Al-Mustaqbal University
College of Pharmacy
5th stage
Clinical Toxicology
Lecture: 4

Hypoglycemic drugs & CNS Toxicity

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Oral Hypoglycemic Drugs Toxicity

Sulfonylurea(Secretagogues)

compounds are among the most widely prescribed medications in the world to treat patients with type II diabetes.

First-generation sulfonylureas (chlorpropamide and tolbutamide) have longer half-lives.

Second-generation sulfonylureas were introduced in 1984 (as glipizide and glimepiride) are more potent and have shorter half-lives than the first-generation sulfonylureas.

Oral Hypoglycemic Drugs Toxicity

Other agents besides sulfonylureas are used to treat type II diabetes, including

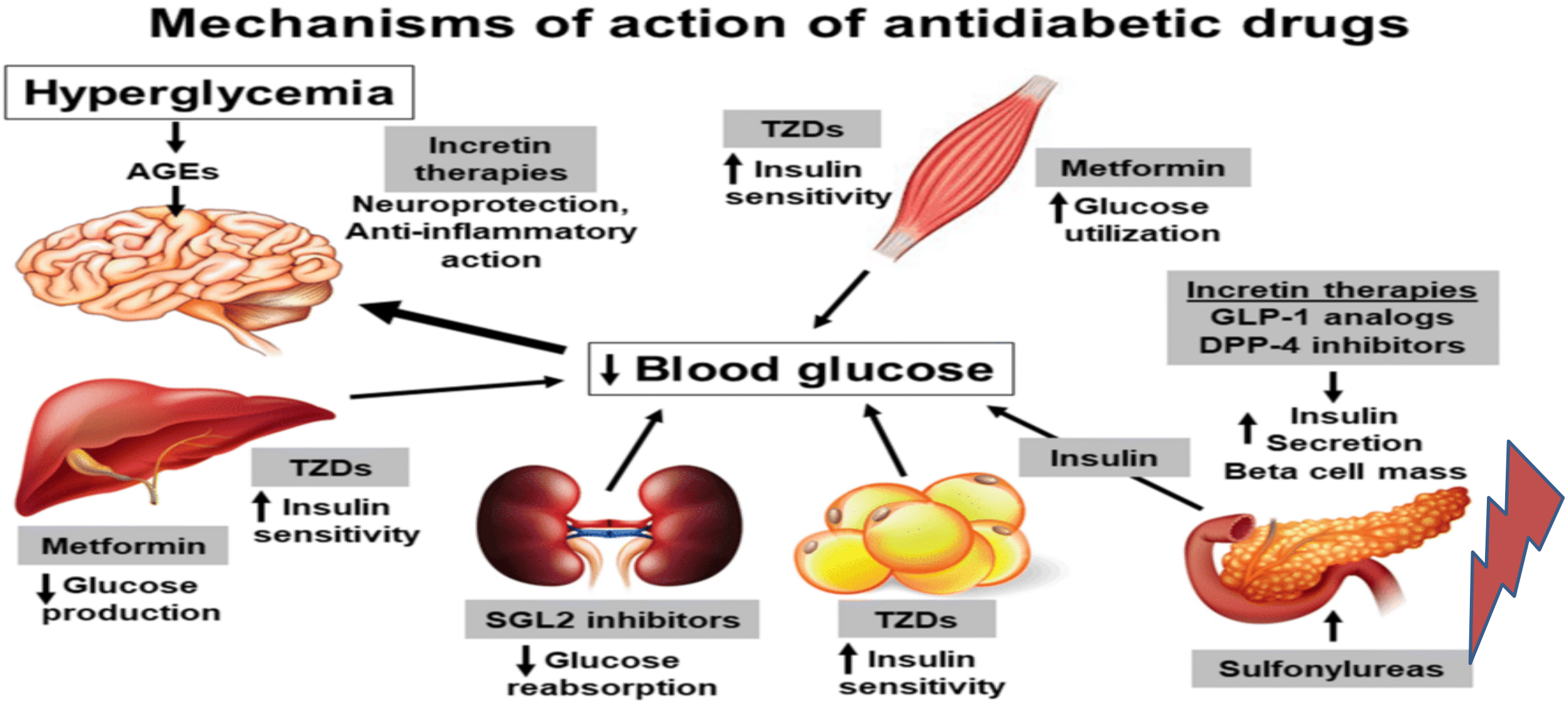
- ✓ **Biguanides** (Metformin)
- ✓ **Alpha-glucosidase inhibitors**

(Acarbose and Miglitol)

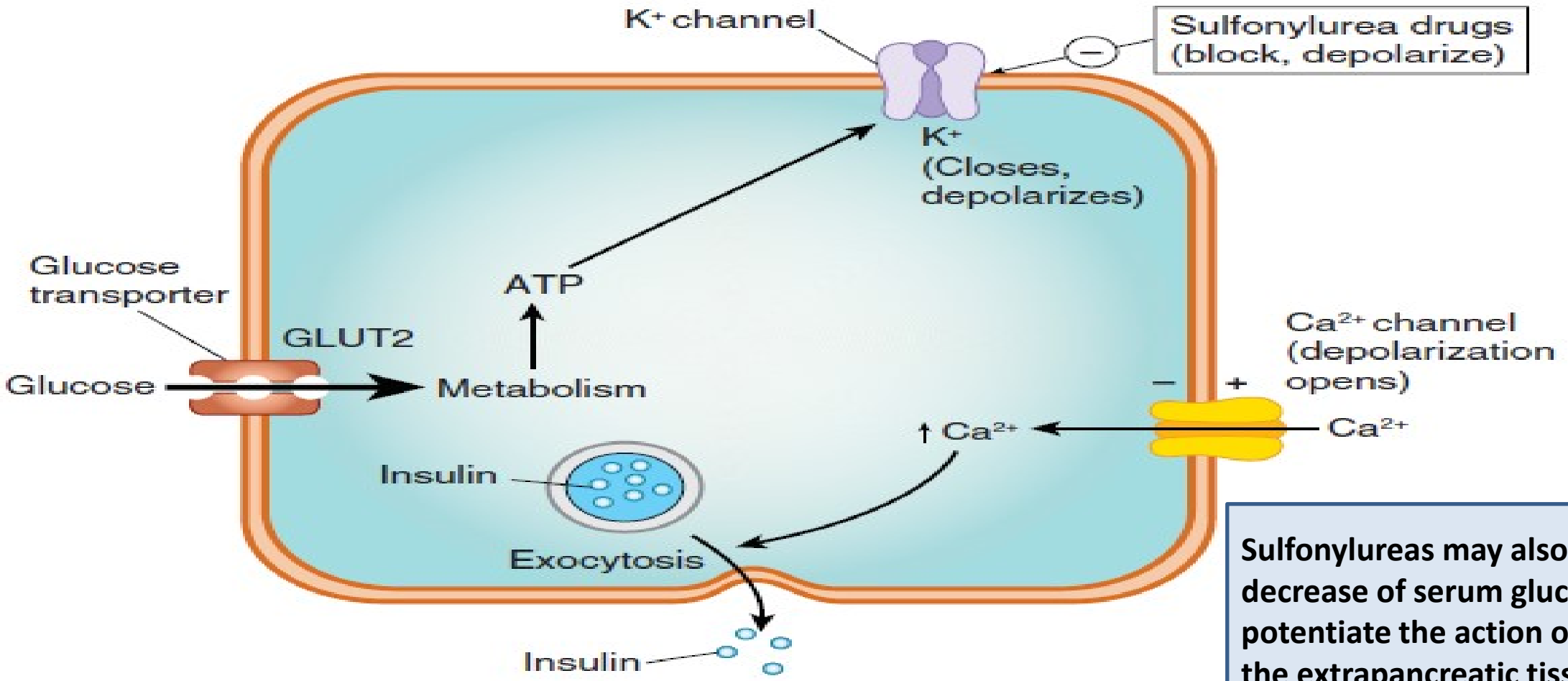
- ✓ **Thiazolidinediones** (Pioglitazone and Rosiglitazone)

These drugs even in excessive dosage, these agents do not induce hypoglycemia.

Oral Hypoglycemic Drugs Toxicity



Sulfonylurea mechanism of action



Sulfonylureas may also cause the decrease of serum glucagon and potentiate the action of insulin at the extrapancreatic tissues.

Toxidrome or clinical manifestations

- **Clinical manifestations are Patient presentation depends on the severity and duration of hypoglycemia.**

Altered mental status, Generalized weakness, Diaphoresis (sever sweating)

Tachycardia, Difficulty speaking
Tachypnea, Transient neurologic deficit

Pallor, Seizure, Cyanosis, Coma, Hypothermia

Symptoms of

Hypoglycemia	Hyperglycemia
* Sweating	* Excessive thirst
* Fatigue	* Increased appetite
* Dizziness	* Frequent urination
* Confusion	* Weakness or feeling tired
* Feeling weak	* Loss of weight
* Blurred vision	* Vision blurring
* Being pale	
* Increased appetite	
* Convulsions	
* Loss of consciousness	
* A higher heart rate than usual	
* And in extreme cases coma	

Investigation of toxicity

Laboratory Studies:

Tests for oral hypoglycemic agent exposure may include the following:

- ✓ **Finger stick and/or serum glucose test to detect hypoglycemia**

(If hypoglycemia does not occur within the first 2-4 hours after suspected ingestion, then other laboratory tests are unnecessary.)

- ✓ **Baseline CBC count (in symptomatic patients)**
- ✓ **Baseline electrolytes, especially potassium (in symptomatic patients)**

Imaging Studies:

- ✓ **Head CT scanning is recommended in patients with an altered mental status, a focal neurologic defect, or new-onset seizures.**

Levels of hypoglycemia

level 1 70 mg\dl

level 2 54mg\dl

level 3 54 mg\dl

Manangement

- ✓ **The main goal in oral hypoglycemic agent exposure is supportive care, which includes ABC,,**
- ✓ **Ipecac is not recommended because of the possibility of aspiration in patients with a depressed mental status.**
- ✓ **Administer activated charcoal as soon as possible, preferably within 1 hour of ingestion.**
- ✓ **Hemodialysis is not indicated because most sulfonylureas have high protein binding.**

Management

- ✓ **Intravenous administration of dextrose rapidly resolves the effects of hypoglycemia. Its onset is quicker than oral administration of sugar, and it is safer in patients with a depressed mental status who should not take anything by mouth for fear of aspiration.**
- ✓ **Glucagon is helpful and can be administered intravenously, intramuscularly, or subcutaneously.**

Glucagon is particularly useful in the intramuscular mode when intravenous access cannot be obtained immediately.

Octreotide Im ,Sc can be give

- ✓ **If a patient is lethargic, then oxygen and continuous cardiac monitoring are indicated. Until the patient totally regains mental status, do not administer anything by mouth**

Treatment: IV 50 %Dextrose , glucagon IM, O2 + cardiac monitoring

CNS Stimulant Toxicity

Stimulants are substances that **induce** a number of characteristic symptoms.

CNS effects include **alertness** with increased **vigilance**, a sense of **well-being**, and **euphoria**.

Many users experience **insomnia** and **anorexia**, and some may develop **psychotic** symptoms

CNS Stimulant Toxicity

- Stimulants have peripheral cardiovascular activity, including increased blood pressure and heart rate.

- They include a broad category of substances, including those prescribed for medical conditions; those manufactured for illegal substance abuse; and those found in over-the-counter (OTC) decongestants, herbal extracts, caffeinated beverages, and cigarettes

CNS Stimulant Toxicity -Amphetamines

- **Amphetamines are a class of compounds progressively abused in wide regions of the world.**
- **The phenylethylamine structure of amphetamines is similar to catecholamine, dopamine, and serotonin agonists (biogenic amines) which may explain their actions.**

- **The routes of amphetamine administration may be oral (ingestion), inhalation (smoke), or injection (intravenous).**
- **Oral use is associated with an approximate 1-hour delay time before onset of symptoms.**

CNS Stimulant Toxicity -Amphetamines

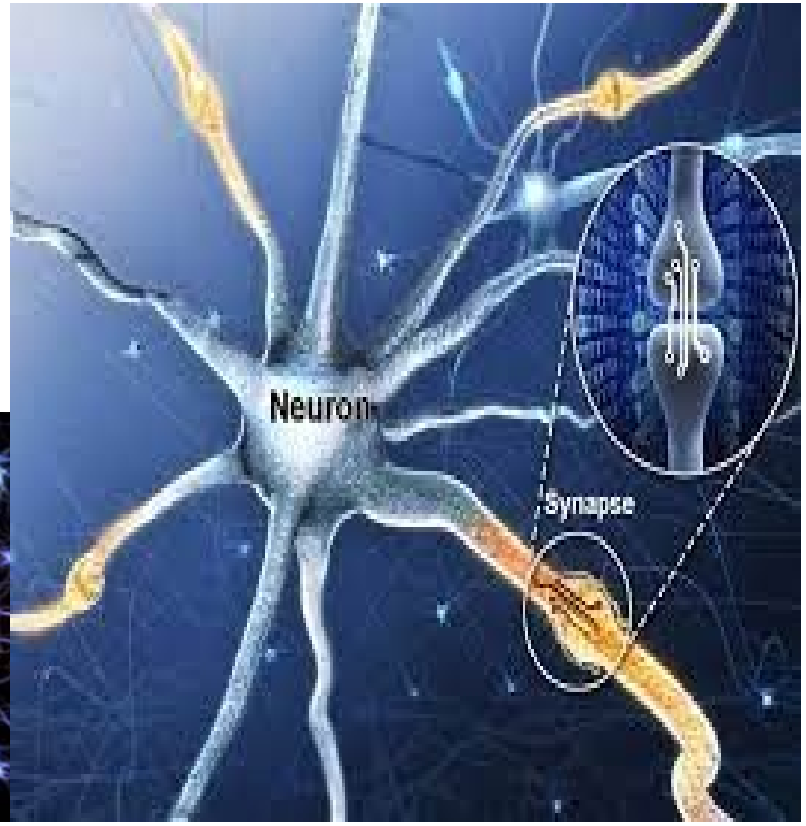
Amphetamines are a group of structurally related compounds that produce

Central Nervous System (CNS)

And

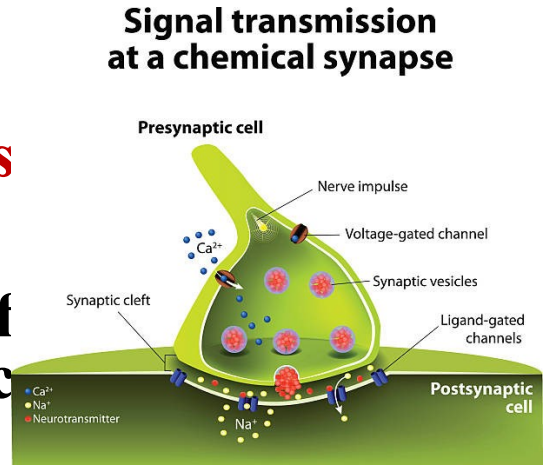
Peripheral Nervous System (PNS)

stimulation.



Amphetamines Pathophysiology:

Central nervous system effects



- Amphetamine compounds cause a general **efflux** of **biogenic amines** from neuronal synaptic terminals (**indirect** sympathomimetics).
- They **inhibit** specific transporters responsible for **reuptake** of biogenic amines from the synaptic nerve ending and presynaptic vesicles.
- Amphetamines also **inhibit monoamine oxidase**,which degrade biogenic amine neurotransmitters **intracellularly**.
- The **net effect** is

NTs
Neurotransmitters
in
synapse

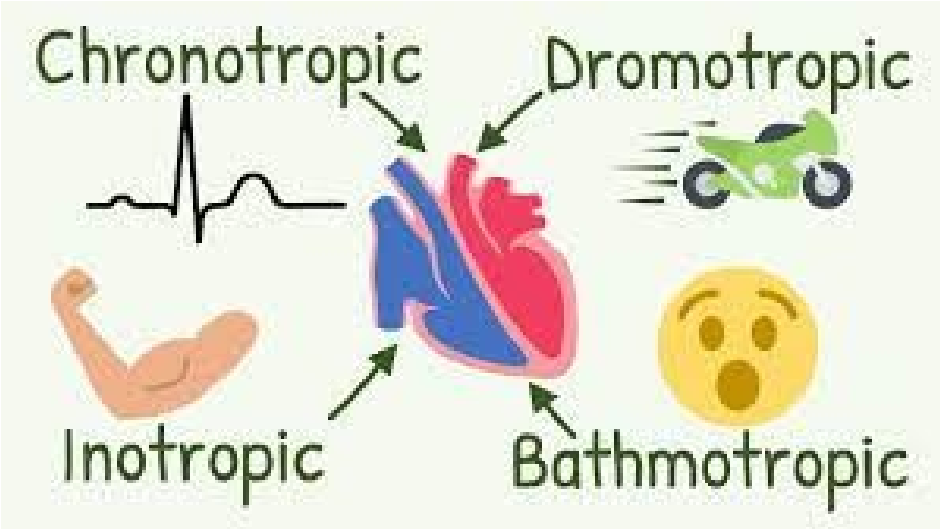
- Elevated **catecholamine** levels usually lead to a state of **increased arousal** and **decreased fatigue**.
- Increased **dopamine** levels at synapses in the **CNS** may be responsible for **movement disorders** , **schizophrenia**, and **euphoria**.

Amphetamines Pathophysiology

Peripheral nervous system effects

Catecholaminergic (sympathomimetic) effects of amphetamines include inotropic and chronotropic effects on the heart, which can lead to tachycardia and other dysrhythmias.

The vasoconstrictive properties of the drugs can lead to hypertension and/or coronary



Clinical Presentation -Amphetamines

- **Physical examination findings may demonstrate the strong central nervous system and peripheral nervous system stimulation produced by amphetamine compounds.**
- **Modification of the basic amphetamine molecule produces compounds with variable effects on target organs.**
- **Methamphetamine produces prominent central nervous system effects with minimal cardiovascular stimulation.**
- **Individuals who chronically use amphetamines intravenously are at risk of infection and vascular injury.**

Clinical Presentation -Amphetamines

Cardiovascular Clinical Presentation

- ✓ Alpha- and beta-adrenergic stimulation can lead to systolic and diastolic blood pressure increases.
- ✓ Heart rate may be unchanged or slow in response to hypertension.
- ✓ Increasing doses produce tachycardia and other dysrhythmias
- ✓ Hypertensive crisis or vasospasm may lead to stroke.

Respiratory Clinical Presentation

- ✓ Persons who smoke amphetamines can develop respiratory distress secondary to acute lung injury.

General Clinical Presentation- Amphetamines

- ✓ **Weight loss**
- ✓ **Hyperactivity, confusion, and agitation (may combine to produce severe hyperthermia, which can be worse in physically restrained individuals)**
- ✓ **Diaphoresis**
- ✓ **Mydriasis**
- ✓ **Anorexia**

Clinical Presentation -Amphetamines

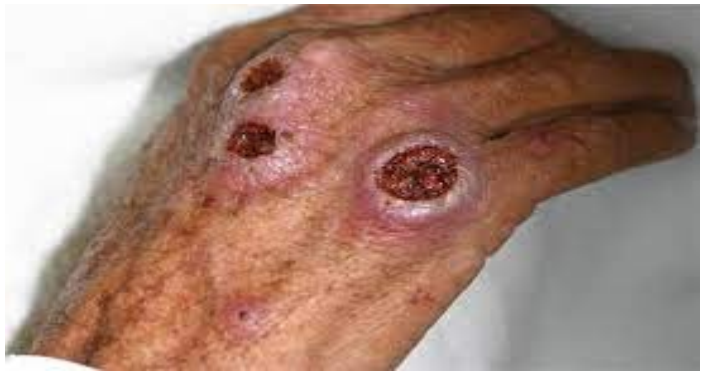
CNS Clinical Presentation

- ✓ Increased alertness
- ✓ Euphoria
- ✓ Confusion or agitation
- ✓ Stroke caused by acute amphetamine toxicity

Clinical Presentation- Amphetamines

Cutaneous Clinical Presentation

- ✓ Skin flushing
- ✓ Infected deep ulcerations (ecthyma)
- ✓ Skin track marks, cellulitis, abscesses, phlebitis, or vasculitis with intravenous use

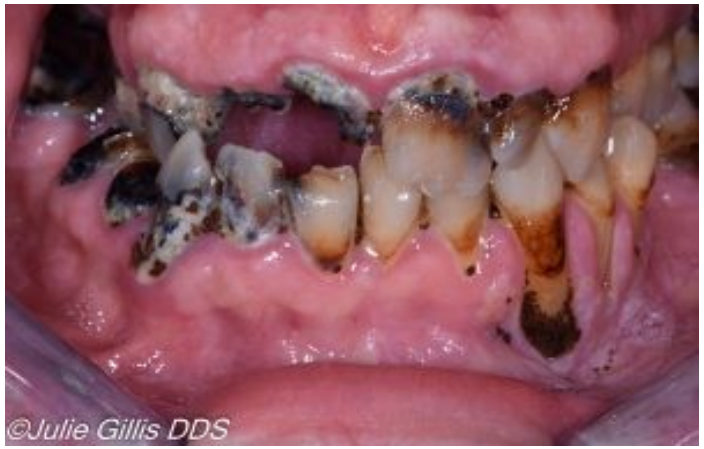


Gastrointestinal Clinical Presentation

- ✓ Nausea or vomiting

Dental Clinical Presentation

- ✓ "Meth mouth," a condition of eroded teeth



Management - Amphetamines Toxicity

- ✓ Patients with amphetamine intoxication who present with no life-threatening signs or symptoms may be treated with sedation and observation.
- ✓ In patients with acute oral ingestion, GI decontamination is performed by the administration of activated charcoal.
- ✓ Gastric lavage often is not necessary but may be performed when the patient presents with immediately life-threatening intoxication shortly after ingestion.
- ✓ Whole-bowel irrigation may be indicated in suspected cases of body stuffing or body packing (large quantities of drugs in wrapping for international transport or drug hiding, respectively).
- ✓ Foley catheter placement may be useful to monitor urine output, particularly in situations in which diuretics are administered to manage pulmonary edema. Patients often have decreased urination due to the effects on bladder sphincter muscles to prevent passing urine.

Management - Amphetamines Toxicity

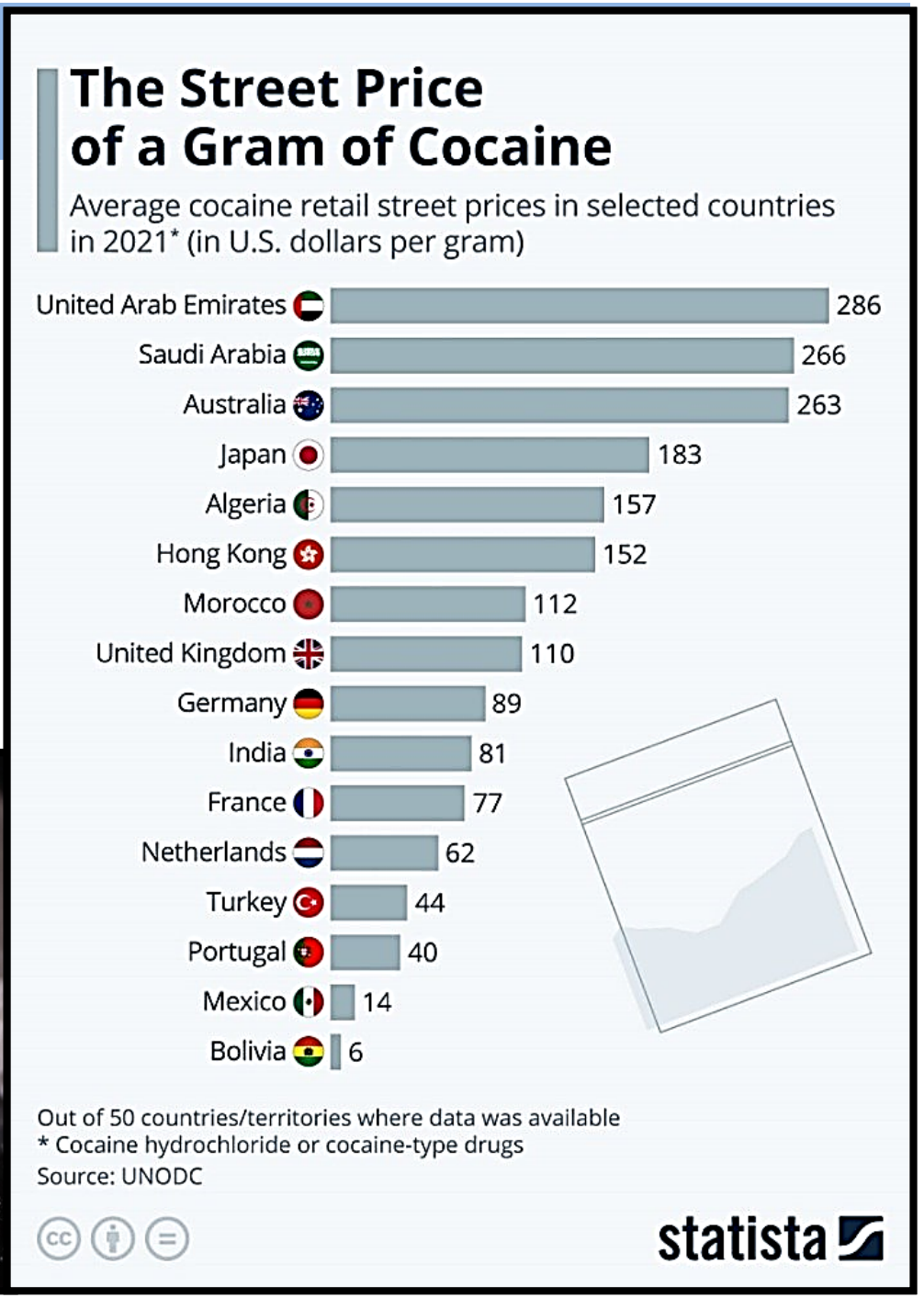
Amphetamine Toxicity Treatment

- ✓ **Agitation or persisting seizures in patients with amphetamine toxicity requires generous titration of benzodiazepines and a calm soothing environment.**
- ✓ **Significant cardiac dysrhythmias may require antidysrhythmic.**
- ✓ **Cardiogenic pulmonary edema can be managed with nitroglycerin and diuretics**

In 2021, approximately 32,537 people died from an overdose involving psychostimulants other than cocaine (primarily methamphetamine).
Source: Centers for Disease Control and Prevention

CNS stimulant - Cocaine

- **Cocaine is a powerfully addictive stimulant drug made from the leaves of the coca plant native to South America.**
- **Although it can be use for valid medical purposes, such as local anesthesia for some surgeries, recreational cocaine use is illegal.**
- **Cocaine looks like a fine, white, crystal powder.**



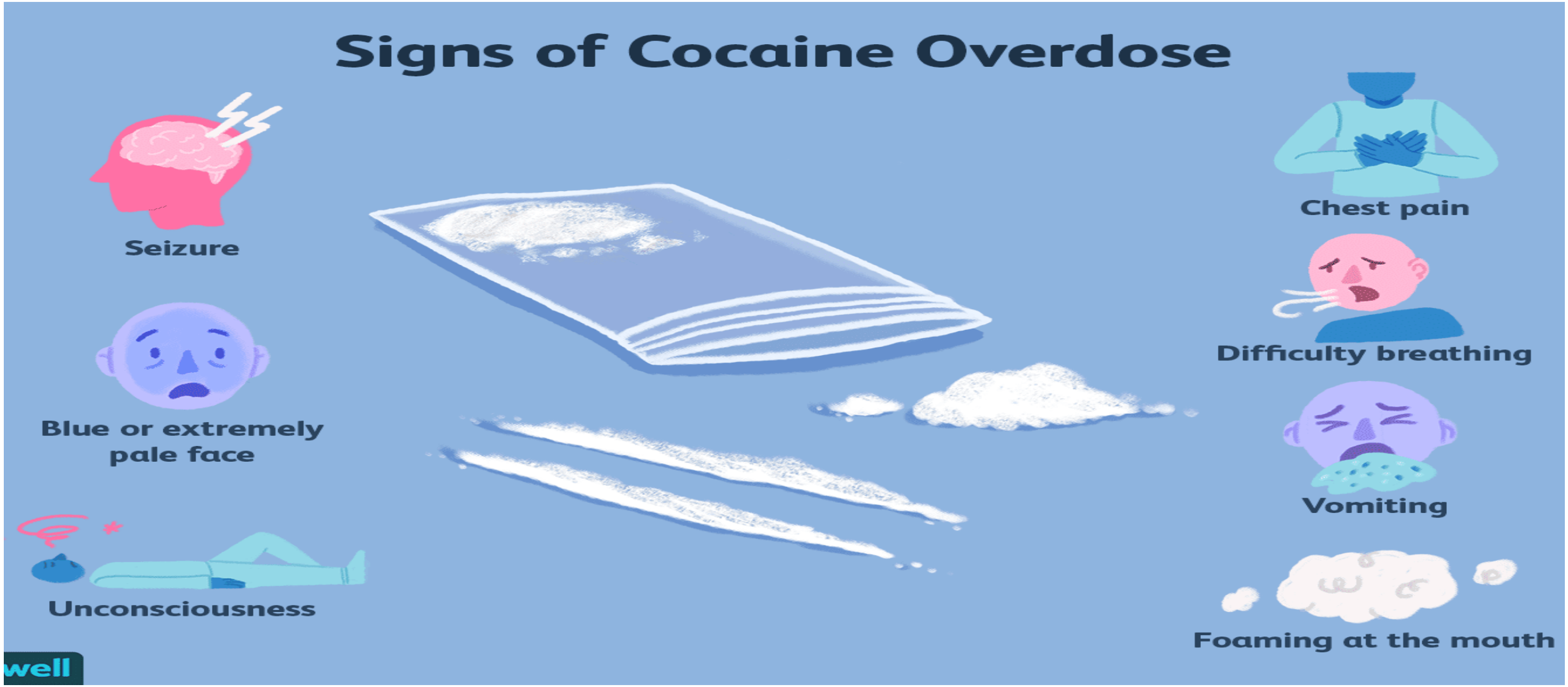
CNS stimulant - Cocaine

Signs and Symptoms:

There are 3 phases of acute cocaine toxicity.

In fatal cases, the onset and progression are accelerated, with convulsions and death frequently occurring in 2-3 minutes, though sometimes in 30 minutes.

CNS stimulant - Cocaine



CNS stimulant - Cocaine

Pathophysiology

Tachydysrhythmias cause most acute cocaine-related deaths.

Other causes of sudden death include stroke, hyperthermia, and the consequences of agitated delirium.

Multisystem effects of cocaine pay particular attention to the assessment of vital signs and to a detailed examination of the cardiac, pulmonary, and neurologic systems.

Trauma is associated with use of cocaine can cause agitation, paranoia, distractibility, distorted perception, and depression. All of these may increase the likelihood of violence, suicide, or accidental injury.

CNS stimulant - Cocaine

Management:

- ✓ The general objectives of pharmacotherapeutic intervention in cocaine toxicity are to reduce the CNS and cardiovascular effects of the drug by using benzodiazepines initially.
- ✓ Then to control clinically significant tachycardia and hypertension while simultaneously attempting to limit deleterious drug interactions.
- ✓ Hyperthermia may be treated with convection cooling, which involves spraying the patient's body with water.
- ✓ Rapid fluid resuscitation promotes urine output.

Toxic Friends

Signs of Toxic Friendship