- It has minimal systemic absorption and is mainly excreted in the feces
- No dosage adjustments are required in patients with renal or hepatic dysfunction.

Orlistat

- Adverse effects:
- Gastrointestinal symptoms, such as oily spotting, flatulence with discharge, fecal urgency, and increased defecation
  - These effects may be minimized through a low-fat diet and the use of cholestyramine
- Pancreatitis and liver injury (Rare)

- Contraindicated in pregnancy and in patients with chronic malabsorption syndrome or cholestasis.
- Interferes with the absorption of fat-soluble vitamins and β-carotene

GLP 1 agonists

- Liraglutide
- Semaglutide

- Injectable glucagon-like peptide-1 (GLP-1) receptor agonists that are indicated for chronic weight management.
- GLP-1 is important in regulation of appetite and food intake, and administration of these agents reduces hunger, thereby leading to decreased caloric intake and weight loss.

- Liraglutide is dosed daily and semaglutide has a once- weekly dosing schedule.
- Also indicated for the treatment of type 2 diabetes

Combination products

- The combination of **phentermine and topiramate** has been approved for long-term use in the treatment of obesity
- Because of the sedating effects of topiramate, the stimulant phentermine was added

Phentermine and Topiramate

- The dose is escalated every 2 weeks
- If a patient does not achieve a 5% weight loss after 12 weeks on the highest dose, it should be discontinued
- Should not be stopped abruptly as seizures may be precipitated.
- Topiramate has been associated with birth defects including cleft palate

- Adverse effects
  - Paresthesias, suicidal ideation, and cognitive dysfunction
  - Increased heart rate

- Topiramate may reduce the efficacy of oral contraceptives