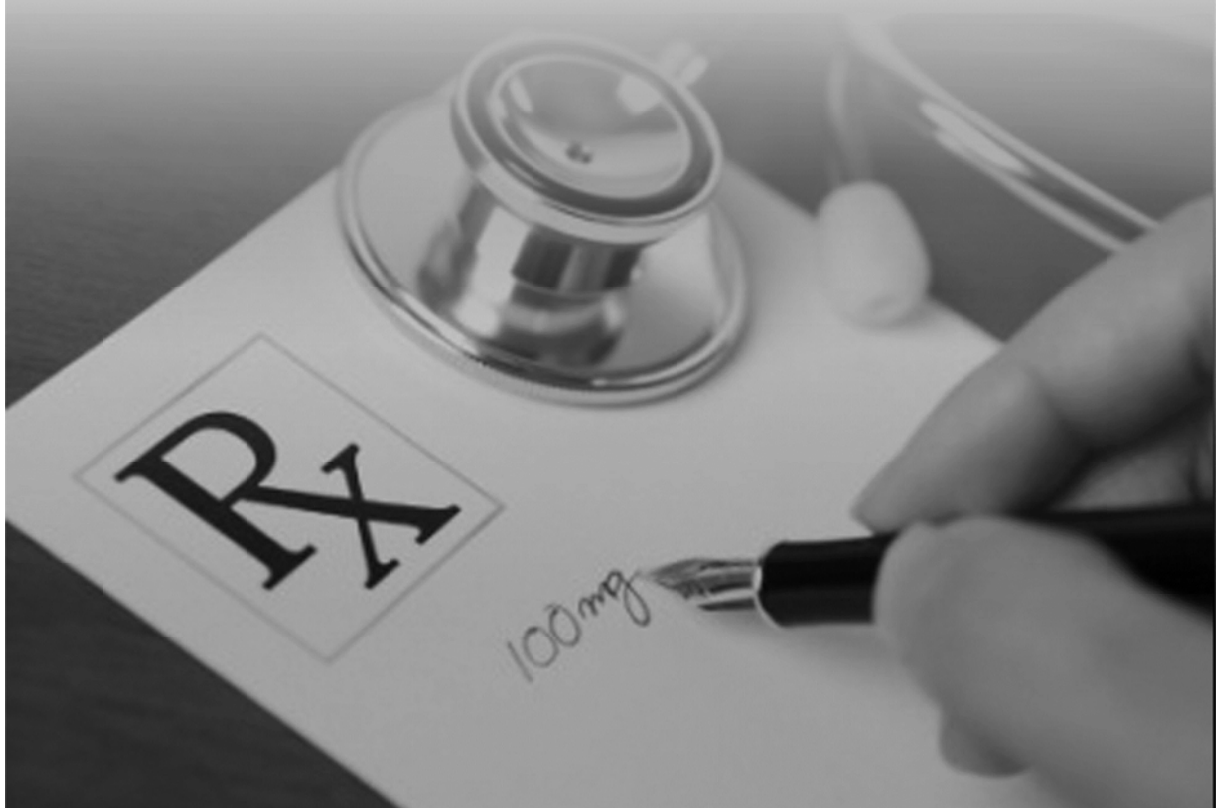




Chapter 10

CNS Pharmacology



Chapter 10

CNS Pharmacology

Part 1: CNS Stimulants

Classification:

- | | | | |
|---|---|--|---|
| 1 Respiratory stimulants
theophylline,
nikethamide | 2 Psychomotor stimulants
amphetamines,
antidepressants | 3 Psychotomimetic drugs
LSD,
cannabis | 4 Spinal cord stimulants
strychnine |
|---|---|--|---|

■ RESPIRATORY STIMULANTS (ANALEPTICS)

Definition: drugs that stimulate the depressed respiratory center (RC).

Classification:

■! Specific analeptics:

- ! Naloxon and nalorphine → used to treat opiates respiratory depression.
- ! Flumazenil → used to treat benzodiazepines toxicity.

■! Non-specific analeptics:

- ! Direct RC stimulation: e.g. Xanthines (caffeine, theophylline) – Ethamivan - Heptaminol. They antagonize the GABA-mediated RC depression.
- ! Indirect RC stimulation (reflex): e.g. Nicotine and lobeline. They stimulate RC indirectly through stimulation of the chemoreceptors in the carotid body.
- ! Both (direct and indirect): Nikethamide - Doxapram

Therapeutic uses: all cases of RC depression (postanaesthetic, CNS depressants, COPD and some premature babies)

Adverse effects

- ! Tachypnea, tachycardia and hypertension.
- ! High doses can cause convulsions.

Contraindications

- ! Epilepsy (to avoid CNS stimulation).
- ! Severe hypertension, arrhythmia or IHD (to avoid cardiac arrhythmia).
- ! Thyrotoxicosis.
- ! Severe bronchial asthma.

■ PSYCHOMOTOR STIMULANTS

Definition: drugs that induce **euphoria** with **increased motor activity**.

Classification

- ! **Amphetamine and related drugs:** see ANS
- ! **Cocaine**
 - ! Cocaine inhibits tissue uptake of catecholamines.
 - ! Behavioral effects of cocaine are very similar to amphetamine.
 - ! Cocaine is used topically as a local anesthetic eye drops.
- ! **Xanthines:** see respiratory pharmacology.
- ! **Antidepressants:** see later.

■ PSYCHOTOMIMETIC DRUGS (HALLUCINOGENS)

Definition: drugs that affect **thought, perception** and **mood** with no effect on motor activity. They have **no clinical applications** but important for **drug abuse**.

Examples and Mechanisms

- ! **LSD (Lysergic acid diethylamide):** It stimulates central **5-HT** receptors and affects catecholamine action → severe hallucinations and delusions resembling acute **schizophrenia**.
- ! **Cannabis (hashish, marijuana):** It acts on cannabinoid receptors in the CNS (**CB₁**) causing loss of judgment of time & place and dream-like state. It does not cause physical dependence but psychological dependence. **CB₂** receptors are found in peripheral tissue and immune system.
- ! **Phencyclidine:** It stimulates **δ-opioid** receptors and blocks the NMDA receptors and may interact with other neurotransmitter systems.

Part 2: Analgesics

Definition: drugs that relieve or decrease pain sensation.

Classification of analgesics:

- ! **Opioid (narcotic) analgesics**
- ! **NSAIDs** (see chapter 4).
- ! **Analgesic antipyretics:** e.g. paracetamol, Dipyrone & Nefopam.
- ! **Drugs used for specific painful conditions** e.g. carbamazepine for trigeminal neuralgia, ergotamine for migraine.

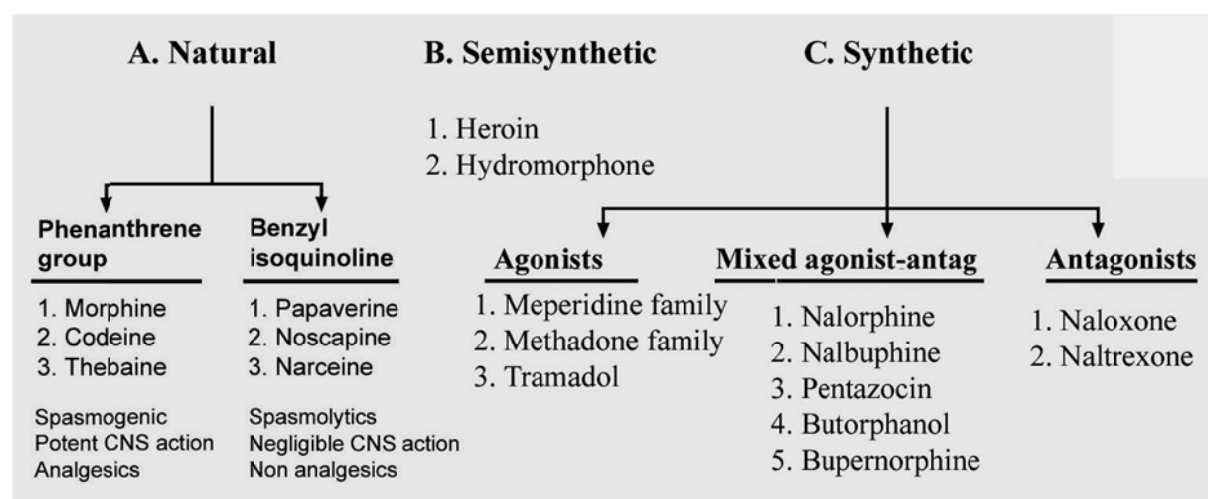
OPIOID ANALGESICS

- ! They are drugs that decrease pain sensation without loss of consciousness and can induce physical dependence.
- ! **Opiates:** are drugs derived from opium plant (*Papaver somniferum*). They include mainly morphine, codeine and papaverine.
- ! **Opioids:** are drugs with morphine-like activity.
- ! **Opiopeptides:** are endogenous peptides with opioid-like activity e.g. endorphins & enkephalins
- ! **Narcotics:** are drugs that produce narcosis i.e. drowsiness or stupor, with analgesia (stupor means marked impairment, but not complete loss of consciousness). These drugs are usually addictive. It is a **legal**, not a medical, term.



Papaver somniferum

Classification of opioid drugs



Mechanism of action

- ! Opioids such as morphine are believed to interact with three major receptors (**μ**, **δ**, **κ**). Each opioid receptor has distinct subtypes (e.g., μ_1 , μ_2). All three major receptors are present in high concentrations in the dorsal horn of the spinal cord.
- ! Interaction with **μ-receptors** contributes to supraspinal and spinal analgesia, respiratory depression, sedation, euphoria, decreased GI peristalsis, and physical dependence (addiction).
- ! The significance of interaction with **κ-receptors** is unclear, but it may contribute to analgesia (through inhibition of release of substance P at dorsal horn).

NATURAL OPIOID AGONISTS

1. Morphine

Pharmacokinetics

- ! **Oral absorption:** good (bioavailability is 25% due to significant first-pass effect). However, the analgesic effect is greater when the drug is administered parentally
- ! **t_{1/2}** : 4-5 hrs.
- ! **Metabolism:** in the liver by conjugation leading to inactive metabolites.
- ! **Excretion:** renal (90%) – bile (10% as conjugated morphine).

Pharmacological effects

- ! **Analgesia**
 - ! **Dose-dependent analgesia (sensory & emotional):** consciousness is not lost and the patient can still locate the source of pain. Analgesia may be associated with **euphoria** and decreased anxiety.
 - ! Analgesia results from direct activation of **μ** and **δ** receptors in the spinal cord and possibly higher centers (thalamus) leading to:
 - ! Activation of descending inhibitory pathways.
 - ! ↓ release of substance-P in pain transmission neurons in the spinal cord.
 - ! The psychic effect results from ↓ **NA release** in some CNS areas leading to decrease anxiety and reaction of the patient to pain.
 - ! Morphine and other exogenously administered opioids may also have some action on **peripheral** inflamed tissue.

N.B. Morphine can treat all types of pain **except itching**. **Why?**

a)! Because morphine stimulates **histamine release** → ↑ itching.

b)! Itching is different from pain sensation and has different receptors and centers.

- ! **Euphoria** (large doses produce dysphoria).
- ! **Miosis:** due to central stimulation of Edinger-Wistphal nucleus. **Severe miosis** is indicative of toxic doses.
- ! **Respiratory center depression.** This RC depression leads to CO₂ retention and cerebral VD → ↑↑ **intracranial tension**.
- ! **Cough suppression.**
- ! **Vagal stimulation.**
- ! **Nausea & vomiting:** due to stimulation of chemoreceptor trigger zone (CTZ).

CVS effects:

- ! **Orthostatic hypotension:** due to (a) Histamine release; (b) vagal stimulation.
- ! **Bradycardia:** due to vagal stimulation.

Smooth ms (Spasmogenic effects):

- ! **Bronchoconstriction:** due to: (a) Vagal stimulation. (b) Histamine release.
- ! **Constipation:** due to (a) spasmodic non-propulsive contractions of intestinal smoothms & decreased peristalsis; (b) ↑ intestinal water absorption.
- ! Spasm of the **sphincter of Oddi** → ↑ biliary pressure.
- ! **Feeling of urgency with difficult micturition** due to ↑ detrusor muscle tone with spasm of the internal urethral sphincter.
- ! **Uterus:** prolongation of labor by unclear mechanism.

Therapeutic uses

- ! **Analgesia:** for severe pain e.g. acute MI, cancer, surgery, etc.
- ! **Acute pulmonary edema (cardiac asthma). Why?**
 - ! ↓ stress & anxiety of the patient.
 - ! Venodilatation → ↓ VR & preload → ↓ pulmonary congestion.
 - ! Decrease tachypnea caused by the CNS response to hypoxic drive (due to its depressant effect on RC).
- ! **In anesthesia:**
 - ! As adjuvant to anesthetic agents (preanesthetic medication).
 - ! Regional anesthesia (epidural) to achieve long lasting analgesia by its effect on the spinal cord.
- ! **In severe colic: (morphine combined with atropine). Why?**
 - ! Because morphine is spasmogenic and atropine is spasmolytic.
 - ! To counteract muscarinic effects caused by excessive vagal stimulation (e.g. bronchoconstriction and bradycardia).

Preparations and doses

- ! Morphine sulphate: 10 mg s.c. or i.m. In acute MI it is given **5 mg i.v.**
- ! Intrathecal (epidural) injection: produce long lasting analgesia which is useful for critically ill patients at risk of RC depression.
- ! Sustained release preparations & transdermal patches are available.

Adverse effects:

- CNS**
- ! **Tolerance & physical dependence** (addiction) with prolonged use:
 - ! Physical dependence can occur within 24 h if given /4 h.
 - ! Tolerance may occur to analgesia and euphoria but not to respiratory depression.
 - ! ↑↑ intracranial tension.
 - ! **RC depression**: the most important effect and is dose-dependent.
- Resp**
- ! Bronchoconstriction.
- CVS**
- ! Postural hypotension
- GIT**
- ! Nausea, vomiting, and constipation.
 - ! Increased biliary tract pressure and biliary colic.
- Genito-Urinary**
- ! Urine retention especially in patients with enlarged prostate.
 - ! Prolongation of labor.
- Eye**
- ! Miosis is a consistent finding in morphine addiction.

Contraindications & precautions

- ! **Head injury & increased intracranial pressure**: Morphine causes respiratory depression & CO₂ retention. The ↑ CO₂ causes cerebral VD and ↑ intracranial tension.
- ! **Respiratory depression**.
- ! **Bronchial asthma**: Morphine causes bronchoconstriction due to (a) vagal stimulation; (b) histamine release. It also causes RC depression.
- ! **Biliary colic & gallstones**: due to spasm of the sphincter of Oddi → ↑ biliary pressure.
- ! **Senile enlarged prostate**: Morphine ↑ detrusor muscle tone with spasm of the internal urethral sphincter → feeling of urinary urgency with difficult micturition.
- ! **Hypotension and hypovolemia**: because morphine causes postural hypotension.
- ! **Hepatic damage**: Due to: (a) morphine is metabolized by the liver; (b) morphine increases the risk of hepatic encephalopathy due to marked CNS depression.
- ! **Hypothyroidism and adrenal insufficiency** (Addison's disease). **Why?**
Because those patients have prolonged and exaggerated response to morphine.

- ! **Undiagnosed acute abdominal pain:** Morphine masks the pain (which may be dangerous e.g. appendicitis) and interferes with the correct diagnosis.
- ! **Infants and old patients:** are more susceptible to respiratory depression.

Chronic opioid toxicity (addiction)

- ! There are behavioral changes, constipation, itching & miosis.
- ! Sudden withdrawal (abstinence syndrome):
 - ! *Consists of:* irritability, nervousness, tremors, hypertension & ms cramps starts after 6-10 hrs from the last dose - peak effect at 48 hrs - gradually subsides over 5-10 days.
 - ! *Mechanism:* chronic administration of opioids ↓↓ endogenous production of endorphins and NA. Following sudden withdrawal, there is an immediate deficiency of endogenous opioids with rebound ↑ of NA release.

Treatment of chronic morphine addiction:

- ! Gradual withdrawal of morphine with substitution by **methadone**, then gradual withdrawal of methadone.
- ! **Clonidine:** to stimulate central α₂ receptors and ↓ NA release.
- ! Sedatives: e.g. diazepam.

Acute opioid toxicity

- Manifestations:**
- Coma with depressed respiration, miosis, and shock.
 - ! Death occurs from respiratory depression.

- Treatment:**
- Gastric lavage.
 - ! Establish a patent airway and artificial respiration if needed.

- ! Opioid antagonists:

- ! **Naloxone:** pure opioid antagonist and can reverse RC depression within minutes (0.4 - 0.8 mg i.v. for 2-3 doses).

- ! **Nalorphine:** it is mixed agonist-antagonist (partial blocker).

N.B.

Opioid blockers are **indicated** in **acute** morphine toxicity but they are absolutely **contraindicated** in **chronic** morphine addiction because they precipitate severe withdrawal syndrome.

N.B.

- ! The duration of opioid antagonists is **shorter** than morphine. The patient should be watched carefully because he may go back into coma.
- ! Care should be taken to avoid **withdrawal** syndrome.

2. Codeine

Similar to morphine with the following differences:

- ! Has **greater oral bioavailability** (60%) due to **less first-pass effect**.
- ! The **analgesic** potency is **20%** of morphine, but more potent cough suppressant
- ! It has **little euphoric** effect.
- ! Most of the systemic effects of codeine are due to conversion in the liver into morphine by *demethylation* (codeine is *methyilmorphine*).

Therapeutic uses

- ! Analgesic for mild to moderate pain (usually combined with paracetamol).
- ! As central antitussive (see chapter 7).

Adverse effects: (less than morphine)

- ! Constipation
- ! RC depression and addiction liability but it is fewer than morphine.

	Morphine	Codeine
Oral bioavailability:	25%	60%
Analgesic effects:	Strong	Weak (20%).
Antitussive effect:	Weak	Strong
Uses:	Mention its 4 uses	Analgesic and antitussive

!

■ SYNTHETIC AND SEMISYNTHETIC OPIOID AGONISTS

1. Heroin and hydromorphone

- ! They are semisynthetic opioids (heroin is diacetylmorphine).
- ! They are **more potent** than morphine but with rapid onset and shorter duration.
- ! They are **not used clinically** because they are **highly addictive**.

2. Meperidine (Pethidine)

Synthetic opioid similar to morphine with the following differences:

- ! **Better absorbed** orally and has **greater bioavailability** than morphine.
- ! The **analgesic** potency is **10%** of morphine.
- ! It is used as analgesic alternative to morphine in the following cases:
 - ! **Inferior MI** because in this case the patient usually has bradycardia.
 - ! It is preferred than morphine **during labor** because it has short duration and doesn't prolong labor (little or no spasmogenic action).

Adverse effects

- ! It causes **RC depression** and **addiction liability** but weaker than morphine.
- ! It causes **histamine release** and **bronchoconstriction**
- ! It has weak **atropine-like actions** → dry mouth, tachycardia, etc.
- ! It has **No** GIT, **No** antitussive, and **No** vagal stimulant effects.

	Morphine	Meperidine
Chemistry	Natural opioid	Synthetic opioid
Bioavailability	25%	Greater (50%)
Analgesic effect	Strong	Weak (10% of morphine)
Spasmogenic effects	Present	Absent
Autonomic effects	Vagal stimulation	Atropine-like action
Uses	Mention its 4 uses	Analgesic only

3. Fentanyl and alfentanil

- ! They are synthetic derivatives of meperidine. They are the **most potent** and the **shortest duration** opioid agonists.
- ! They are used as analgesic in **severe pain** (as long-acting transdermal skin patch). A transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily.

4. Methadone

Synthetic opioid similar to morphine with the following differences:

- ! The analgesic effect is **equal** to morphine.
- ! Has **longer duration** of action than morphine ($t_{1/2}$ is 24h).

Uses:

- ! As analgesic.
- ! **Treatment of chronic opiate addiction and heroin users:**
 - ! It can satisfy the craving needs of the patient with less addictive features.
 - ! Methadone withdrawal symptoms are less severe than other opioids.

5. Tramadol

- ! It has two different mechanisms. First, it binds to the **μ -opioid receptor**. Second, it inhibits the reuptake of serotonin and NA.
- ! **Uses:** as **analgesic** for moderate to severe pain, especially musculoskeletal pain
- ! **Adverse effects:** It has relatively fewer side-effects than most opioids (but **addiction** can occur). It may induce **seizures** in epileptic patients.

6. Diphenoxylate and loperamide (see chapter 8)

!

SEMISYNTHETIC MIXED AGONISTS-ANTAGONISTS (partial agonists)**Nalorphine – Nalbuphine – Pentazocin – Butorphanol**

- ! All these drugs have **agonist** activity on κ receptors and **antagonist** or **partial agonist** activity on μ receptors.
- ! They are used as **analgesics** alternative to morphine but their analgesic activity and respiratory depression are **less marked** than morphine.
- ! All these drugs (except nalbuphine) increase systemic and pulmonary vascular resistance leading to $\uparrow$ **cardiac load**, so they are, thus, **contraindicated to relieve pain of acute MI**.
- ! They can lead to **withdrawal symptoms** if given to opioid **addict** patients.

N.B.

For opioid analgesics, **potency** of the analgesic should be considered **more important** than efficacy because respiratory depression is dose-dependent.

SYNTHETIC FULL ANTAGONISTS**Naloxone and naltrexone**

- ! They are competitive **blockers of all** opioid receptors.
- ! Naloxone is given **i.v.** and has short $t_{1/2}$ (~1h) but naltrexone could be administered orally and has longer $t_{1/2}$ (~48 h).
- ! They can precipitate **severe withdrawal** syndrome if administered to opioid-addict patient.

Therapeutic uses of naloxone

- ! **Acute opioid toxicity:** given i.v., the adverse respiratory and CVS effects of opioids are reversed within 1-2 min and lasts for 1-2 hrs.
- ! It is given during labor to mothers who received opioids **to prevent neonatal respiratory depression**, or it can be given to the neonate via the umbilical vein.

■ NON-OPIOID ANALGESICS

1. Acetaminophen (Paracetamol)

Pharmacokinetics

- ! Absorption is complete and rapid from GIT with peak levels after 30 min.
- ! Metabolism: liver by conjugation. At high doses, it is converted into **toxic metabolite** (*N-acetyl-benzoquinone*) that is responsible for hepatotoxicity.
- ! Excretion: mainly renal.

Mechanism & Pharmacological effects

- ! It is a **selective Cox III inhibitor** so it inhibits PGs synthesis in the brain only and has **analgesic & antipyretic** actions **without** effects on the enzymes that are responsible for synthesis of peripheral PGs and so it has **no anti-inflammatory action**.
- ! It has **little or No** effects on the CVS, GIT, respiratory or platelet functions.

Therapeutic uses

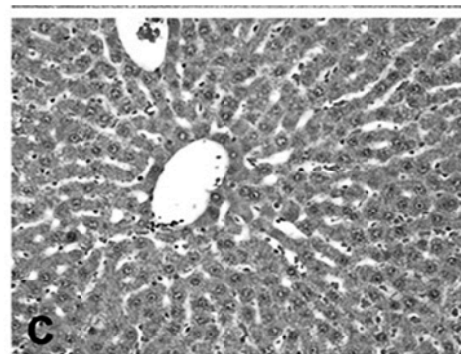
As analgesic and antipyretic **when aspirin is contraindicated** (e.g. patients with peptic ulcer, hemophilia, etc). Acetaminophen can be administered in **pregnancy** with greater safety than aspirin.

Adverse effects

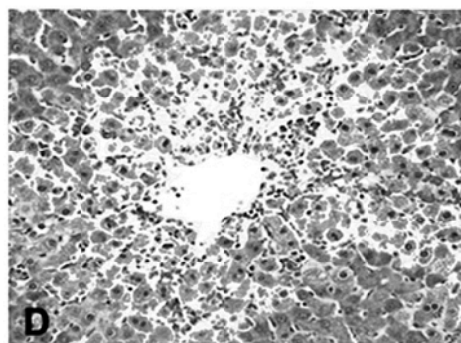
- ! **At therapeutic doses:** acetaminophen is well-tolerated but may cause:
 - ! Skin rash & drug fever (as allergic reactions).
 - ! Long term use may lead to renal failure.
- ! **In toxic doses:** **dose-dependent hepatotoxicity** (centrilobular necrosis): It occurs with large doses (about **15 gm** in adults and **4 gm** in children)

Mechanism of hepatotoxicity

- ! Acetaminophen is converted to toxic metabolite (*N-acetyl-benzoquinone*) in the liver that needs detoxification by reduced **glutathione**.



Normal liver section



Hepatic cell necrosis
caused by acetaminophen toxicity

- ❗ When glutathione store is depleted, the toxic metabolite binds covalently to cellular proteins producing hepatocellular damage.
- ❗ Clinical symptoms of toxicity (e.g. vomiting) occur within 24 hrs but signs of hepatic damage (e.g. jaundice) occur after 2-6 days.

Treatment of toxicity

- ❗ Gastric lavage with activated charcoal.
- ❗ **Sulfhydryl donors (acetylcysteine)** to restore hepatic glutathione. It must be started within **8** hours of toxicity.
- ❗ **Hemodialysis**: better within the first 12 hrs after ingestion.

The 20 hour IV protocol of acetylcysteine

- ! First, administer an initial loading dose of **150 mg/kg IV** over 60 minutes.
- ! Next, administer **12.5 mg /kg per hour IV** for 4 hours.
- ! Finally, administer **6.25 mg /kg per hour IV** for 16 hours.

Nefopam (Acupan)

Mechanism and effects

- ❗ It is a **central analgesic** without antipyretic or anti-inflammatory activity. It is more potent than NSAIDs.
- ❗ The analgesic mechanism is **unclear** but may be related to inhibition of many transmitters reuptake or blocking central voltage-gated Na⁺ channels.
- ❗ Nefopam is also used to combat severe **hiccups**.

Adverse effects

- ! Precipitation of epileptic convulsions in patients with epilepsy.
- ! Weak atropine-like actions: dry mouth, urine retention, etc.

Contraindications: history of epilepsy

Dipyrone (Novalgin)

Mechanism and effects

- ❗ **Analgesic antipyretic** that is more potent than aspirin. It has no anti-inflammatory action.
- ❗ Its use was restricted in many countries because of risk of **agranulocytosis** which is not dose-dependent.

Adverse effects

- ! Agranulocytosis: reversible in 10 days after stoppage of the drug but lethal in 10% of cases.
- ! Allergic reactions and anaphylaxis.
- ! It can trigger bronchoconstriction in patients with **Asthma**.

Part 3: Sedative-Hypnotic Drugs

- These are drugs that cause sedation and relieve anxiety (anxiolytics), or can induce sleep. They are used primarily to treat anxiety and insomnia.
- Because there is considerable chemical variation within the group, these drugs are classified based on their clinical uses rather than on chemical structure.

Drugs with main use as sedatives:

- Benzodiazepines
- Buspirone

Drugs with main use as hypnotics:

- Barbiturates
- Ramelteon
- Chloral hydrate

1. Benzodiazepines

- Benzodiazepines (BDZ) have a **great margin of safety** over previously available sedative–hypnotic agents (e.g., barbiturates).
- Most benzodiazepines have qualitatively similar therapeutic actions but differ in their relative lipid solubility, metabolism, and elimination half-life.

Classification

- **Short acting ($t_{1/2} < 5\text{h}$):** midazolam – triazolam
- **Intermediate acting ($t_{1/2}$ 5–24 h):** alprazolam – lorazepam – clonazepam
- **Long acting ($t_{1/2} > 24\text{h}$):** diazepam – clorazepate – flurazepam

Pharmacokinetics

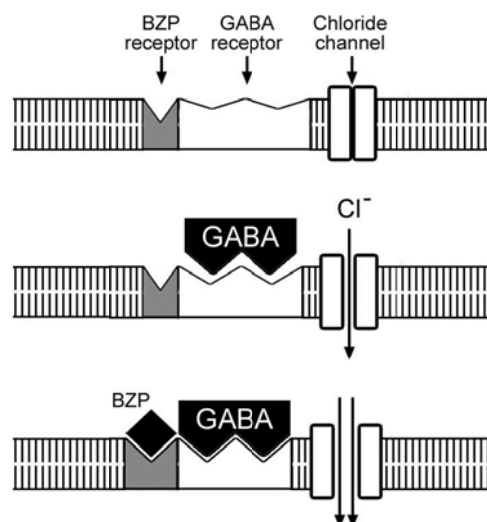
- Oral absorption is good and rapid. Highly lipid soluble drugs (e.g., midazolam, triazolam) have fast onset of action.
- Long acting drugs are metabolized by **oxidation** (CYP450) into **active** metabolites giving them long duration of action (e.g. diazepam).
- Short acting drugs are metabolized by **conjugation** into **inactive** metabolites followed by renal clearance.
- In a patient with liver dysfunction, **lorazepam** and **oxazepam**, which are metabolized **extrahepatically**, are less likely to cause excessive CNS depression.

Mechanism of action

- BDZ have special receptors in the CNS and peripheral tissue.
- By acting on these receptors, BDZ cause allosteric modulation of GABA action on GABA_A receptors resulting in ↑ Cl[−] conductance and hyperpolarization.
- Six BDZ receptor subtypes have been discovered; **subtype 1** is the most widely expressed and mediates most of the effects of BDZ.

Pharmacological effects

- **Reduction of anxiety** (anxiolytic effect) in small dose producing calming effect in man & taming effect in animals
- **Hypnotic effect:** in higher doses.
- **Central skeletal muscle relaxation:** this is useful since increased ms tone is a common feature in anxiety and may lead to headache and ms pain.
- **Anticonvulsant effect.**
- **Acute amnesia:** after high doses.



Therapeutic uses

- **Anxiety disorders: e.g.**
 - ! Acute anxiety.
 - ! Generalized anxiety disorders (GAD).
 - ! Social phobia (social anxiety disorder).

BDZ are effective for the **short-term** management (<6 weeks) of these anxiety disorders (*selective serotonin-reuptake inhibitors [SSRIs; see later]* are now considered the first-line choices for the **long-term** management of anxiety disorders).

- **Insomnia:** BDZ that have a rapid onset and sufficient duration are widely used (e.g., temazepam).
- **Anticonvulsants: Lorazepam** (and **diazepam**), given by i.v. may be used for initial treatment of status epilepticus and drug-induced seizures. The development of tolerance precludes their long-term use.
- **Short surgical procedures:** Shorter acting benzodiazepines (e.g., **midazolam**) are preferred before during surgery or endoscopy.
- **Preanesthetic medication.**

Adverse effects

- ! **Sedation, memory disturbance, dull attention** (interfere with learning ability).
- ! **Tolerance and physical dependence** (treated by gradual withdrawal).
- ! **Rebound insomnia** after discontinuation.
- ! **Hangover:** a state of psychomotor depression occurs in the following day after the use of long acting drugs (i.e. residual effect).
- ! **Apnea** after rapid i.v. injection (*flumazenil is the antidote*)

Flumazenil

Flumazenil is a **competitive antagonist** at benzodiazepine receptors. It is used to prevent or reverse the CNS effects from benzodiazepine overdose or to speed recovery from the effects of benzodiazepines used in anesthetic and diagnostic procedures.

Precautions: avoid BDZ use in the following conditions:

- ! Drivers and machine workers needing high attention.
- ! Pregnancy and lactation: fetal muscular hypotonia and impaired suckling may occur.
- ! Hepatic encephalopathy.
- ! Respiratory depression.
- ! Combination with other CNS depressants e.g. alcohol.

2. Buspirone

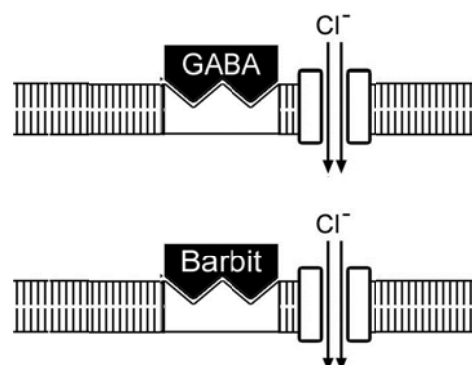
- ! It is partial agonist on **5-HT_{1A}** receptors in the midbrain.
- ! Selective anxiolytic without hypnotic or muscle relaxant effect.
- ! It suppresses anxiety after a long delay (2 or more weeks).
- ! It is the anxiolytic of choice in the elderly.
- ! No liability for drug dependence.
- ! **Adverse effects** include dizziness, headache, tachycardia and nervousness.

3. Barbiturates

- ! Barbiturates have been largely **replaced** by the more safe benzodiazepines and the SSRIs, for the treatment of anxiety and sleep disorders.
- ! **Phenobarbital** is a long acting barbiturate (~6-8h) used as an **anticonvulsant**; **thiopental** is ultrashort agent (~15-20 min) used as an i.v. **general anesthetic**.

Mechanism of action

- ! Barbiturates have either GABA-like action OR enhance the effects of GABA at GABA_A receptors resulting in ↑ Cl⁻ conductance and hyperpolarization.
- ! The action of barbiturates is non-selective i.e. increasing the dose of barbiturates → generalized CNS and **medullary depression**.

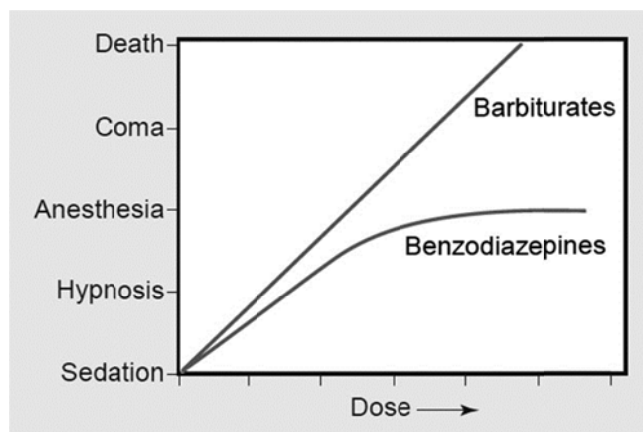


Therapeutic uses

- ! As sedative and hypnotics in the treatment of insomnia. They are largely replaced by benzodiazepines.
- ! **Phenobarbital** is used in the treatment of grand mal epilepsy.
- ! **Phenobarbital** is microsomal enzyme inducer. It is used in the treatment of hyperbilirubinaemia in neonates (physiological jaundice) to activate liver enzymes (glucuronyl transferase) and fasten metabolism of bilirubin.
- ! **Thiopental** is used as short i.v. anaesthetic in short procedures.

Adverse effects

- ! Physical dependence.
- ! **Respiratory** and **myocardial depression** (in acute toxicity)
- ! Phenobarbital is hepatic microsomal enzyme inducer.
- ! Phenobarbital may increase **porphyrin** synthesis. It can precipitate the symptoms of acute intermittent porphyria.



4. Ramelteon

- ! Ramelteon is prescribed for patients who have difficulty falling asleep. It is a selective agonist at **melatonin MT1** and **MT2** receptors that are involved in the promotion of sleep and that maintain the normal circadian rhythm.
- ! **Adverse effects** include dizziness and fatigue.

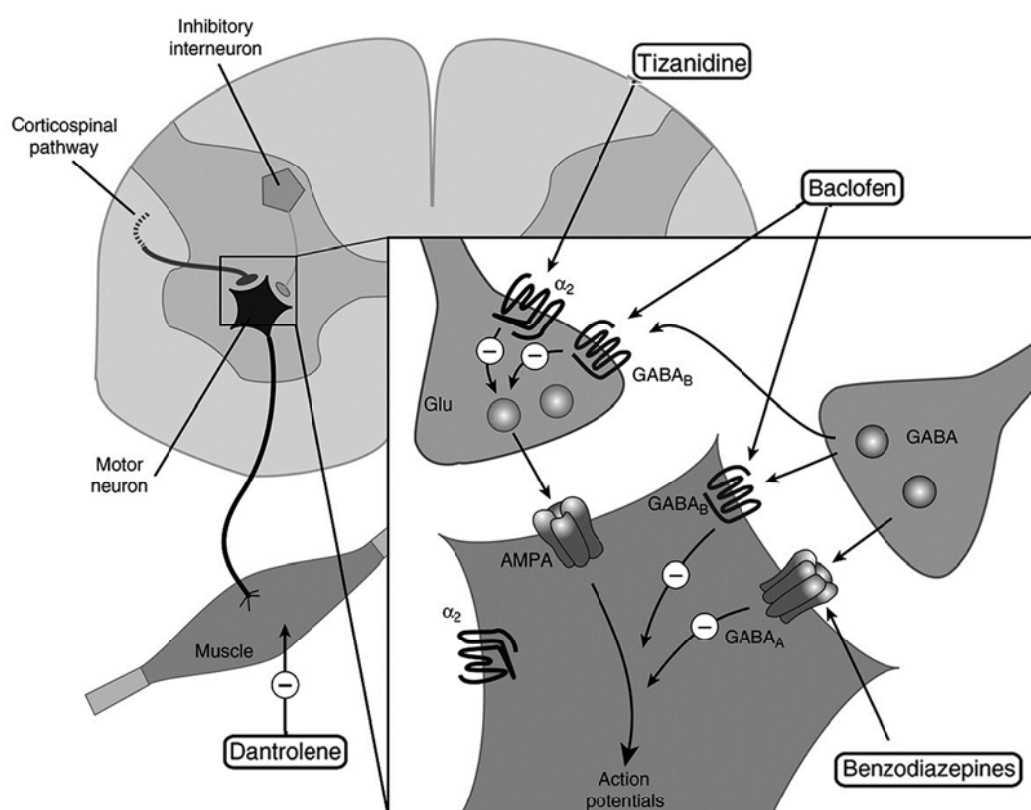
5. Chloral hydrate

- ! It is one of the oldest hypnotic drugs. It is an alcohol derivative.
- ! It produces hypnosis in 30 min and last for 6 hrs.
- ! It is used mainly as a hypnotic in children and elderly before short surgical or dental procedures but its use now is **very limited**.

Part 4: Skeletal Muscle Relaxants

Classification

- **Drugs act on brain higher centers:** e.g. carisoprodol, benzodiazepines, general anesthetics, anticonvulsant drugs, and antiparkinsonian drugs (see later).
- **Drugs act on neuronal transmission in the spinal cord:** e.g. tizanidine and baclofen.
- **Drugs act on the neuromuscular junction:** e.g. neuromuscular blockers and botulinum toxin.
- **Drugs act directly on the muscle contractile mechanisms:** e.g. dantrolene.



Sites of spasmolytic action of benzodiazepines ($GABA_A$), baclofen ($GABA_B$), tizanidine (α_2) in the spinal cord and dantrolene (skeletal muscle). AMPA, amino-hydroxyl-methyl-isoxazole-propionic acid, a ligand for a glutamate receptor subtype; Glu, glutamatergic neuron.

1. Carisoprodol

- Carisoprodol – (and its metabolite **mebrobamate**) – are centrally acting skeletal muscle relaxants. Their mechanism is unclear but seems to be similar to **barbiturates**. They bind to $GABA_A$ receptors in the CNS leading to antianxiety, anticonvulsant, and skeletal muscle relaxation.
- The drug and its metabolite have **abuse** potential, so some countries limit its use.

2. Baclofen

- ! Baclofen is a GABA derivative that selectively stimulates **GABA_B** receptors in the spinal cord → ↓ release of excitatory transmitters.
- ! It is used as a skeletal muscle relaxant in neurological spastic conditions.

3. Tizanidine

- ! Tizanidine is a centrally acting α₂ agonist with greater effect on presynaptic α₂ in the **spinal cord**, so it inhibits neurotransmission and reduces muscle spasm with minimal effect on blood pressure.

4. Dantrolene

- ! Dantrolene inhibits Ca²⁺ release from the sarcoplasmic reticulum of skeletal ms cells. It acts directly on the muscle contractile mechanisms.
- ! It is used for emergency management of **malignant hyperthermia** (1 mg/kg i.v.)

5. Botulinum toxin (Botox)

- ! Botulinum toxin is a neurotoxic protein produced by the bacterium *Clostridium botulinum*. It inhibits the release of ACh from motor nerve terminals leading to skeletal muscle paralysis.
- ! It is injected locally to treat local muscle spasm e.g. in cervical dystonia (spasmodic torticollis), and blepharospasm (uncontrolled muscle contraction or twitch of the eyelid). It is also used for cosmetic reduction of facial wrinkles.

6. Neuromuscular blockers: see ANS.

Therapeutic uses of skeletal muscle relaxants

- ! Neurological spastic conditions such as multiple sclerosis, back pain, and spine injuries.
- ! Dantrolene is used for emergency management of malignant hyperthermia.
- ! Botulinum toxin is injected locally to relieve blepharospasm and for cosmetic reduction of facial wrinkles.
- ! Neuromuscular blockers are used to produce muscle relaxation during surgical procedures.

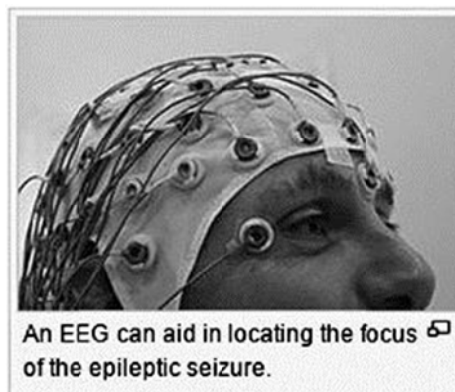
Mephensin

- ! Mephensin is a selective inhibitor of polysynaptic excitation of the spinal motor neurons through stimulation of **glycine receptors** in the spinal cord.
- ! It was historically used as antidote for treatment of **strychnine poisoning** but its clinical use now is **very limited** because of **serious side effects** including respiratory depression and hemolysis.

Part 5: Antiepileptic Drugs

Basic information

- ! **Epilepsy**, a chronic disease, occurs in approximately 1% of the population. The cause of most cases of epilepsy is unknown, although some people develop epilepsy as the result of brain injury, stroke, brain tumor, and drug toxicity. Genetic mutations are linked to a small proportion of the disease.
- ! Epileptic seizures result from excessive and abnormal cortical nerve cell activity in the brain.
- ! The diagnosis typically involves ruling out other conditions that cause similar neurological symptoms. This may be confirmed by brain imaging and electroencephalogram (EEG) but a normal test does not exclude the condition.
- ! Antiepileptic drugs (AEDs) are effective for about 80% of these patients. Lifelong treatment may be necessary.
- ! It may take weeks to establish adequate drug plasma levels and to determine the adequacy of therapeutic improvement. **Lack of compliance** is responsible for many treatment failures.
- ! AEDs are **most effective** and have the **least adverse effects** when they are used as **monotherapy**.
- ! Addition or withdrawal of any drug should be **gradual**, because seizures may occur on withdrawal.
- ! Some AEDs are **teratogenic**; this may call for the reduction or termination of therapy during pregnancy.



Classification of epilepsies:

Epilepsies are characterized by either focal or generalized abnormal neuronal discharges. Drug selection, based on seizure classification, is listed below in the order of general choice.

Partial seizures	Simple partial	Localized discharge; consciousness is not altered.	1.!Carbamazepine 2.!Lamotrigine 3.!Valproic acid
	Complex partial	Localized discharge that becomes widespread; accompanied by loss of consciousness.	

Generalized seizures	Tonic-clonic (grand mal)	Dramatic convulsions with either jerking of the extremities or rigidity of the entire body; accompanied by loss of consciousness.	1.!Valproic acid 2.!Lamotrigine 3.!Carbamazepine
	Absence (petit mal)	Sudden onset of altered consciousness that lasts 10–45 seconds, with up to hundreds of seizures per day; begins in childhood or adolescence.	1.!Ethosuximide 2.!Valproic acid 3.!Clonazepam
	Myoclonic syndromes	Lightning-like jerks of one or more extremities occurring singly or in bursts of up to a hundred; accompanied by alteration of consciousness.	1.!Valproic acid 2.!Lamotrigine

■! **Status epilepticus:**

Prolonged seizure (>20 min) of any of the types previously described; the most common is life-threatening generalized tonic-clonic status epilepticus.

1. Diphenylhydantoin (Phenytoin)

Mechanism: it blocks Na^+ , K^+ and Ca^{2+} channels in the **brain** (and **heart**) leading to decrease propagation of abnormal impulses. It produces some degree of drowsiness.

Therapeutic uses

- ! Partial and generalized seizures
- ! Status epilepticus: it should be given **i.v.** in the form of **fosphenytoin** (prodrug).
- ! Ventricular arrhythmia.

Adverse effects

- ! CNS: Nystagmus, diplopia, ataxia.
- ! Hepatotoxicity.
- ! Microsomal enzyme induction.
- ! Bone marrow depression & Megaloblastic anemia (due to ↓ folic acid).
- ! Teratogenicity: craniofacial abnormalities.
- ! Gingival hyperplasia: 2ry to increased expression of platelet derived growth factor (PDGF).
- ! Lymphadenopathy.

Any antiepileptic drug must have one or more of the **following mechanisms:**

1. **Decrease brain excitability** through blocking Na^+ or Ca^{2+} influx.
2. **Enhancement of GABA action.**
3. **Inhibition of excitatory transmitters** (aspartate and glutamate).

2. Carbamazepine (Tegretol)

Mechanism: it blocks Na^+ channels & ↓ excitability of cortical neurons.

Therapeutic uses

- ! Partial and generalized seizures (grand mal epilepsy).
- ! Trigeminal neuralgia.

Adverse effects

- ! CNS: diplopia & ataxia.
- ! Hepatotoxicity.
- ! Microsomal enzyme induction.
- ! Bone marrow depression.
- ! Congestive heart failure (CHF).

3. Valproic acid (Depakene)

Mechanism: it activates *glutamic acid decarboxylase* enzyme → ↑ GABA synthesis.

Therapeutic uses: all types of epilepsy.

Adverse effects

- ! Sedation
- ! Microsomal enzyme inhibition
- ! Teratogenicity.
- ! Alopecia
- ! Pancreatitis

4. Ethosuximide (Zarontin)

Mechanism: blocks neuronal voltage-dependent Ca^{2+} and Na^+ channels.

Therapeutic uses: absence seizures (petit mal epilepsy) **(1st choice)**.

Adverse effects

- ! Sedation
- ! Vomiting
- ! Leucopenia

5. Benzodiazepines: Clonazepam and diazepam

Mechanism: allosteric modulation of GABA action to facilitate its effects.

Therapeutic uses

- ! Clonazepam: petit mal epilepsy.
- ! Diazepam: status epilepticus.

Adverse effects: see before.

6. Barbiturates: Phenobarbitone

Mechanism: enhancement of GABA-mediated inhibition of glutamate excitation.

Therapeutic uses: grand mal epilepsy (contraindicated in petit mal epilepsy).

Adverse effects: see before.

NEWER ANTIEPILEPTIC DRUGS

1. Felbamate**Mechanism**

- ! Block glycine site on the N-methyl-D-aspartate (NMDA) receptors.
- ! Block voltage-dependent Ca^{2+} & Na^{+} channels.

Therapeutic uses: wide variety of partial and generalized seizures.

Adverse effects

- ! Hepatotoxicity
- ! Microsomal enzyme induction.
- ! Bone marrow depression.

2. Lamotrigine**Mechanism**

- ! Decreases glutamate and aspartate, which are excitatory neurotransmitters
- ! Blocks sodium channels and high voltage-dependent calcium channels leading to ↓ excitability.

Therapeutic uses: wide variety of partial and generalized seizures and typical absence seizures in children and adults.

3. Gabapentin

Mechanism: unknown but may interfere with voltage-dependent Ca^{2+} channels

Therapeutic uses: as adjuvant therapy in wide variety of partial and generalized seizures.

Adverse effects: headache, nystagmus, dizziness & ataxia.

4. Tiagabine

Potent and specific inhibitor of GABA uptake into glial and other neurons. Thus, it enhances the action of GABA by decreasing its removal from the synaptic space.

Precautions during antiepileptic therapy

- ! Proper **choice** of the antiepileptic drug according to type of epilepsy.
- ! Start with **single drug** and if fails, substitute it or add another drug.
- ! **Dose** of the drug is adjusted according to:
 - *Plasma concentration of the drug.*
 - *Patient's response.*
- ! Therapy is given for 2-3 years then withdrawn **gradually**.

Drugs used for treatment of Status epilepticus

Diazepam (drug of choice) 10 mg i.v. or 500 µg/kg **rectal** (in children) **OR:**

- ! Fosphenytoin: 100 mg i.v.
- ! Phenobarbitone: 200 mg i.v.
- ! In severe cases:
 - a)! Thiopental i.v.
 - b)! Artificial respiration.

Part 6: Antidepressant Drugs

Basic information

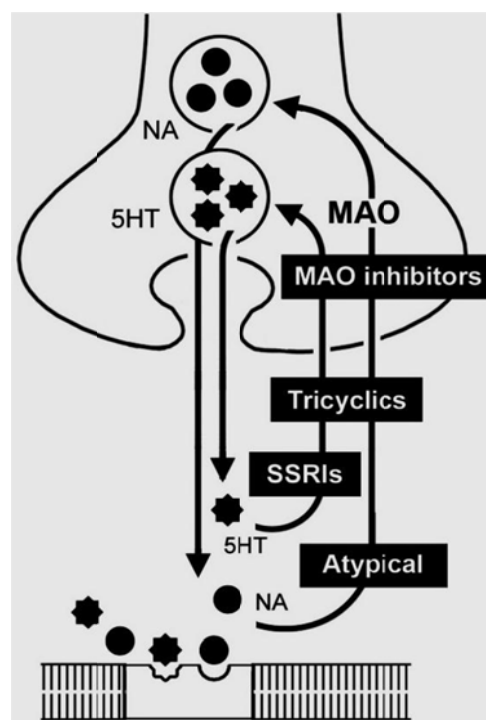
- ! Depression is a disorder of mood rather than disturbance of thought or cognition. It is postulated that depression is due to **deficiency** of **NA** and/or **5-HT** in the CNS while **mania** results from functional **excess**. Psychic depression is characterized by both **emotional** and **biological** symptoms.
- ! Recent studies suggest that overactivity of post-synaptic **5-HT_{2A}** receptors in some brain areas is involved in the pathogenesis of depression and psychosis.
- ! **Unipolar depression (major depressive disorder)**: more common, may be **reactive** (70%) or **endogenous** (25%), characterized by low mood and loss of interest or pleasure in normally enjoyable activities.
- ! **Bipolar depression (manic-depressive disorder)**: less common, characterized by oscillating periods of depression and mania. There is strong hereditary origin.
- ! The therapeutic effect occurs only after **2-3 weeks** of drug administration and is more closely associated with adaptive changes in neuronal receptors and brain neurotropic factors.

Classification of antidepressant drugs:

- ! **Tricyclic antidepressants (TCA)** e.g. imipramine, amitriptyline.
- ! **Selective serotonin reuptake inhibitors (SSRI)**: e.g. fluoxetine, sertraline.
- ! **Atypical heterocyclic antidepressants**: e.g. maprotiline, trazodone.
- ! **Monoamine oxidase inhibitors (MAOI)** e.g. clorgyline, selegiline.



The sad woman by Edith Wilkinson



1. Tricyclic antidepressants (TCA)

Imipramine, Desipramine, Clomipramine, Amitriptyline, Nortriptyline

Pharmacokinetics

- ! They are well absorbed after oral administration. They have **large Vd**.
- ! Most TCA have **long $t_{1/2}$** because they are metabolized into active metabolites and undergo enterohepatic cycling.

Mechanism of action: (*inhibition of the amine pump*)

- ! TCA inhibit neuronal reuptake of both 5-HT & NA leading to their accumulation in synaptic spaces and the brain tissue.
- ! It has been suggested that improvement of the **emotional** symptoms is related to enhancement of **5-HT** transmission while improvement of **biological** symptoms is related to enhancement of **NA** transmission.
- ! Elevation of mood in depressed patients occurs after 2-3 weeks

Therapeutic uses

- ! Major depressive disorder.
- ! Nocturnal enuresis in children (**imipramine**).
- ! Chronic pain syndromes, neuropathic pain, and prophylaxis of migraine (unclear mechanism).

Adverse effects

- ! **Sedation** is common at the start of therapy but tolerance develops later. It may be due to antagonism with histamine H1 and/or muscarinic receptors.
- ! **CNS troubles:** memory dysfunction, agitation, seizures, and suicidal thoughts.
- ! **Atropine-like action:** very common - dry mouth, blurred vision, urine retention, etc.
- ! **Orthostatic (postural) hypotension:** due to peripheral **α_1** receptor blockade.
- ! Cardiac **arrhythmias:** tachycardia, widening of QRS, and $\uparrow$ QT interval.
- ! **Hepatotoxicity:** cholestatic hepatitis.
- ! Weight gain.

Drug interactions

- ! Toxic synergism with **MAOIs** and **SSRIs** (irritability and convulsions).
- ! TCA antagonize the antihypertensive effect of **clonidine** and **methyldopa**.
- ! TCA have additive **anticholinergic effect** with other drugs having anticholinergic activity.

TCA overdose

- ! Metabolic acidosis
- ! Atropine-like effects
- ! Cardiac arrhythmia

Management

- ! IV NaHCO₃ (1st step).
- ! IV lidocaine
- ! Dialysis is ineffective

2. Selective serotonin reuptake inhibitors (SSRIs)**Fluoxetine, Paroxetine, Sertraline, Citalopram, Escitalopram**

- ! They are the most commonly prescribed antidepressants due to their limited toxicity. They are also used for some other psychiatric disorders.
- ! **Sertraline** is the preferred antidepressant following **myocardial infarction** as there is more evidence for its safe use in this situation than other antidepressants.
- ! When stopping an SSRI the dose should be **gradually** reduced over a 4 week period, this reduces the risk of relapse.

Mechanism of action

- ! They selectively block 5HT reuptake leading to accumulation of 5-HT in brain tissue.
- ! Their effect appears after 2-3 weeks like other antidepressants.

Therapeutic uses

- ! Major depressive disorder.
- ! Obsessive-compulsive disorder (OCD).
- ! Anxiety disorders (generalized anxiety disorder, social phobia, panic disorder).

Adverse effects

- ! **GIT irritation** is the most common side effect. A **proton pump inhibitor** should be prescribed if a patient is also taking a NSAID to avoid GIT bleeding.
- ! **Sedation** or **insomnia** at the start of therapy but tolerance develops later.
- ! **Muscle cramps** and twitches.
- ! **Sexual dysfunction** in up to 40% of patients – the main cause of noncompliance.
- ! Dangerous “**serotonin reaction**” may occur if given with **MAOIs** or **TCA** (hyperthermia, muscle rigidity, cardiovascular collapse).

3. Atypical antidepressants

The pharmacological properties of atypical heterocyclic antidepressant agents are similar to those of TCAs.

Mechanism of action

- ! **Trazodone:** blocks mainly **5HT_{2A}** receptors in addition to **H₁**, and **α₁** receptors. It is highly sedating and can cause postural hypotension.
- ! **Mertazapine:** blocks mainly **5HT_{2A}** receptors in addition to **H₁**, and **α₂** receptors. It causes weight gain.
- ! **Maprotiline:** selective blocker of **NA reuptake**. It is highly sedating and can cause seizures.

4. Monoamine oxidase inhibitors (MAOIs)

Clorgyline, Selegiline, Pargyline, Moclobemide

Mechanism of action

- ! They inhibit MAO enzyme leading to accumulation of active monoamines (NA, 5-HT, dopamine) in neuronal tissue.
- ! Most MAOIs are **irreversible inhibitors**. Recovery of MAO takes several weeks. **Moclobemide** is a **reversible** inhibitor.

Therapeutic uses

- ! **Major depression:** they are **not** used as a first-line, but usually reserved as a last line after other classes of drugs have failed.
- ! **Selegiline** (selective MAO-B inhibitor) is used for treatment of **Parkinsonism** (see later).

Adverse effects

- ! **CNS stimulation:** irritability, insomnia, tremors, hyperthermia, convulsions
- ! **Hepatotoxicity:** occurs more with the old members.
- ! **Orthostatic (postural) hypotension** and **sexual dysfunction**.

Interactions

■! Drug-drug interactions:

- ! Toxic synergism with **tricyclic antidepressants** and **SSRIs**.
- ! Potentiation of **sympathomimetics** (including cold remedies & nasal decongestants).

■! Drug-food interactions: Hypertensive crisis (cheese reaction):

- ! **Tyramine** is an indirect sympathomimetic present in some food and normally metabolized by MAO-A in the liver.
- ! When the patient takes MAO-A inhibitor or non-selective MAOIs, severe hypertension can occur after eating tyramine-rich food *e.g. fermented cheese, yogurt, beer, herrings*.
- ! Treatment: by giving combined $\alpha + \beta$ blockers (prazosin + propranolol). !

!

!

N.B. There are 2 isotypes of MAO enzyme:

MAO-A enzyme

- ! Present in the cytoplasm of neurons (CNS) and peripheral tissues (e.g. liver).
- ! It acts non-specifically on NA, 5-HT, and dopamine.
- ! **Clorgyline** is a specific inhibitor.

MAO-B enzyme

- ! Present mainly in the CNS and acts more on dopamine.
- ! **Selegiline** is a specific inhibitor.

Part 7:**Mood Stabilizing Drugs (treatment of mania and bipolar disorder)**

- ❗ **Sodium valproate** is the only specific antimanic agent and is the treatment of choice in the **acute stages**.
- ❗ **Lithium** is the drug of choice for **long-term** treatment to prevent relapse.

Lithium carbonate**Mechanism of action**

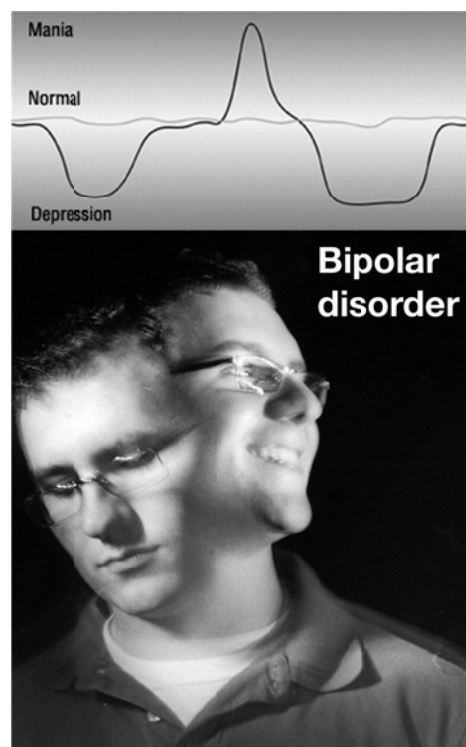
- ❗ It ↓ cAMP in neuronal cells and ↓ NA release → ↓ neuronal firing.
- ❗ It inhibits many metabolic processes in the nerve tissue.

Therapeutic uses

- ❗ Treatment of **mania** (*valproate is the 1st choice*).
- ❗ Treatment of **manic-depressive disorder** (bipolar depression). It is given in the manic phase while TCA or SSRIs are given in the depressive phase.

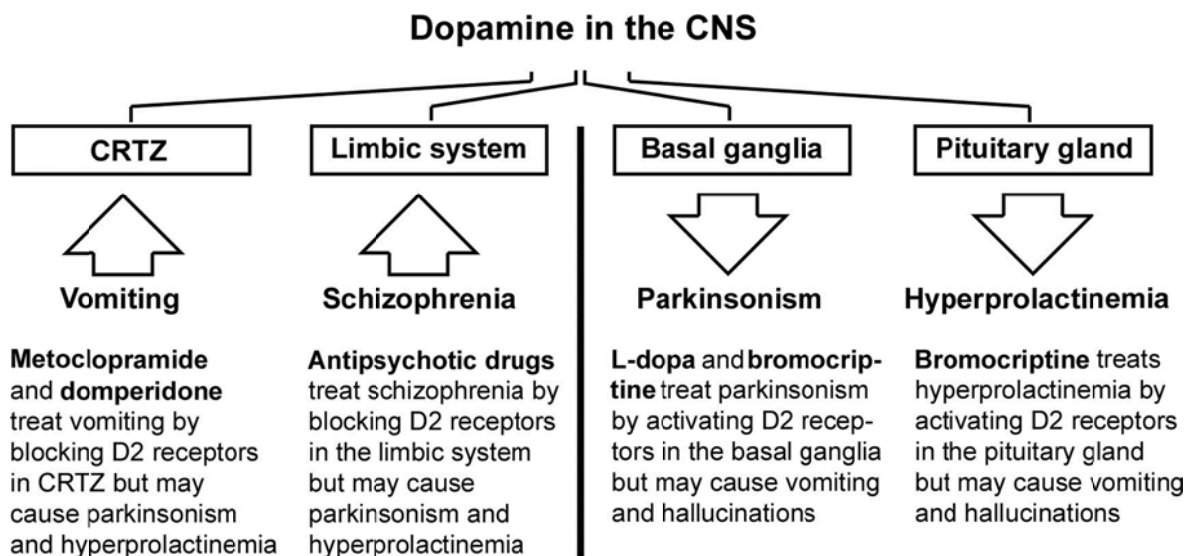
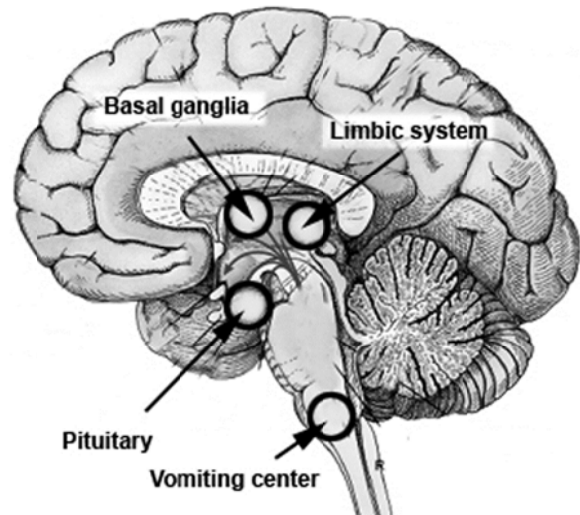
Adverse effects

- ❗ Lithium has a very narrow therapeutic index, monitoring of plasma levels is essential.
- ❗ It has long plasma half-life being excreted entirely by the kidneys.
- ❗ Toxicity may be precipitated by dehydration, renal failure, diuretics (especially thiazide) or ACE inhibitors.
- ! Anorexia, nausea, vomiting and diarrhea.
- ! Nephrogenic **diabetes insipidus** leading to polyurea and thirst.
- ! Hypotension and cardiac **arrhythmia**.
- ! **Thyroid** dysfunction
- ! **Fine tremors** (coarse tremors are seen with toxic levels).
- ! Teratogenicity.



Part 8: Antipsychotic Drugs (Neuroleptics)**Basic information**

Central dopaminergic pathways
and drugs affecting them:



- ! The term “**psychosis**” denotes a variety of mental disorders. **Schizophrenia** is a particular kind of psychosis characterized by abnormal social behavior and failure to recognize what is real.
- ! Common “**positive**” symptoms include false beliefs (delusions), unclear or confused thinking, and auditory hallucinations. “**Negative**” symptoms include reduced social engagement, blunted emotions, and inactivity.
- ! It is suggested that **central dopamine overactivity** and **5HT_{2A} receptors** play important role in the pathogenesis.



Self-portrait of a person with schizophrenia, representing that individual's perception of the distorted experience of reality in the disorder

Classification of drugs■! **Typical (classic; old) neuroleptics:**

- ! **Phenothiazines:** chlorpromazine, promethazine.
- ! **Butyrophenones:** haloperidol, droperidol.
- ! **Thioxanthenes:** thiothixene, chlorprothixene.

■! **Atypical (newer) neuroleptics:**

- ! **Risperidone– Olanzapine – Clozapine**

Mechanism and therapeutic action

- ! The **typical antipsychotic** drugs primarily block central **D₂** receptors in the mesolimbic and mesocortical areas of the CNS leading to ↓ hallucinations and delusions but can lead to serious **extrapyramidal** adverse effects.
- ! The **atypical antipsychotic** drugs combine between blockade of **D₂** (to a lesser degree) and **5-HT_{2A}** receptors, so they have **fewer extrapyramidal** side effects.
- ! The **typical antipsychotic** drugs have greater effect on the control of **positive** symptoms (hallucinations and thought disturbances), while **atypical** drugs have greater effect on **negative** symptoms (social withdrawal).

Therapeutic uses■! **Schizophrenia & mania (typical and atypical antipsychotics):**

- ! Antipsychotic drugs produce an **immediate quieting action**. However, their antipsychotic effects typically take **longer** time to occur (a week or more).

■! **Other therapeutic uses of typical antipsychotics:**

- ! **Chlorpromazine** is sometimes used to relieve **intractable hiccough** and as anaesthetic adjuvant in certain operations to produce **hypothermia**.
- ! **Severe nausea or vomiting** associated with, e.g., radiation treatment and cancer chemotherapy. Typical antipsychotic agents have strong antiemetic activity due to D₂-receptor blockade in the chemoreceptor trigger zone (CTZ) of the medulla. The most commonly used are the phenothiazines **chlorpromazine** and **promethazine**

Adverse effects■! **CNS:**■! **Extrapyramidal manifestations:**

- ! These adverse effects are related to a **D₂-receptor blockade** in the basal ganglia. They occur most likely with **old** generation drugs.

–! They include:

- ! Parkinsonian-like syndrome
- ! Dystonia: sustained muscle contractions cause twisting movements or abnormal postures
- ! Dyskinesia: involuntary repetitive facial, lip, and tongue movements occurs with chronic therapy. It may be irreversible.

■! **Neuroleptic malignant syndrome:**

- ! It is a serious complication with mortality rate 20%, occurs more with old generation drugs.
- ! It consists of autonomic disturbance, ms rigidity, hyperthermia, and sweating.
- ! It needs immediate stopping of the antipsychotic therapy.



Dystonia caused by antipsychotic drugs.

■! **Autonomic side effects:**

- ! **α -receptor blockade** leading to postural hypotension and sexual dysfunction
- ! **Muscarinic blockade** → atropine-like actions

■! **Endocrine disturbance (occurs more with atypical agents):**

- ! Weight gain
- ! Hyperglycemia and precipitation of DM.
- ! Gynecomastia, amenorrhoea

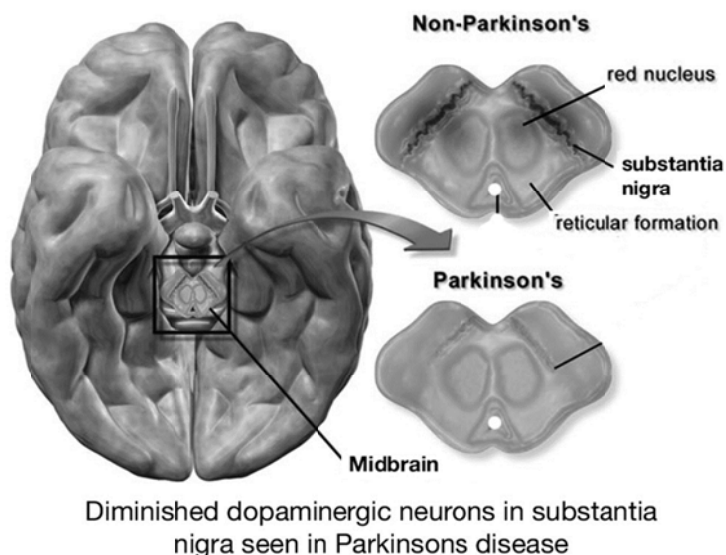
■! **Other adverse effects:**

- ! Cardiac arrhythmia
- ! Cholestatic jaundice
- ! Agranulocytosis (particularly associated with **clozapine**)

	Typical drugs	Atypical drugs
Mechanism	Block mainly D2 receptors	Block D2 (less) and 5HT _{2A} (more)
Effect	More effect on +ve symptoms	More effect on – ve symptoms
Extrapyramidal side effects	Common	Less common
Neuroleptic malignant synd	Common	Less common
Endocrinal side effects	Less common	Common
Agranulocytosis	Less common	Common

Part 9: Antiparkinsonian Drugs

Parkinsonism is a movement disorder characterized by muscle rigidity, tremors, and postural instability due to loss of **dopaminergic neurons in substantia nigra and locus ceruleus** resulting in imbalance of dopaminergic (inhibitory) and cholinergic (excitatory) influences on the extrapyramidal system. Recently, a heroin substitute (MPTP) was found to cause irreversible damage of the nigrostriatal dopaminergic neurons and a parkinsonism-like state.



Classification of antiparkinsonian drugs:

■! Dopaminergic drugs:

- ! **Dopamine precursors:** Levodopa (L-dopa).
- ! **COMT inhibitors:** Tolcapone - Entacapone
- ! **Selective MAO-B inhibitors:** Selegiline
- ! **Dopamine agonists:** Bromocriptine
- ! **Release of dopamine** and inhibition of its reuptake: Amantadine

■! Anticholinergic drugs:

- ! **Synthetic atropine substitutes:** Benztropine – Orphenadrine – Trihexyphenidyl

1. Levodopa (L-dopa)

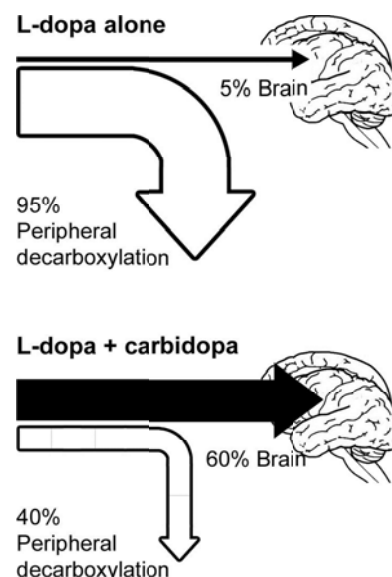
Pharmacokinetics

- ! Absorbed rapidly from the small intestine.
- ! It has **short $t_{1/2}$** (1-2 h). This short $t_{1/2}$ may produce "*on-off phenomenon*" i.e. rapid fluctuation of the clinical state in the form of sudden tremors & immobility after short period of recovery.
- ! **Amino acids** (e.g. leucine & isoleucine) compete with L-dopa absorption from the gut so it should be taken on an empty stomach.



Mechanism of action

- ❑ Dopamine can't cross BBB but L-dopa can. It is considered the **1st line** treatment of parkinsonism.
- ❑ More than 95% of the administered dose is rapidly decarboxylated into dopamine in the peripheral tissues. Only a small fraction escapes and crosses BBB.
- ❑ Peripheral decarboxylation can be minimized by administration of a decarboxylase inhibitor which can't cross BBB e.g. **carbidopa** or **benserazide**.
- ❑ Such a combination helps to reduce the dose of L-dopa and hence the adverse effects



Adverse effects

- ❑ **GIT:** nausea & vomiting (*domperidone is the drug of choice to treat this vomiting because it does not cross the BBB. It acts on the bare area of the barrier*).
- ❑ **CNS:**
 - ! Mood changes, hallucinations and nightmares.
 - ! Dyskinesia: involuntary movements of the head, lips, and tongue.
 - ! On-off phenomenon: rapid fluctuation of the clinical state in the form of sudden tremors and immobility after a short period of recovery due to the short $t_{1/2}$ of the drug.
- ❑ **Autonomic:** postural hypotension, arrhythmias, mydriasis and acute rise of IOP.
- ❑ **Brownish** body secretions & red urine due to the metabolite *homovanillic acid*.

Interactions

- ❑ **Food:** amino acids (e.g. leucine & isoleucine) compete with L-dopa absorption.
- ❑ **Dopamine blockers** (antipsychotic drugs and metoclopramide) antagonize the effects of L-dopa.
- ❑ **Pyridoxine** (vitamin B6) enhances peripheral decarboxylation into dopamine.
- ❑ **COMT inhibitors** and **selective MAO-B inhibitors**: make synergism with L-dopa.

2. COMT inhibitors (L-Dopa adjuvants): Tolcapone - Entacapone

Mechanism of action

- ❑ They inhibit COMT enzyme selectively & reversibly, the enzyme that converts L-dopa to 3-O-methyldopa (3OMD) in the gut and liver.

- ! By inhibiting COMT enzyme, tolcapone increases the efficacy of L-dopa and stabilizes dopamine levels in the striatum and improves motor function.

Adverse effects

- ! Same side effects of L-dopa (nausea, vomiting, hallucination, mood changes).
- ! Tolcapone causes fulminating hepatic necrosis.

3. Selective MAO-B inhibitors: Selegiline

Mechanism of action

- ! It is a selective MAO-B inhibitor **decreasing breakdown** of dopamine in the brain.
- ! Unlike MAO-A inhibitors, it does not precipitate "**cheese reaction**" since tyramine is metabolized in the liver by MAO-A.

Adverse effects

- ! Nausea, vomiting & GIT upset.
- ! Hallucinations & mood changes.
- ! Insomnia.

4. Dopamine agonists: Bromocriptine

- ! It is dopamine (D₂) agonist derived from ergot alkaloids.
- ! It differs from L-dopa in: **Faster** onset, **longer** duration, **No** on-off effect.

Other uses

- ! To treat hyperprolactinemia and to suppress lactation (dopamine agonists ↓ prolactin secretion from pituitary gland).
- ! Acromegaly (dopamine agonists ↓ GH secretion from pituitary gland).

Adverse effects

- ! Nausea, vomiting & GIT upset.
- ! Hallucinations & mood changes in large doses.
- ! Postural hypotension.

5. Dopamine release stimulation: Amantadine

- ! It is an antiviral drug for influenza A2 virus.
- ! The antiparkinsonian mechanism is unclear but may be due to ↑ dopamine release, ↓ dopamine reuptake, or direct action on dopamine receptors.

Adverse effects

- ! Nausea, vomiting & GIT upset.
- ! Hallucinations & mood changes in large doses.
- ! Postural hypotension.
- ! Skin pigmentation.



Skin pigmentation “levido reticularis” caused by amantadine.

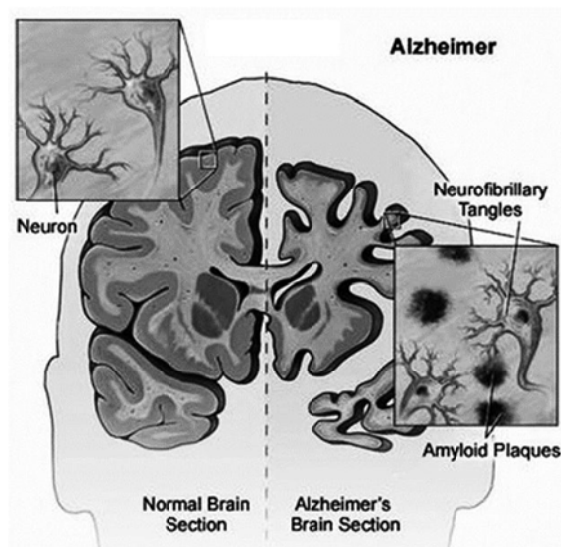
6. Anticholinergic drugs:**Benztropine – Orphenadrine – Trihexyphenidyl**

- ! These drugs have **greater selectivity** for blocking central than peripheral muscarinic receptors.
- ! They produce moderate improvement of tremors and **sialorrhea** but little effect on muscle rigidity.
- ! They are used also to control acute drug-induced extrapyramidal side effects.
- ! These drugs are **contraindicated** in patients with **prostatic** hypertrophy, obstructive GI disease (e.g., paralytic ileus) and narrow-angle **glaucoma**.
- ! In patients suffering from Parkinsonism, there is some degree of **dementia** associated with atrophy of cortical neurons. Anticholinergic drugs may aggravate dementia and memory loss.

Part 10: Drugs Used in Alzheimer's Disease

Alzheimer is a neurodegenerative disease characterized by progressive loss of memory and dementia due to **loss of cholinergic neurons** and deposition of abnormal protein “amyloid plaques”. Overstimulation of **glutamate receptors** may be responsible for this neurodegenerative process.

The aim of therapy is to either improving cholinergic transmission within the CNS or preventing the excitatory actions of NMDA glutamate receptors in selected brain areas.

**1. Cholinesterase inhibitors: Donepezil - Rivastigmine**

- ! They are more selective for ChE enzyme in the CNS
- ! They provide a modest reduction in the rate of loss of cognitive functions.
- ! **Side effects:** nausea, vomiting, anorexia, and muscle cramps.

2. NMDA receptor antagonist: Memantine

- ! It is a derivative of amantadine
- ! It prevents rate of memory loss in both vascular-associated and Alzheimer dementia.
- ! **Side effects are rare:** confusion, agitation, restlessness.

3. Recent trials:**■! β & γ -secretase inhibitors:**

The enzymes β & γ -secretase are responsible for formation of amyloid proteins A β 40 and A β 42 that are found in the brain of Alzheimer patients. Inhibition of these enzymes reduces deposition of these amyloid deposits.

■! Ibuprofen and indomethacin

These NSAIDs reduce formation of A β 42 by inhibition of γ -secretase enzyme which is unrelated to their COX inhibition. Aspirin and corticosteroids do not produce this effect.

■! Copper and zinc chelating agents:

Removal of these metals promotes dissolution of amyloid plaques in brain tissue.

Part 11: General Anesthetics

General anesthesia is characterized by a loss of consciousness, analgesia, amnesia, skeletal muscle relaxation, and inhibition of autonomic and sensory reflexes.

Balanced anesthesia

- ! Balanced anesthesia refers to a combination of drugs used to take advantage of individual drug properties and minimizing their adverse actions.
- ! In addition to anesthetic drugs and neuromuscular blocking drugs, other drugs are administered preoperatively, intraoperatively, and postoperatively to ensure smooth induction, sedation, and smooth recovery (e.g., benzodiazepines, opioids).

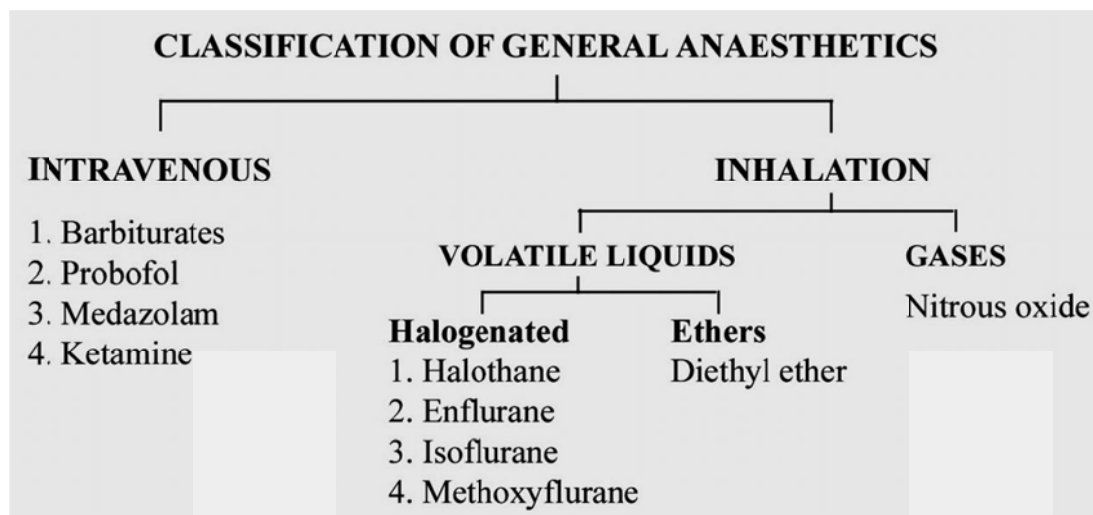
Stages and planes of anesthesia

- ! The stages and planes of anesthesia identify the progression of physical signs that indicate the depth of anesthesia. Newer, more potent agents progress through these stages rapidly, and therefore, the stages are often obscured.
- ! Mechanical ventilation and the use of adjunct drugs also obscure the signs indicating the depth of anesthesia.
 - ! **Stage I:** Analgesia and amnesia.
 - ! **Stage II:** Excitation.
 - ! **Stage III:** Surgical anesthesia: loss of consciousness.
 - ! Four planes have been described relating to increased depth of anesthesia.
 - ! Plane IV includes maximal pupil dilation, apnea, and circulatory depression.
 - ! The loss of the eyelash reflex and a pattern of respiration that is regular in rate and depth are the most reliable signs of stage III anesthesia.
 - ! **Stage IV:** Medullary depression: respiratory and cardiovascular failure.

Mechanism of anesthetic action

Inhalation and IV anesthetic agent interaction with **discrete protein binding sites in nerve endings to activate ligand-gated ion channels:**

- ! **GABA-A-receptor chloride channels:** anesthetic agents directly and indirectly facilitate a GABA-mediated increase in chloride conductance to hyperpolarize and inhibit neuronal membrane activity.
- ! **Ligand-gated potassium channels:** anesthetic agents increase potassium conductance to hyperpolarize and inhibit neuronal membrane activity.
- ! **NMDA receptors:** certain anesthetics (e.g., nitrous oxide, ketamine) inhibit excitatory glutamate gated ion channels.

Classification of general anesthetics**INTRAVENOUS ANAESTHETICS****1. Ultrashort acting barbiturates: thiopental****Advantages**

- ! Produces rapid and pleasant induction with rapid recovery.
- ! Does not increase intracranial pressure.
- ! Used for induction before stronger anesthetic and for short procedures.

Disadvantages

- ! Poor analgesia and skeletal muscle relaxation.
- ! Induce cough, laryngospasm, bronchospasm and apnea avoided by atropine and ready artificial respiration.
- ! Extravasation induces necrosis.
- ! Contraindicated absolutely in cases of porphyria (defect of ALA synthetase) barbiturates increase synthesis of porphyrins which precipitates acute attack inducing paralysis and death.

2. Etomidate**Advantages:** It is very similar to thiopental but:

- ! Larger margin between the anaesthetic dose and the dose producing respiratory and cardiovascular depression than with thiopental.
- ! It is more rapidly metabolized than thiopental and, therefore, less likely to cause a prolonged hangover.
- ! It is used only as an induction agent, and is preferable to thiopental in patients at risk of circulatory failure.

Disadvantages

- ! More likely to cause involuntary movements during induction.
- ! And to cause postoperative nausea and vomiting.
- ! Suppresses the adrenal cortex with prolonged use which has been associated with an increase in mortality in severely ill patients.

3. Propofol**Advantages**

- ! Rapid and pleasant induction with rapid recovery and clarity of mental status.
- ! Does not increase intracranial pressure.
- ! Used for induction or maintenance.

Disadvantages

- ! Respiratory center depressant less than thiopental.
- ! Markedly decreases the blood pressure.

4. Midazolam (see under Benzodiazepines)

- ! They are used in conjunction with anaesthetics to sedate the patient.
- ! The most commonly employed is midazolam.
- ! Diazepam and lorazepam are alternatives. All three facilitate amnesia while causing sedation.

Advantages

- ! Used for induction
- ! 3-4 times as potent as diazepam.
- ! Does not cause local irritation after injection as diazepam.
- ! Little cardiovascular or respiratory depression.

Disadvantages

- ! Light anaesthesia.
- ! Can cause respiratory depression.
- ! Anterograde amnesia which lasts for at least 2 hours.

5. Ketamine (Dissociative Anaesthesia)**Advantages**

- ! Profound analgesia and amnesia
- ! The only intravenous anesthetic that routinely produces cardiovascular stimulation through central sympathetic stimulation (increases B.I.P. H.R and C.O.). So, it is beneficial in cases of shock.
- ! No respiratory depression and has a potent bronchodilator effects.

Disadvantages

- ! Increases intracranial pressure (due to increased cerebral blood flow).
- ! Unpleasant dreams.
- ! Recovery often is accompanied by delirium and psychomotor activity).
- ! Diplopia and nystagmus may occur due to increased muscle tone.
- ! Contraindicated in cases of hypertension and stroke.

■ INHALATION ANAESTHETICS

An important characteristic of an inhalation anaesthetic is the speed at which the arterial blood concentration, which governs the pharmacological effect, follows changes in the concentration of the drug in the inspired air.

Measure of potency

- ! Through the minimum alveolar concentration (MAC). It is the anaesthetic (MAC) alveolar concentration at 1 atmosphere that will produce loss of movement in 50% of subjects exposed to a noxious stimulus.
- ! Methoxyflurane is highly potent while nitrous oxide is of low potency.

Rapidity of induction

- ! Gas of little solubility in blood as nitrous oxide has a high blood gas tension, a small Vd, with a consequent rapid induction and rapid recovery.
- ! Gas of high solubility in blood e.g. methoxyflurane has a low blood gas tension, a big Vd, with a slow induction and a slow recovery.

Pharmacological effects

- ! Inhalation anaesthetics produce descending depression of all brain functions in the following order: Cortex > Subcortex > Mid-brain > Spinal cord > Medullary centers.
- ! The highly developed functions like memory are the first to be lost, but the vital functions as respiration and circulation are the last.
- ! With modern balanced anaesthesia no more notable staging. Loss of consciousness, analgesia and muscle relaxation is produced with a combination of drugs rather than with a single anaesthetic agent.
- ! Unconsciousness rapidly produced with an i.v. induction agent (e.g. propofol), to maintain unconsciousness and produce analgesia with one or more inhalation agent which might be supplemented with an i.v. analgesic agent, and to produce muscle paralysis with a neuromuscular blocking drug.
- ! The following table shows points of difference in between the currently used inhalation anesthetics:

Inhalation anesthetics

	Ether	Nitrous Oxide	Halothane	Enflurane	Methoxy Flurane
1- MAC	1.9	> 100 (the least potent)	0.75	1.7	0.16 (the most potent)
2- Induction and recovery	rapid	rapid	Slow	slow	slow
3- Analgesia	good	good	Inadequate	potent	potent (continues after recovery)
4- Skeletal muscle relaxation	good	not relaxant	Inadequate	good	good
5- C.V.S	-----	-----	Bradycardia, arrhythmias and hypotension	less than halothane	less than halothane
6- Respiration	Bronchodilation by the sympathetic stimulation	Diffusion hypoxia at the termination	Respiratory center depression	- more respiratory center depression - Inhibits bronchoconstriction	more
7- Liver	Increased glycogenolysis by the sympathetic stimulation	-----	autoimmune hepatitis	less than halothane (rare)	less than halothane (rare)
8- Uterus	-----	No uterine relaxation	potent uterine relaxant	less uterine relaxation	No uterine relaxation
9- Hyperthermia	-----	-----	rare	rare	rare
10- Use	* Suitable for most types of operations * Of wide safety margin	* The most widely used * Obstetric anaesthesia * Neuroleptanaesthesia	- Safe for children and for asthmatics	lower incidence of arrhythmias than halothane	* Limited use because of nephrotoxicity * Obsetetric anaesthetic.
11- Disadvantages	* Inflammable * Irritant * Precipitates convulsions	* Weak anaesthetic * Has no skeletal muscle relaxant effect * Diffusion hypoxia	* Hepatitis * Malignant hyperthermia * Contraindicated in cardiac	* Nephrotoxic * EEG. seizure activity (contraindicated in epileptics)	Nephrotoxic (damage of tubules by the liberated fluoride diabetes insipidus induced by fluoride)

Preanesthetic medications (anesthetic adjuvant):

They are drugs given to reduce anxiety, providing analgesia and amnesia, and prevent salivation, bradycardia, and other side effects of anesthesia.

- ! **Anxiolytics (e.g. diazepam):** given at night preoperatively to provide sedation & amnesia.
- ! **Opioid analgesics (e.g. morphine, fentanyl, or alfentanil):**
 - ! They are given 1½ hrs before anesthesia to inforce low potency anesthetics as nitrous oxide. Alfentanil may offer faster recovery than fentanyl.
- ! **Anticholinergic drugs (e.g. atropine or scopolamine):**
 - ! They are given 1½ hrs before anesthesia to reduce respiratory secretions and prevent occurrence of aspiration pneumonia.
 - ! They block the reflex vagal stimulation induced by some inhalation anesthetics.
- ! **Muscle relaxants & others drugs:** e.g. **vasopressors** to prevent hypotension and **hypothermics** (chlorpromazine) to lower the normal body temperature in cases of cardiac surgery.

Part 12: Local Anesthetics**Classification**

There are two classes of local anesthetics: **amides** and **esters**. The primary differences between the two classes are in their relative metabolism (amides have primarily a hepatic metabolism, whereas esters are metabolized by plasma cholinesterases) and their potential for allergic reactions (esters more than amides).

	Esters	Amides
Members	Cocaine, procaine, tetracaine, benzocaine	Lidocaine, prilocaine, mepivacaine, bupivacaine
Metabolism	Plasma cholinesterase	Liver
Hypersensitivity reactions	May occur	Rare

Mechanism of action

- ! Local anesthetics block voltage dependent Na^+ channels within the nerve fibers $\rightarrow \downarrow$ nerve conduction.
- ! In general, small nerve fibers (that carry pain sensation) are more sensitive to local anesthetics than large fibers (motor and other sensations).
- ! Myelinated fibers are blocked before non-myelinated fibers of the same diameter.

Pharmacological properties

	Chemistry	Anesthetic potency	Duration	Onset
Procaine	Ester	Low	Short	Moderate
Mepivacaine	Amide	Moderate	Moderate	Fast
Prilocaine	Amide	Moderate	Moderate	Fast
Lidocaine	Amide	Moderate	Moderate	Fast
Tetracaine	Ester	High	Long	Moderate

Adjuvants of local anesthetics■! **Vasoconstrictors e.g. adrenaline:**

- ! They are added to produce local VC; this will reduce wash of the anesthetic by the local blood flow and thus prolongs the duration of the anesthetic.

–! Vasoconstrictors should not be added for ring block of hands, feet, fingers, toes, and ear pinna to avoid tissue damage.

■! **Sodium bicarbonate:**

–! All local anesthetics are weak **bases**. Addition of bicarbonate to the anesthetic solution maintains the anesthetic in the non-ionized state and this increases lipid solubility and enhances penetration of the anesthetic into the nerve sheath.

Techniques and clinical uses

■! **Surface (topical) anesthesia:** is used for anesthetization of the skin, mucous membranes, or cornea.

- ! Treatment of itching caused by insect bites or irritant condition.
- ! To relieve pain caused by oral, laryngeal, or rectal disorders e.g. piles.
- ! Corneal anesthesia in ophthalmic surgery.

■! **Infiltration anesthesia:** injecting an anesthetic directly into the subcutaneous tissue for minor surgical procedures e.g. dental procedures. Epinephrine may be added to prolong the duration of action.

■! **Nerve block:** injecting the local anesthetic close to the appropriate nerve trunk proximal to the intended area of anesthesia e.g. radial nerve block or retro-orbital block for ocular surgery.

■! **Spinal anesthesia:** is used for surgeries of the lower limb or pelvic structures. A local anesthetic is injected into the subarachnoid space below the terminal end of the spinal cord (usually between 3rd and 4th lumbar vertebra).

■! **Epidural anesthesia:** the anesthetic is infused into the space between the dura mater and the connective tissue lining the vertebral canal as alternative to subarachnoid anesthesia.

Adverse effects

–! **Surface anesthesia:** allergic dermatitis.

–! **Infiltration anesthesia:** faulty intravascular injection can lead to:

- ! CNS excitation: irritability and convulsions
- ! CVS depression: bradycardia, hypotension, myocardial depression or cardiac arrest.

–! **Vasovagal syncope:** vasovagal (also called neurocardiogenic) syncope is usually associated with bradycardia (rather than tachycardia) and pallor (rather

than flushing). These differences can be helpful in distinguishing it from anaphylaxis.

–! **Spinal anesthesia:**

- ! Spinal shock due to sympathetic outflow paralysis.
- ! Headache due to CSF leakage.
- ! Respiratory paralysis.
- ! Septic meningitis.

Recommendations

- ! The **choice** of local anesthetic for infiltration depends on several factors, including duration of the procedure, need for hemostasis, patient sensitivity to catecholamines, and patient allergy to local anesthetics.
- ! Prior to infiltration, the clinician should determine if the patient has any **history of allergy**. Patients with a true allergic reaction to a local anesthetic need evaluation by an allergy specialist.
- ! Local anesthetic infiltration is **contraindicated** in the following conditions:
 - ! If the area needed to be anesthetized is so large because the amount of anesthetic needed exceeds the maximal safe dose.
 - ! If the patient has history of allergy to local anesthesia.

Treatment of spinal shock

- ! **Place the patient in the supine position with the legs elevated.**
- ! **Airway support:** oxygen and artificial respiration.
- ! **If there are convulsions, give i.v. diazepam.**
- ! **If there is hypotension,** give i.v. fluids plus vasoconstrictors.
- ! Cardiopulmonary resuscitation (CPR) is necessary when cardiac function is interrupted.

Notes

Clinical
Pharmacology
Department

Mansoura Faculty of Medicine

Review Questions

Long questions:

- 1.! Classify **opioid analgesics** and discuss mechanism, uses, & contraindications of morphine.
- 2.! Anxiety is a common medical disorder. Classify **antianxiety drugs** and discuss in details the differences between barbiturates and benzodiazepines.
- 3.! **Depression is an important medical disease. Classify** antidepressant drugs; **mention their mechanism, indications and side effects.**
- 4.! Classify **antiepileptic drugs**; mention their mechanism, indications and side effects.
- 5.! **Dopamine** is found in many areas in the CNS. Discuss the drugs that act by inhibiting these central dopamine sites.
- 6.! **Dopamine** is found in many areas in the CNS. Discuss the drugs that act by activating these central dopamine sites.

Short questions:

- 1.! **Give an account on:**
 - a)! Mechanism and treatment of paracetamol toxicity
 - b)! Drug treatment of Alzheimer's disease.
- 2.! **Discuss the pharmacodynamic principles underlying the use of:**
 - a)! Morphine in acute pulmonary edema.
 - b)! Acetylcysteine in paracetamol toxicity
 - c)! Naloxone in acute opioid toxicity.
 - d)! Selegiline in parkinsonism.
- 3.! **Discuss on pharmacological basis of each of the following:**
 - a)! Nalorphine is contraindicated to relieve pain in addict patient.
 - b)! Reserpine is contraindicated with MAOIs.
 - c)! Anticholinergic drugs are not preferred to treat parkinsonism in old patients.
- 4.! **Mention drug interactions of each of the following drugs:**
 - (1) L-Dopa
 - (2) MAOIs
- 5.! **Mention the main differences between:**
 - a)! Valproic acid and lamotrigine
 - b)! L-Dopa and bromocriptine.
 - c)! Chlorpromazine and olanzapine

Of each of the following questions, select ONE BEST answer:

1. Morphine, all are true EXCEPT:

- A. Acts as an agonist at opioid receptors (especially μ) in the brain and spinal cord
- B. Causes pupillary constriction by stimulation of the Edinger–Westphal nucleus in the mid-brain
- C. Acts as an antihistamine
- D. Is subject to presystemic metabolism
- E. Stimulates the chemoreceptor trigger zone

2. Which of the following is not true for meperidine?

- A. It has less analgesic potency than morphine
- B. It has less spasmogenic effect than morphine
- C. It can cause histamine release and bronchoconstriction
- D. It has greater bioavailability than morphine
- E. It does not cause physical dependence

3. Morphine causes all of the following EXCEPT:

- A. Diarrhoea
- B. Increased intrabiliary pressure
- C. Histamine release
- D. Reduced sensitivity of the respiratory centre to carbon dioxide
- E. Hypotension

4. The following are particularly sensitive to the pharmacological actions of morphine EXCEPT:

- A. Young children
- B. The elderly
- C. Patients with hepatic failure
- D. Patients with renal failure
- E. Patients with hyperthyroidism

5. The pharmacologic effects of acetylsalicylic acid include:

- A. Reduction of high body temperature
- B. Promotion of platelet aggregation
- C. Reduction of pain by stimulation of PGs synthesis
- D. Efficacy equals to that of probenecid as uricosuric agent

- E. Less gastric irritation than other NSAIDs

6. Aspirin reduces the synthesis of the following eicosanoids EXCEPT:

- A. TXA₂
- B. PGE₂
- C. PGF₂ α
- D. LTB₄
- E. PGI₂

7. The following statements about NSAIDs are correct EXCEPT:

- A. Diclofenac may cause permanent platelet dysfunction
- B. Indomethacin may cause neurological side effects (neurotoxicity).
- C. Sulindac is a prodrug
- D. They may impair renal function
- E. Aspirin may displace coumarin anticoagulants from plasma proteins

8. The following statements about aspirin are correct EXCEPT:

- A. May cause GIT hemorrhage after a single dose
- B. Enteric-coated tablets cause less gastric bleeding
- C. May cause metabolic alkalosis in high doses
- D. May cause Rye's syndrome in children
- E. Its toxicity may require treatment with hemodialysis

9. Which one of the following statements concerning Cox-2 inhibitors is correct:

- A. They show greater analgesic activity than traditional NSAIDs
- B. They show anti-inflammatory activity greater than traditional NSAIDs
- C. They harm the stomach as do non-selective cox inhibitors
- D. They increase platelet aggregation
- E. They are cardio protective

10. Non-narcotic analgesics are all of the following drugs EXCEPT:

- A. Paracetamol
- B. Acetylsalicylic acid
- C. Codiene
- D. Ketorolac
- E. Dipyrrone

11. Which one of the following non-narcotic agents inhibits mainly cyclooxygenase (COX) in CNS?

- A. Paracetamol
- B. Ketorolac
- C. Acetylsalicylic acid
- D. Ibuprofen
- E. Celecoxib

12. For which of the following conditions could aspirin be used prophylactically?

- A. Noncardiogenic pulmonary edema
- B. Peptic ulcers
- C. Thromboembolism
- D. Metabolic acidosis
- E. Periodontitis

13. Nefopam:

- A. Is associated with gastrointestinal haemorrhage
- B. Causes miosis
- C. Causes more respiratory depression than morphine
- D. Potentiates the dysrhythmogenic effect of halothane anaesthesia
- E. Is contraindicated in epilepsy

14. Indicate the benzodiazepine, which has the shortest elimination half-life:

- A. Nitrazepam
- B. Alprazolam
- C. Triazolam
- D. Diazepam
- E. Clorazepate

15. Which of the following benzodiazepines is preferred for elderly patients?

- A. Clorazepate
- B. Clonazepam
- C. Triazolam
- D. Prazepam
- E. Diazepam

16. Which of the following benzodiazepines is preferred for patients with liver disease?

- A. Clorazepate
- B. Nitrazepam
- C. Lorazepam
- D. Prazepam
- E. Diazepam

17. The following drug can be given to reverse benzodiazepine overdose:

- A. Cocaine
- B. Flumazenil
- C. Buspirone
- D. PicROTOXIN
- E. Diazepam

18. Indicate the anxiolytic agent, which relieves anxiety without causing marked sedative effects:

- A. Diazepam
- B. Buspirone
- C. Lorazepam
- D. Clorazepate
- E. Zolpidem

19. Local anesthetics produce:

- A. Analgesia, amnesia, loss of consciousness
- B. Blocking pain sensation without loss of consciousness
- C. Alleviation of anxiety and pain with an altered level of consciousness
- D. A stupor or somnolent state
- E. Physical dependence

20. Local anesthetics act by:

- A. Blocking voltage-gated sodium channels
- B. Blocking voltage-gated calcium channels
- C. Blocking voltage-gated potassium channels
- D. Blocking chloride conductance
- E. Blocking NMDA receptors

21. Which of the following local anesthetics has short duration?

- A. Procaine
- B. Mepivacaine
- C. Prilocaine
- D. Lidocaine
- E. Tetracaine

22. Which drug does not activate opioid receptors, has been proposed as a maintenance drug in treatment programs for opioid addicts, and with a single oral dose, will block the effects of injected heroin for up to 48 h?

- (A) Fentanyl
- (B) Nalbuphine
- (C) Naloxone

- (D) Naltrexone
- (E) Propoxyphene

23. Which drug is a full agonist at opioid receptors with analgesic activity equivalent to morphine, a longer duration of action, and fewer withdrawal signs on abrupt discontinuance than morphine?

- (A) Fentanyl
- (B) Hydromorphone
- (C) Methadone
- (D) Nalbuphine
- (E) Oxycodone

24. Which drug used in the maintenance treatment of patients with tonic-clonic or partial seizure states increases the hepatic metabolism of many drugs including both phenytoin and warfarin?

- (A) Buspirone
- (B) Clonazepam
- (C) Eszopiclone
- (D) Phenobarbital
- (E) Triazolam

25. A patient with liver dysfunction is scheduled for a surgical procedure. Lorazepam or oxazepam can be used for preanesthetic sedation in this patient without special concern regarding excessive CNS depression because these drugs are

- (A) Actively secreted in the renal proximal tubule
- (B) Conjugated extrahepatically
- (C) Eliminated via the lungs
- (D) Reversible by administration of naloxone
- (E) Selective anxiolytics like buspirone

26. This drug used in the management of insomnia facilitates the inhibitory actions of GABA. Its actions are antagonized by flumazenil.

- (A) Buspirone
- (B) Temazepam
- (C) Eszopiclone
- (D) Ramelteon
- (E) Phenobarbital

27. A 9-year-old child is having learning difficulties at school. He has brief lapses of awareness with eyelid fluttering that occur every 5–10 min. Which drug would be effective in this child without the disadvantages of excessive sedation?

- (A) Clonazepam
- (B) Diazepam
- (C) Ethosuximide
- (D) Gabapentin
- (E) Phenobarbital

28. Which antiepileptic drug is most likely to elevate the plasma concentration of other drugs administered concomitantly?

- (A) Carbamazepine
- (B) Clonazepam
- (C) Phenobarbital
- (D) Phenytoin
- (E) Valproic acid

29. With chronic use in seizure states, the adverse effects of this drug include coarsening of facial features, hirsutism, and gingival hyperplasia.

- (A) Carbamazepine
- (B) Ethosuximide
- (C) Zonisamide
- (D) Tiagabine
- (E) Phenytoin

30. The mechanism of antiseizure activity of carbamazepine is

- (A) Block of sodium ion channels
- (B) Block of calcium ion channels
- (C) Facilitation of GABA actions on chloride ion channels
- (D) Glutamate receptor antagonism
- (E) Inhibition of GABA transaminase

31. Which statement about phenytoin is accurate?

- (A) Displaces sulfonamides from plasma proteins
- (B) Drug of choice in myoclonic seizures
- (C) Half-life is increased if used with phenobarbital
- (D) Isoniazid (INH) decreases steady-state blood levels of phenytoin
- (E) Toxic effects may occur with only small increments in the dose

32. Which of the following drugs is the most effective in the emergency management of malignant hyperthermia?

- (A) Atropine
- (B) Dantrolene
- (C) Haloperidol
- (D) Succinylcholine
- (E) Vecuronium

33. Which drug is most likely to cause hyperkalemia leading to cardiac arrest in patients with spinal cord injuries?

- (A) Baclofen
- (B) Dantrolene
- (C) Pancuronium
- (D) Succinylcholine
- (E) Vecuronium

34. Tolcapone may be of value in patients being treated with levodopa-carbidopa because it:

- (A) Activates COMT
- (B) Decreases the formation of 3-O-methyldopa
- (C) Inhibits monoamine oxidase type A
- (D) Inhibits neuronal reuptake of dopamine
- (E) Releases dopamine from nerve endings

35. Concerning the drugs used in parkinsonism, which statement is accurate?

- (A) Dopamine receptor agonists should never be used in Parkinson's disease before a trial of levodopa
- (B) Levodopa causes mydriasis and may precipitate an acute attack of glaucoma
- (C) Selegiline is a selective inhibitor of COMT
- (D) The primary benefit of antimuscarinic drugs in parkinsonism is their ability to relieve bradykinesia
- (E) Therapeutic effects of amantadine continue for several years

36. Which drug is an antagonist at 5-HT₂ receptors and can be used for the management of insomnia?

- (A) Estazolam
- (B) Flurazepam
- (C) Trazodone
- (D) Triazolam
- (E) Zolpidem

37. Which of the following drugs is most likely to be of value in obsessive-compulsive disorders?

- (A) Amitriptyline
- (B) Bupropion
- (C) Sertraline
- (D) Trazodone
- (E) Venlafaxine

38. A patient under treatment for a major depression is brought to the emergency department after ingesting 30 tablets of imipramine. Which of the following would be LEAST useful?

- (A) Administer bicarbonate to correct acidosis.
- (B) Administer lidocaine to control cardiac arrhythmias.
- (C) Initiate hemodialysis to hasten drug elimination.
- (D) Maintain heart rhythm by electrical pacing
- (E) Use intravenous diazepam to control seizures

39. A 36-year-old woman presents with symptoms of major depression. Drug treatment is to be initiated with sertraline. In your information to the patient, you would tell her that

- (A) Sertraline may take 2 wk or more to become effective
- (B) It is preferable that she take the drug in the morning
- (C) Muscle cramps and twitches can occur
- (D) She should notify you if she anticipates using other prescription drugs
- (E) All of the above

Answers

1 C	10 C	19 B	28 E	37 C
2 E	11 A	20 A	29 E	38 C
3 A	12 C	21 A	30 A	39 E
4 E	13 E	22 D	31 E	
5 A	14 C	23 C	32 B	
6 D	15 C	24 D	33 D	
7 A	16 C	25 B	34 B	
8 C	17 B	26 B	35 B	
9 D	18 B	27 C	36 C	