



Round : Anesthesia - Lecture 6.....

Group no : B8.....

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IV Anesthetic Agents

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Goals of General Anesthesia

- **Hypnosis**
- **Amnesia and loss of awareness**
- **Analgesia**
- **Relaxation of skeletal muscles**
- **Suppression of undesired reflexes**

Triad of anesthesia:

1. Analgesia. 2. Hypnosis. 3. Muscle relaxation

Classification of general anesthetic drugs

IV Anesthetics
(Mainly for Induction)
Rapid induction of anesthesia

Inhalation Anesthetics
(Mainly for Maintenance)
provide minute to minute control over depth of anesthesia

★ All these drugs are used to induce anesthesia, so they have high lipid solubility + can cross the BBB

★ And they have rapid onset of action, but also diffuse quickly to other compartments and thus have a short duration of action

1-Barbiturate

2-Propofol

3-Benzodiazepine

4-Ketamine

5-Etomidate

6) Opioid analgesics. BUT at high dose

★ It is the only drug that has an antidote (flumazenil)

★ Ketamine is the only drug that results in cerebral vasodilation which elevates ICP.

★ And it is the only drug that works on NMDA receptors (inhibition)
★ Has an analgesic effect.

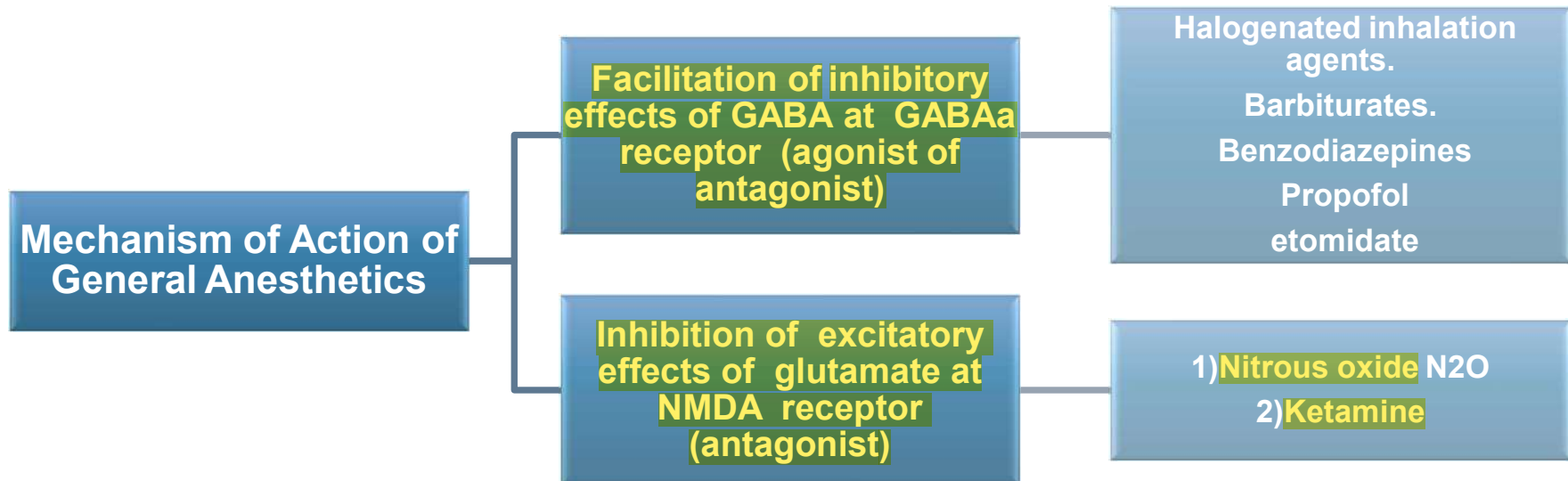
★ All these drugs result in cerebral vasoconstriction which decreases ICP.
★ All of them work on GABA receptors (activating them)

Mode of administration

- Drugs given to induce general anesthesia can be either as **vapors**, or as **injections**
- It is possible to deliver anesthesia solely by inhalation or injection, but **most commonly** the two forms are combined, with an injection given to induce anesthesia and a gases to maintain it

Mechanism of action of general anesthetics

General anesthetics **inhibit neuronal activity** in many brain regions, specially the **midbrain reticular activating system & thalamus**



1. Ideal Intravenous anesthetic

- Water-soluble, no pain on injection
- provides analgesia even at subanaesthetic concentration
- Rapid onset, rapid recovery, little accumulation.
- little depression on respiratory-cardiovascular system.
- No nausea and vomiting,
- no interact with muscle relaxant,
- no release of histamine
- No hypersensitivity reaction
- No adrenocortical suppression

NO SINGLE DRUG HAS ALL THESE CHARACTERISTICS!

The physical characteristics of IV drugs:

- There are 5 drugs in this lecture :

- 1) Propofol
- 2) Etomidate
- 3) Ketamine
- 4) Barbiturate (Thiopental)
- 5) Benzodiazepines. (Midazolam)

GENERAL ANESTHETICS: INTRAVENOUS

Barbiturates
Benzodiazepines
Dexmedetomidine PRECEDEX
Etomidate AMIDATE
Ketamine KETALAR
Opioids
Propofol DIPRIVAN

- They should act on CNS so they should be lipid soluble to cross the BBB
- Highly lipid soluble so rapid onset (30 second - 1 minute)
- Short duration of action → because of Rapid redistributes from brain to fat & skeletal muscle.

→ In other words, they are quickly redistributed from central to peripheral compartments down their concentration gradient.

The physical characteristics of IV drugs:

❖ Metabolism:

hepatically metabolized
renally excreted

❖ Benefits of metabolism:

- 1) They are **lipophilic** so they can't be excreted by the kidney at this form so they will be **converted from lipophilic to hydrophilic to be excreted in the urine**

→ Renal elimination

- 2) **deactivation of the drugs** (because if they are not metabolized, it will be accumulated in the peripheral compartment and they will act on it again)

The physical characteristics of IV drugs:

- All the drugs in this lecture decrease ICP except the Ketamine increase ICP because it causes cerebral vasodilation while the others causes cerebral vasoconstriction
- all the drugs do not have analgesic effects except the ketamine
- all the drugs do not have antidote except benzodiazepine (Flumazenil) and opioids (Naloxone)

★ Ketamine is the only vasodilator and analgesic drug

1) Barbiturate:

- Mechanisms of Action :
- **depress the reticular activating system** in the brainstem, which controls multiple vital functions, including **consciousness**, affect the function of nerve **synapses** than axons.
- Barbiturates **potentiate the action of GABA** in increasing the duration of openings of a **chloride** specific ion **channel**.

1) Barbiturate:

Does not have any analgesic effect.

Barbiturates are derived from **barbituric acid**

The sodium salts of the barbiturates are water soluble but markedly alkaline (pH of 2.5% thiopental >10) and relatively unstable (2-week shelf-life for 2.5% thiopental solution). Concentrations greater than recommended cause an unacceptable incidence of pain on injection and venous thrombosis.

Alkaline PH (10-10.5) → if it give to artery it will irritate it (vasospasm)

It is highly alkaline so it does not predispose for sepsis development (unlike propofol)

* Today, they have been largely replaced by the **benzodiazepines**, primarily because **barbiturates induce tolerance and physical dependence and are associated with very severe withdrawal symptoms**

★ Due to their narrow therapeutical index (their therapeutical dose is so close to their toxic dose)
SO they can NOT be used for maintenance and continuous infusion.

DURATION OF ACTION OF BARBITURATES

Long-acting



Phenobarbital

Short-acting



3-8 Hours

*Pentobarbital
Secobarbital
Amobarbital*

Ultra-short-acting



20 Minutes

Thiopental

- Pharmacokinetics:

- Absorption:

thiopental :

Intravenously for induction of general anesthesia in adults and children.

Rectal thiopental has been used for induction in children.

Thiopental dose :

moderately slow induction by injection of **50-75 mg (2-3 ml of a 2.5% solution)** at intervals of **20-40 seconds**.

- Distribution:
- The **duration** of highly **lipid-soluble** barbiturates is determined by **redistribution**, not metabolism or elimination.
- If **serum albumin is low** or if **nonionized fraction is increased (acidosis)**, higher brain and heart concentrations will be achieved for a given dose.
- Repetitive dosing saturates peripheral compartments so that duration depends on elimination not redistribution (termed **context sensitivity**).
- Biotransformation:
- via hepatic oxidation (**CYP-450**), which is eliminated by renal excretion.
- Excretion:
- Except for the less protein-bound and less lipid-soluble agents such as **phenobarbital**, renal excretion is limited to water-soluble end products of hepatic biotransformation. **Methohexital** is excreted in the **feces**

- **Effects on Organ Systems:**

- **Cerebral effects:** VC, decrease cerebral blood flow (CBF), decrease ICP, increase cerebral perfusion pressure, and decrease cerebral metabolic rate.

Most important respiratory reflexes (coughing and secretions)

- **Respiratory effects:** cause depression of the medullary ventilatory center, decreasing the ventilatory response to hypercapnia and hypoxia, leading to apnea. They do not completely depress noxious airway reflexes, so beware of laryngospasm and bronchospasm.

That's why it's only given in hospital settings as it causes central apnea

Intubation is needed, as well as applying mechanical ventilation.

- **Cardiovascular effects:** decrease mean arterial pressure (MAP) and increase heart rate, but cardiac output (CO) is maintained by compensatory baroreceptor reflexes. Sympathetically induced vasoconstriction of resistance vessels may increase peripheral vascular resistance. However, in hypovolemia, congestive heart failure (CHF), or β -adrenergic blockade, CO and systolic blood pressure may fall dramatically because of unmasked direct myocardial depression.

- **Renal :**

- **reduce renal blood flow** and glomerular filtration rate in proportion to the fall in blood pressure.

- **Hepatic :**

- **Hepatic blood flow is decreased.** Chronic exposure to barbiturates has opposing effects on drug biotransformation. Induction of hepatic enzymes increases the rate of metabolism of some drugs, whereas binding of barbiturates to the cytochrome P-450 enzyme system interferes with the biotransformation of other drugs (eg, tricyclic antidepressants).
- Barbiturates promote **amino levulinic acid synthetase**, which stimulates the formation of **porphyrin** (an intermediary in heme synthesis). This may precipitate acute intermittent porphyria or variegate porphyria in susceptible individuals.

- **Immunological :**

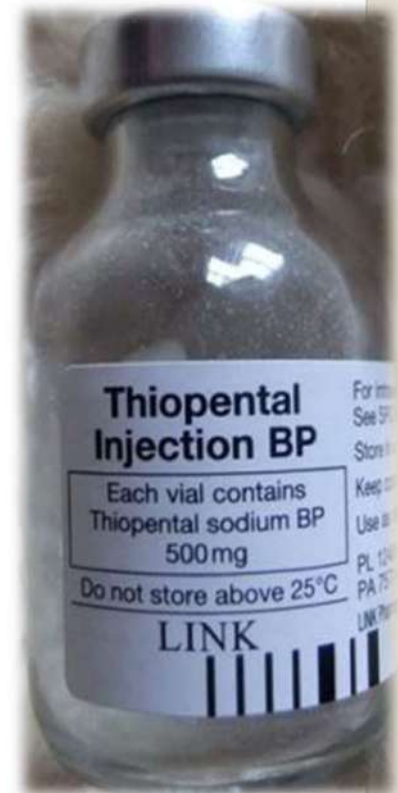
- Anaphylactic or anaphylactoid allergic reactions are rare.
- **Sulfur-containing thiobarbiturates** evoke mast cell **histamine** release in vitro, whereas oxybarbiturates do not. For this reason, **some anesthesiologists prefer induction agents other than thiopental or thiamylal in asthmatic or atopic patients**, but the evidence for this choice is sparse. There is no question that airway instrumentation with light anesthesia is troublesome in patients with reactive airways.

- **Drug Interactions :**

- Contrast media, sulfonamides, and other drugs that occupy the same protein-binding sites as thiopental may displace the barbiturate, increasing the amount of free drug available and **potentiating** the organ system effects of a given dose.
- **Ethanol, opioids, antihistamines**, and other central nervous system **CNS depressants** potentiate the **sedative** effects of barbiturates.
- The common clinical impression that chronic alcohol abuse is associated with increased thiopental requirements during induction lacks scientific proof.

-Thiopental

- **Ultra-short acting barbiturate (rapid acting and short duration of action)**
 - Potent anesthetic – weak analgesic
 - Very lipid soluble → penetrate brain tissue rapidly after IV administration (causes unconsciousness within 30–45 seconds)
 - **short duration** because of **Rapid redistributes from brain to fat & skeletal muscle (5-10 mins)**
- *BUT it Remains in the body for **long periods** after redistribution to tissues Because it **Slowly metabolized** (only 15 % are metabolized in the liver per hour) and **liable to accumulate in body fat**, thus **if given repeatedly** → **toxicity**



-Thiopental

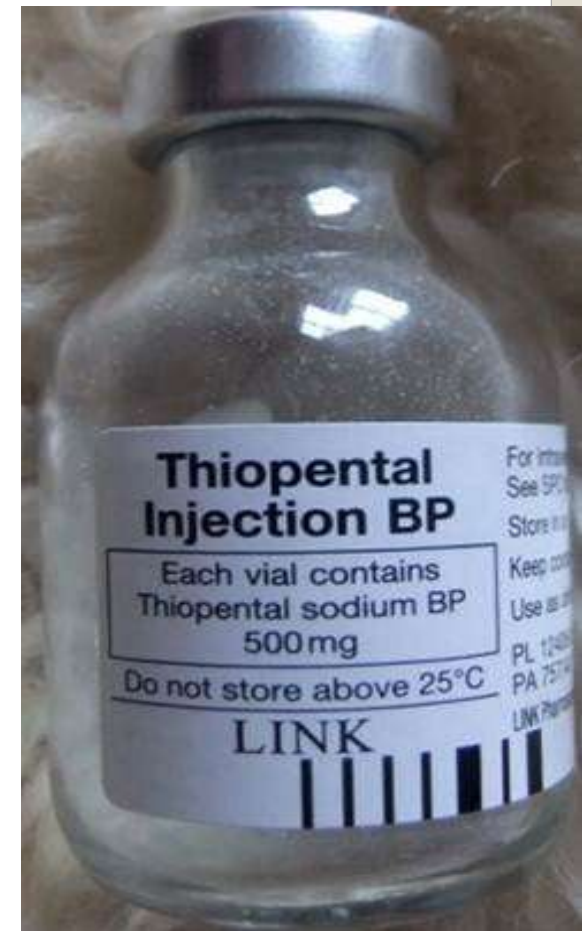
Metabolism:

mainly metabolized by the **liver** into **inactive, water-soluble** compounds by oxidation and then → are renally excreted OR conjugated to glucuronic acid and excreted in bile.

(should be used with caution in cases of liver disease)

USES:

1. Most widely used **IV anesthetic** for **induction** (principle use) → Rapid acting
 2. Given alone in **anesthesia for short procedures** → short duration of action
 3. **status epilepticus (Anticonvulsant)**
 4. **ICP reduction**
- Caused by hyperactivity of the brain. This drug results in zero activity of the brain. (Only used for this type)



-Thiopental

Side effects :

1. Narrow therapeutic index
(acute toxicity → **cardiovascular hypotension** + reflex tachycardia
and respiratory depression apnea  Induced by baroreceptors
,laryngospasm,bronchospasm)
2. Can **precipitate porphyria** Only in patients who have genetic predisposition
contraindicated in patients with a history of acute intermittent porphyria (Porphyrias are caused by deficiencies of specific enzymes responsible for the heme synthesis → **accumulations of toxic heme precursors; protoporphyrins**) >> (attacks of abdominal pain , tachycardia , hypertension , vomiting , ...)
3. **enzyme inducer** (drug-drug interactions) Increases the concentration of metabolites and could lead to toxicities
4. **No specific antidote** is available for barbiturates
5. if accidentally injected intra-arterially → Severe **vasospasm**
→ gangrene. If it was injected by an accident into an artery, it causes irritation which leads to spasm, resulting in severe pain at the area supplied by this artery and subsequential ischemia. Common cause of accidental injection is the presence of a direct invasive BP monitor.

2) Propofol

- **First choice** for **induction of general anesthesia** and **sedation**
- IV sedative/hypnotic
- “**Milk-like appearance**”, poorly water soluble; high lipid content
 ↗ Has a special white color
- Mechanism of Action: **Facilitates inhibitory neurotransmission of GABA**; increases binding affinity of GABA to the GABAA receptor
- Induction: **30-40 seconds (rapid onset)** as thiopental
- Redistribution: 2-4 minutes (fast recovery)
- **Short acting** : last for 5-10 mins.
- **No analgesia** (used with opioid).
- Given as : IV bolus (induction) or infusion (maintenance)



- Does not cause hangover symptoms.*(Fatigue and weakness, Excessive thirst and dry mouth, Headaches and muscle aches, Nausea, vomiting or stomach pain...)
- Cerebral, respiratory, and cardiovascular effects:
- Cerebral: causes decreased CBF and decreased ICP. In patients with elevated ICP, propofol may cause critical decreased cerebral perfusion pressure.
- **Antiemetic** effects.
- RS: causes apnea after induction by inhibiting hypoxic ventilatory drive and depresses normal response to hypercarbia/hypercapnia.
- Propofol can **release histamine** but causes fewer symptoms in individuals with asthma than other agents and is not contraindicated in those with asthma.
- CVS: Decreased PVR, decreased contractility, and decreased preload

 Direct myocardial depressant. + inhibites baroreceptors

Propofol

Metabolism:

Take 4 hours.

It is rapidly **metabolized** in the **liver** and **excreted** in **urine and bile** as **glucuronide** and **sulfate conjugates**. **Less than 1% of the drug is excreted unchanged in urine ; fast recovery.** but elimination is not affected by hepatic or renal failure.

USES: Can be used for induction, maintenance, short procedures and day case surgeries

1) **Maintenance** of General Anesthesia.(infusion)
2) Intensive Care Unit (**ICU**) **sedation** of intubated, mechanically ventilated patients; Adults. In order to blunt airway reflexes (gag reflex and coughing)

3) **Initiation and maintenance** of Monitored Anesthesia Care (**MAC**) **sedation** (ex.colonoscopy);Adults

[MAC → anesthesia with sedation and analgesia titrated to a level preserves spontaneous breathing and airway reflexes]

4) **agent of choice for ambulatory surgery** (out patient surgery)(day case surgery) Only propofol can be used in these surgeries. (Removes hungover symptoms which can be mistaken for complications of surgeries since theyre nonspecific symptoms); headache, N/V



Advantages

Does not prolong neuromuscular blockage but large doses may provide good intubating conditions without paralysis

No adrenal suppression

Pleasant dreams

Anti-emetic even at low doses (10mcg/kg/min)

Advantages of propofol:

1. Rapid onset + short duration of action
2. Anti-emetic; Treats nausea and vomiting in patients who have it but does NOT prevent it.
3. Anti-pruritic; treats it in patients who have it as well.
4. Bronchodilation effect.
5. Doesnt cause hangover symptoms

Reasons for N/V: increased intragastric pressure, hypotension, side effect of other drugs or irritation

Adverse effects/ disadvantages

Cardiorespiratory depression

Pain on injection IV

Hyperlipidemia with repeated doses (High lipid content)

In patients with abnormal lipid profile

Made of egg lecithin and soybean oil and phospholipids

Good media for bacterial growth ---- can cause septicemia if contaminated so if opened more than 6 hours you shouldn't use

Propofol infusion syndrome In ICU patients

Usually for large doses (>4 mg/kg) of period >48h

High doses in a short period of time.

High risk in Pediatric adrenal insufficiency pt (any pt receive catecholamines and glucocorticoids)

Statcal syndrome

- ★ Hyperlipidemia and metabolic acidosis
- ★ Rhabdomyolysis then cardiac arrest

- Preparation:
- Propofol formulations can support the growth of bacteria, so sterile technique must be observed in preparation and handling. Propofol should be administered **within 6 hours** of opening the ampule.
- Dosage:
- Induction: **2 to 2.5mg/kg IV.**

Propofol

Notes on propofol :

***Not recommended for:**

- obstetric including cesarean section deliveries ; neonatal depression.
- use in nursing mothers because propofol has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

***Contraindicated** in patients with allergies to eggs, egg products, soybeans or soy products.



3) ETOMIDATE

STABILIZER

Very minimal effect on RS and CVS

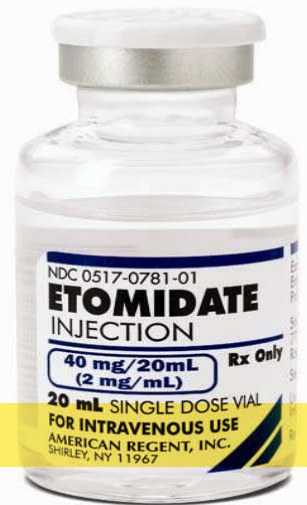


- **MOA:**  Depresses the RAS and mimics the inhibitory effects of GABA, so it is a sedative and hypnotic with no analgesic properties.
 - 1) **rapid onset** of action & **short-acting intravenous** anesthetic agent used for the **induction** of general anesthesia and **sedation**
 - 2) a **safe drug on heart and lung** (**stabilizer**) → is less likely to cause a significant drop in blood pressure than other induction agents → maintain a normal arterial pressure .
#SO protect from myocardial and cerebral ischemia.
 - 3) limited suppression of ventilation
 - 4) is one of the anesthetic agents able to **decrease intracranial pressure** → SO use with **traumatic brain injury**
 - 5) Has **no analgesic effect**
 - 6) Has **no antidote**

ETOMIDATE

Uses:

- 1) rapid onset of action & short-acting → **Sedation** and **anesthesia** for **short** procedures
- 2) **stabilizer** → good induction agent for people who are **hemodynamically unstable**
- 3) It's the **drug of choice in patients with cardiogenic shock**
- 4) **decrease intracranial pressure** → use with **traumatic brain injury**



- Biotransformation and excretion:
- **Redistribution** is responsible for its **short half-life**.
- **Hepatic microsomal enzymes** and **plasma esterases** rapidly hydrolyze etomidate to inactive metabolites. These metabolites are excreted in urine.
- Etomidate induction is associated with a 30-60% incidence of **myoclonus** potentially from disinhibitory effects on the parts of the nervous system that control extrapyramidal motor activity
- Dosage: Induction: 0.2 to 0.6 mg/kg (for age >10 years).
- Cerebral, respiratory, and cardiovascular effects:
- Decreased CMR(cerebral metabolic rate)O₂, decreased CBF, and decreased ICP.
- Ventilation is minimally affected.
- Minimal effects on the cardiovascular system. CO and contractility are usually unchanged.
- However, because etomidate induces **light anesthesia**, **hypertension** and **tachycardia** may be seen **with intubation**

ETOMIDATE

Adverse effects

- 1- **suppresses corticosteroid synthesis** in the adrenal cortex by reversibly inhibiting 11β -hydroxylase, an enzyme important in **adrenal steroid production** → it leads to **primary adrenal suppression**
- 2- **Severe nausea and vomiting**

CI: Adrenal impairment

→ Contraindicated in patients with Addison disease.



Ketamin

No effect on RS (no blunt reflexes/no central apnea)

It's the only drug that has an analgesic effect.

It's the only drug that causes an elevation of the ICP and works on NMDA receptors

- Mechanism of action: ☆ It is a potent sympathetic stimulator so it results in hypertension (elevates HR & BP)
- Blocks postsynaptic reflexes in the SC and inhibit excitatory neurotransmitters in selected areas of the brain. Dissociates thalamus from limbic system involved in awareness. **NMDA receptor antagonist.**
- Cerebral, respiratory, and cardiovascular Effects:
- Increased CMRO₂, increased CBF, and increased ICP.
- Ventilatory drive is minimally affected. **Potent bronchodilator**, so **good induction agent in patients with asthma.**
- Increased MAP, increased heart contractility, increased CO because of central stimulation of the sympathetic nervous system and inhibits reuptake of norepinephrine. Increase PAP(pulmonary artery pressure) and myocardial work.
- Metabolism:
- Duration limited by redistribution (half-life, 10–15 min). Biotransformed in the liver and excreted by the kidneys.

Action of ketamine:

1. Induction and maintenance.
2. Induce **dissociative state** * (the patient is unconscious and doesn't feel pain even he looks awake eye)
3. Induce **profound analgesia** (long-lasting analgesia)
4. **Stimulate sympathetic out flow** ; increase BP + HR + (can be used in **shock States**)
5. Potent **bronchodilator** → the first choice when ventilator is not available

→ It is the drug of choice in cases of hypovolemic shock.

★ Drug of choice in asthmatic patients, if not available then give propofol



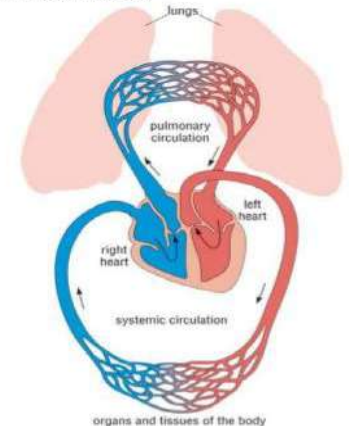
USES:

- 1) profound analgesia ; pediatric surgery , sedative for physically painful
- 2) emergent surgery in war zones (spontaneous ventilation) ; the first choice
- 3) Asthmatics or people with chronic obstructive airway disease.
- 4) hypovolemic shock ; increase CO + BP + HR
- 5) spinal or epidural anesthesia / analgesia (low doses)



Hypovolemic Shock

- Cardiac Output
 - Decreased
- PCWP
 - Low
- CVP/RAP
 - Low
- Blood Pressure
 - Low
- Systemic Vascular Resistance
 - Increases



Side effects :

- 1 **Eye: Diplopia , nystagmus**(repetitive uncontrolled eye movement) , **slight elevation in intraocular pressure.**
- 2 **direct myocardial depression** and may lead to decreased CO in sympathetic blockade, spinal cord transection, or exhaustion of catecholamine stores (severe end-stage shock)
- 3 **Psychological** : psychomimetic reaction ; **hallucinations**



Contraindications

Or any case where there is an evidence of elevated ICP like hydrocephalus, trauma.. etc

★ a very important slide.

1. **Angina, stroke(as it increases ICP)**

2. **Psychiatric disorders** → Causes delusions and hallucinations

3. **Raised intraocular pressure (IOP)** , Penetrating eye injury ★ Glaucoma is a contraindication

4. **Coronary artery disease, CHF, uncontrolled hypertension, and aneurysms.**

★ NOT contraindicated in all types of stroke.

- ONLY contraindicated in hemorrhagic stroke. Can be used in ischemic (embolic) stroke

★ Contraindicated in cardiogenic shock (increases afterload and oxygen demand)

We can give it to hypertensive patients if not malignant.

Drug of choice in this case is etomidate

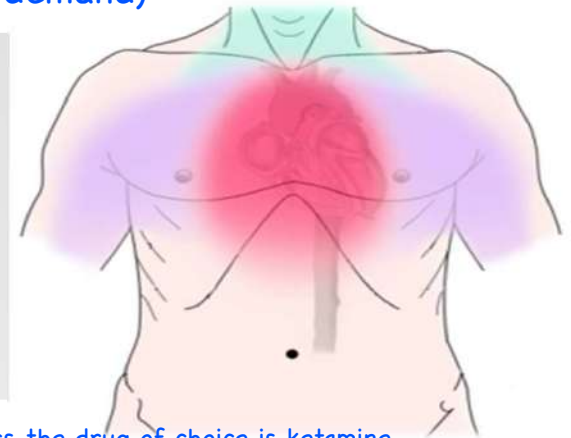
Dosage:

Induction: **1 mg/kg IV** (5–10 mg/kg IM or per rectum)

★ Drug of choice in warzones:

1. Most patients are hypovolemic already.
2. Due to its analgesic effect.
3. Due to its bronchodilation effect.

★ In cases of traumas, if the trauma is below the head and the patient doesn't have a stable hemodynamics the drug of choice is ketamine. but if the trauma includes the head, or we have basal skull fractures (raccoon eyes/rhinorrhea), ketamine is contraindicated. Give etomidate



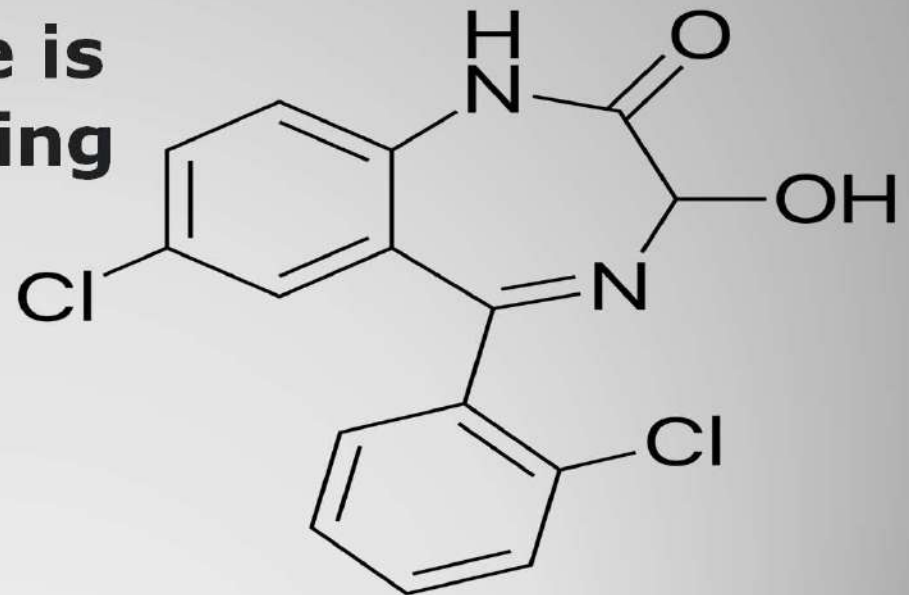
5) Benzodiazepines

* Core chemical structure is the fusion of a benzene ring and a diazepine ring. Substitutions at various positions on these rings affect potency and biotransformation.

They are either short, intermediate or long acting drugs

They're the only drugs that have an antidote.

They can be used to induce anesthesia + anticonvulsions and as antidepressants & anxiolytics (midazolam mainly)



- The **imidazole** ring of **midazolam** contributes to its **water solubility** at low pH.
- Diazepam and lorazepam are insoluble in water so parenteral preparations contain **propylene glycol**, which can produce venous irritation
- Biotransformation and elimination:
 - Action is limited by redistribution.
 - Benzodiazepines are biotransformed by phase I reactions hepatically and excreted in urine.
 - half-life is 3–10 min.
 - Redistribution is fairly rapid for the benzodiazepines .
 - Reduce MAC by as much as 30%.

- Cerebral Effects:

- Decrease the cerebral metabolic rate of oxygen (CMRO₂), decrease CBF, decrease ICP, prevent and control grand mal seizures.

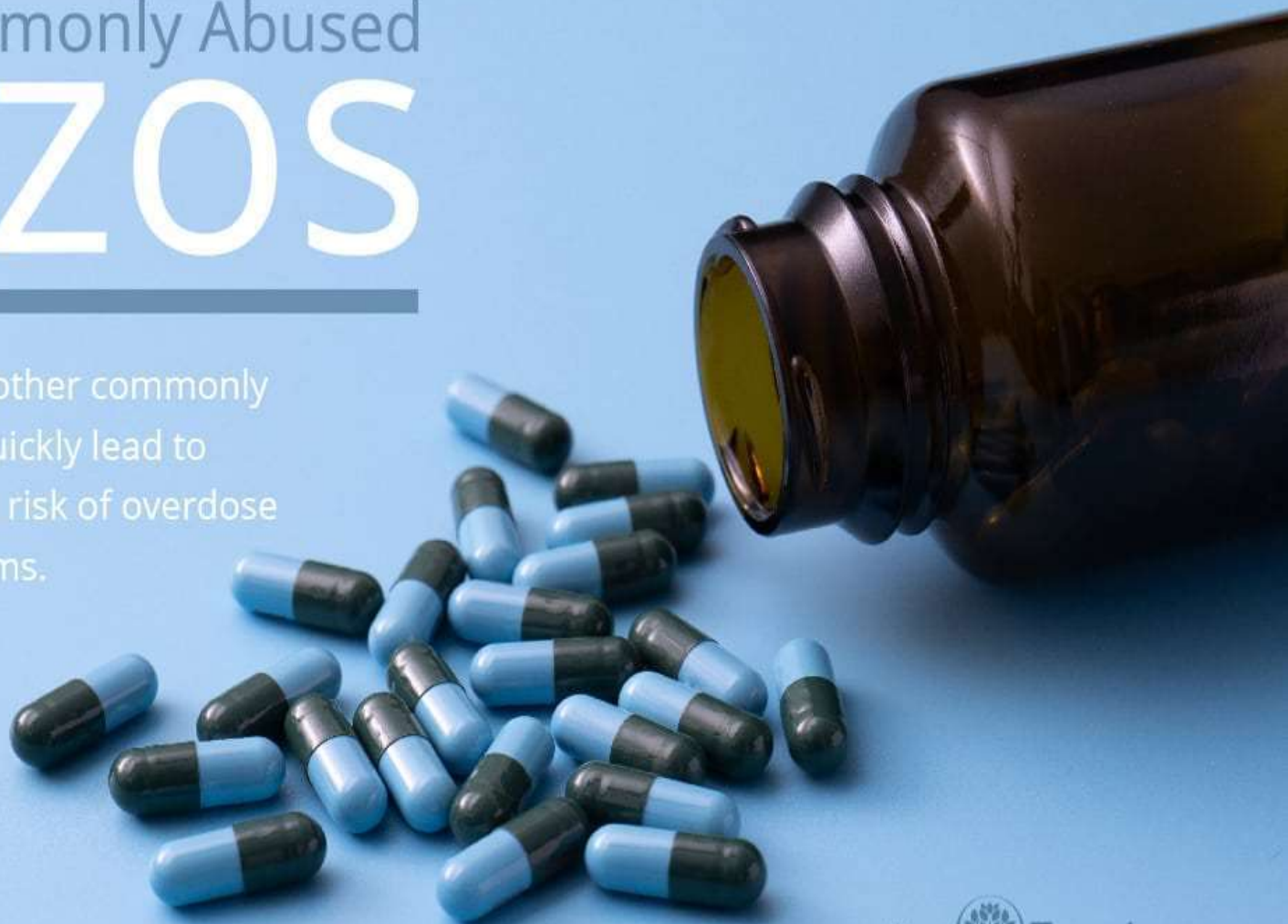
- Respiratory and cardiovascular effects:

- Depress ventilatory response to CO₂. Apnea is relatively uncommon after benzodiazepine induction, but respiratory arrest can occur.
- Minimal cardiovascular depressant effects. When administered with opioids, benzodiazepines rapidly reduce arterial blood pressure and PVR.

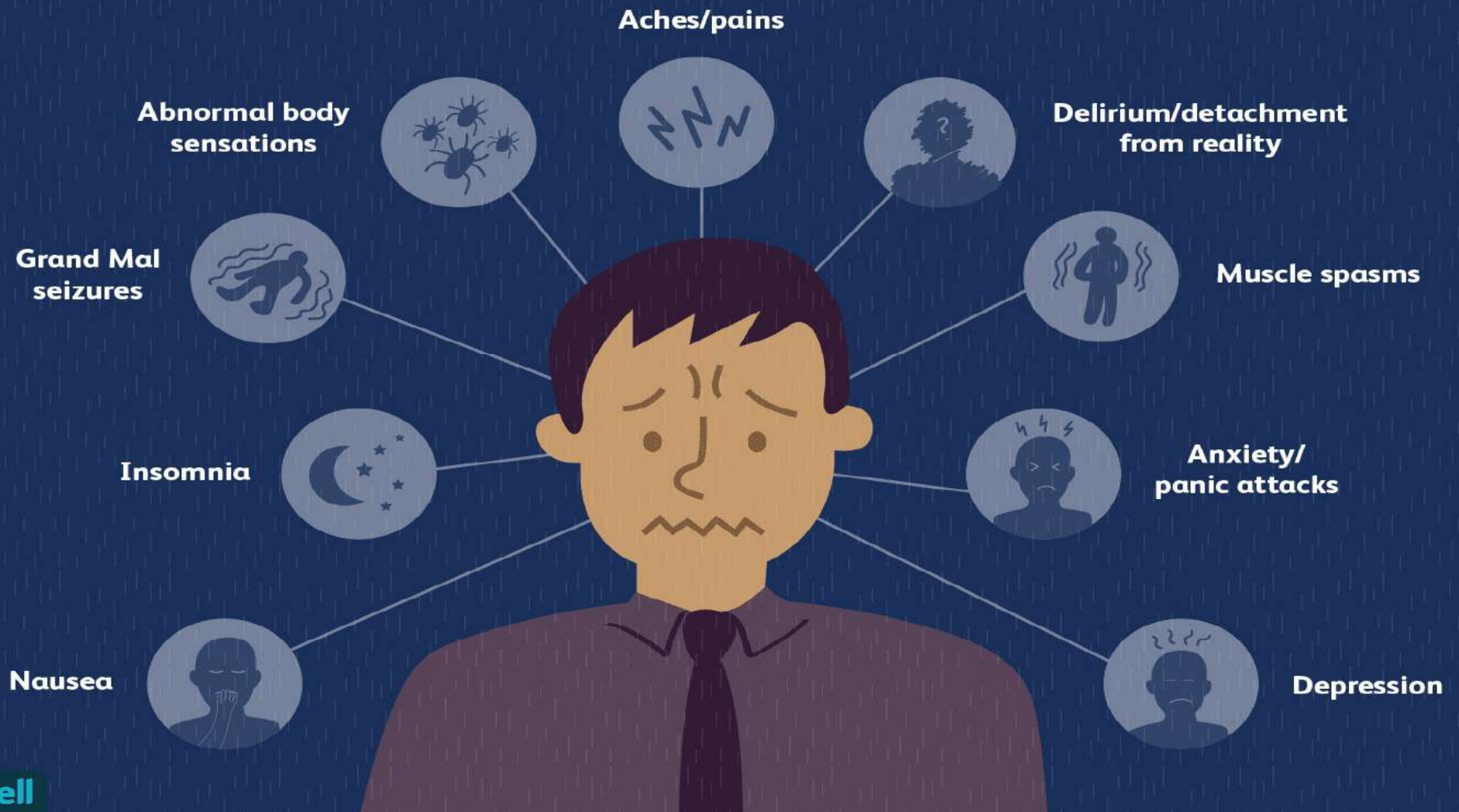
List Of Commonly Abused Benzos

(benzodiazepines)

Abuse of Xanax, Valium or any other commonly abused benzodiazepines can quickly lead to addiction and place a person at risk of overdose and deadly withdrawal symptoms.



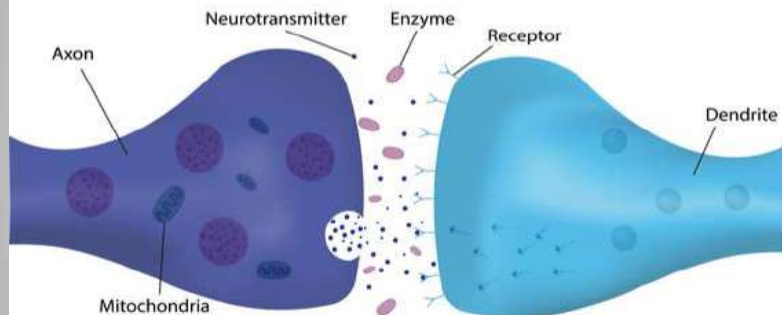
Symptoms of Benzodiazepine Withdrawal



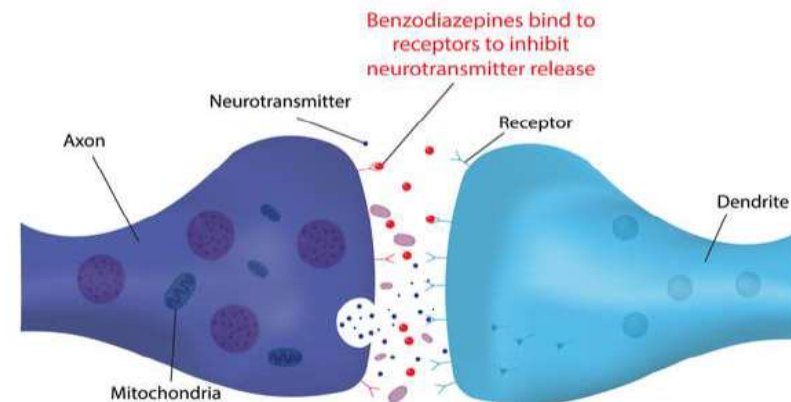
5) Benzodiazepines

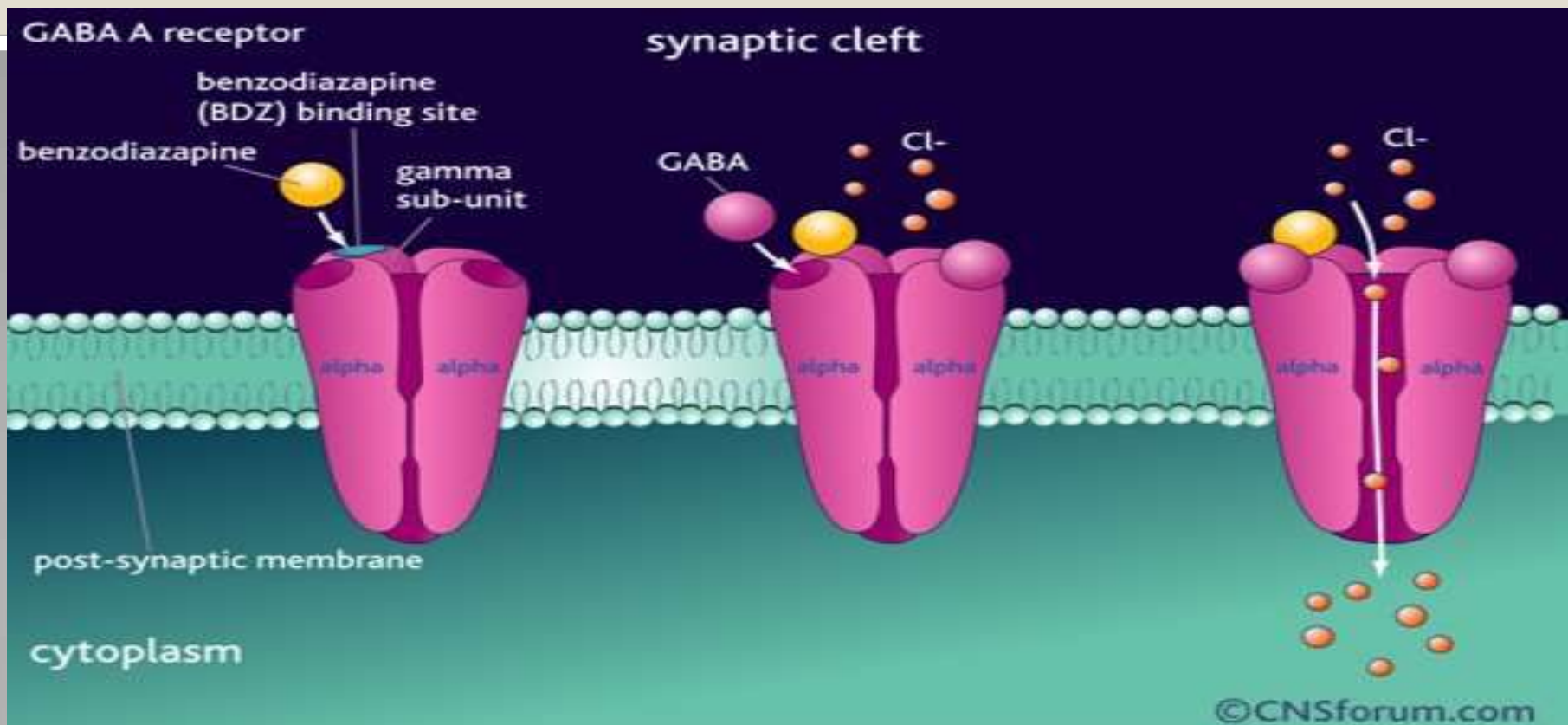
Benzodiazepines

Normal



With Benzodiazepines





Benzodiazepines enhance GABA binding so increase the frequency of the **chloride ion channel** opening, hyperpolarizes the cell , therefore reduces neural excitability.

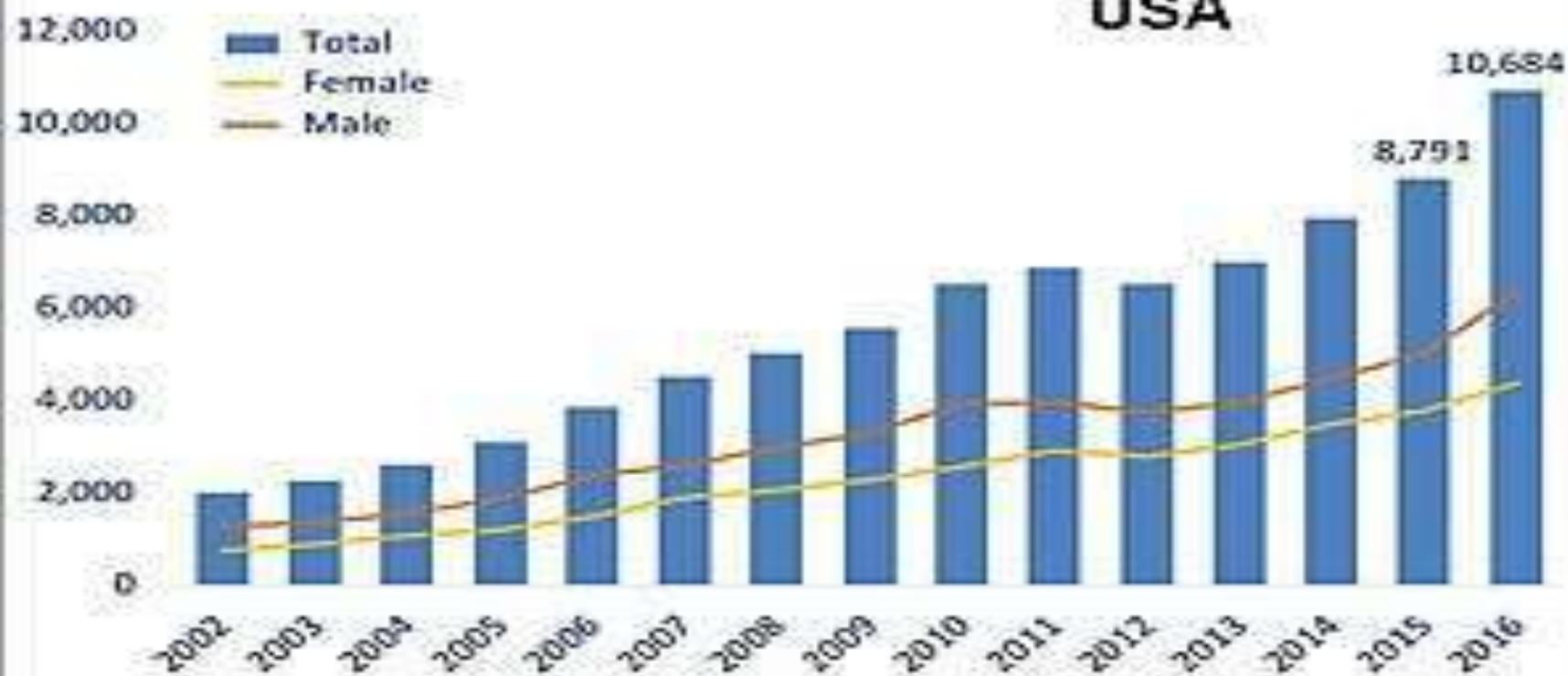
5) Benzodiazepines

- ❖ Benzodiazepines are compounds with **sedative**, **Anxiolytic** and **anticonvulsant** properties.
- ❖ As the dose is increased the effects observed are **first anxiolytic → sedation → hypnosis → unconscious with respiratory depression**
- ❖ Benzodiazepines has specific antagonist:
(Iv , rapid , short)(**Flumazenil** = GABA antagonist)



Number of Deaths Involving Benzodiazepines

USA



Source: National Center for Health Statistics, CDC Wonder

5) Benzodiazepines

❖ Members :

- short acting: midazolam
- intermediate: lorazepam
- long acting: diazepam

Midazolam

- 1) rapid , short action
- 2) less irritant effect.

❖ The most common one used among benzodiazepines family in anesthesia is Midazolam

Uses:

1- sedative, Anxiolytic → Pre-anesthetic

2- causes amnesia (memory loss) and muscle relaxation → IV anesthetic Medications

[so we can use it in dentistry, cardiac surgery, endoscopic procedure as pre-anesthetic medication and as adjunct to local anesthesia]

❖ Metabolism in liver , excreted by kidney



Side effects:

Same side effects as barbiturates but less intense

1. dose dependent respiratory depression.

Overdose leads to serious cardiorespiratory adverse effects ending in death or permanent neurological effects, so continuous monitoring respiratory and cardiac functions until pt is stable.

2. produce decrease in systemic vascular resistant and blood pressure in large doses (VD) → Hypotension

3. Ataxia, Headache, Vertigos, Blurred Vision and Weakness

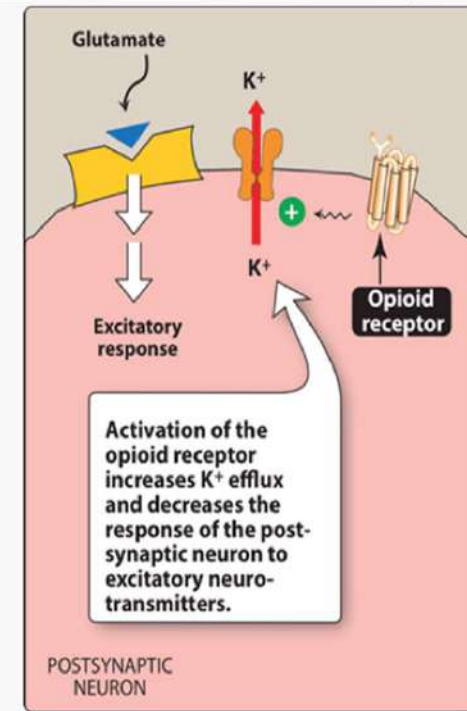
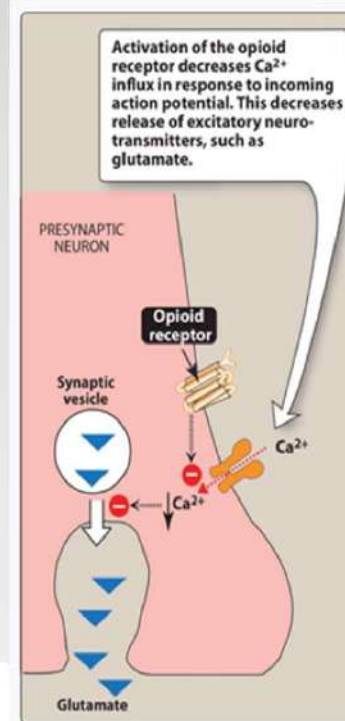


6) Opioids (only on high dose)

☆ Most common adverse effect is chest rigidity which results in difficult ventilation. This indicates toxicity and we can only treat it with naloxone (antidote)

Mechanism of Action :

- Activation of receptors cause neuronal inhibition through: (same as GABA b) *Unknown mechanism of actions*
 - a) **Presynaptic** → **Inhibition of Ca^{2+} influx(entry)** → **inhibit release of excitatory neurotransmitters including substance P, glutamate.**
 - b) **Post synaptic** → **Stimulation of K^{+} efflux** → **hyperpolarization of neuronal membrane**



Opioid receptors

- a group of inhibitory G protein-coupled receptors with opioids as ligands.

- 3 types:
- Delta
- Kappa
- Mu

Receptor	Functions/ effects	Endogenous opioid peptide affinity
μ (mu)	• Supraspinal and spinal anesthesia • Sedation • Inhibition of respiration • Slowed GI transit • Modulation of hormone, neurotransmitter release • Physical dependence • Euphoria	Endorphins > enkephalins > dynorphins
δ (delta)	• Supraspinal and spinal anesthesia • Modulation of hormone, neurotransmitter release	Enkephalins > endorphins and dynorphins
κ (kappa)	• Supraspinal and spinal anesthesia • Psychotomimetic effects • Slowed GI transit	Dynorphins >> endorphins and enkephalins

- Opioid activate receptors in:
 1. **Afferent pain-conducting fibers** → peripheral analgesia.
 2. **Spinal cord** → spinal analgesia.
 3. **Brain stem, thalamus & cerebral cortex** → supraspinal analgesia.
 4. **Limbic system** → euphoria & emotional response to pain
- NOTE : **Naloxone** is the **antidote** to reverse coma and respiratory depression in opioid overdose

1. Morphine

- **Uses :**

1. **Analgesic** (↓ pain sensation)
2. **anesthetic**
3. **Acute pulmonary edema** in **LVF** → decrease preload & after load (due to peripheral VD), ↓ Respiratory distress, ↓ anxiety → because it has Inhibitory Effects on :
 - A. **VMC** → venular & arterial VD
 - B. **inhibit Respiratory Center** → decrease respiratory distress
4. **Antitussive** → inhibit Cough Center
5. **Antidiarrheal** → inhibit peristalsis



- **Adverse effects:**

1. **respiratory depression**
2. **Hypotension** → due to VD
3. **Urine Retention**
4. **Biliary colic** (it increase the tone of wall of sphincters (spasmogenic) and inhibit the peristalsis)
5. **Constipation**
6. **Delayed labor** (has inhibitory effect on Uterine muscle tone)

#Moprhine is contraindicated in labor as it decreases contractions and reaches the fetus



- **Contraindications:**

- 1) **Head injury** → VD in cerebral veins → **increases ICP**
- 2) **pregnancy** → as it reaches the fetus
- 3) **Enlarged prostate** → leads to urine retention
- 4) **in biliary colic** → spasmogenic and causes paralysis
- 5) **Asthma** (secrete histamine)

2. Pethidine (meperidine)

- **USES:**

- 1) in acute, moderate & severe pain e.g, trauma, postoperative pain
- 2) Less biliary colic- constipation- urinary retention → biliary colic (used alone)
- 3) Less respiratory depressant in neonates & does not delay labor → labor pain.

- **S.E:**

1. Atropine-like action: dry mouth, blurred vision, ...
2. increase Risk of convulsions (with high dose)

3. Fentanyl

1. More potent than morphine (100 folds)
2. with rapid onset
3. shorter action
(preferred in anesthesia) → Most commonly used

- *Is a synthetic opioid analgesic
- *During anesthesia it is often used along with a hypnotic agent like Propofol.
- *It is also administered in combination with a benzodiazepine, such as midazolam, to produce procedural sedation for endoscopy, cardiac catheterization, oral surgery, etc

• ***Thank you***

