Lecture 1-3

SEDATIVE Drugs that have an inhibitory effect on the CNS to the degree that they reduce: Nervousness, Excitability, Irritability without causing sleep.

HYPNOTICS Calm or soothe the CNS to the point that they cause sleep a hypnotic drug should produce drowsiness and encourage the onset and maintenance of a state of sleep that as far as possible resembles the natural sleep state.

Anxiolytics: reduce anxiety
Hypnotics: induce sleep
Sedatives: decrease activity, calming effect
Some drugs have anxiolytic and sedative/hypnotic effects
Most anxiolytic and sedative – hypnotic drugs produce dose – depended depression of the central nervous system function (CNS Depression Sedation, Hypnosis, General Anesthesia, Poisoning, and Death)

The ideal anxiolytic drug:
- Should calm the patient without causing too much day time sedation and drowsiness.
- Should not interact with other medications in such way as to produce unwanted or dangerous effect
- Without producing physical or psychological dependence.
- Should have very low toxicity

The ideal hypnotic drug:
- Should allow the patient to fall asleep quickly.
- Should maintain sleep of sufficient quality and duration so that the patient awakes refreshed without a drug hangover) feeling of tiredness well after the patient wakes. This may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur.
Should not interact with other medications in such a way as to produce unwanted or dangerous effect

Without producing physical or psychological dependence.

Should have very low toxicity.

**Summary of anxiolytic and hypnotic drugs:**

1. Barbiturates.
2. Benzodiazepines.
3. Other anxiolytic drugs: buspirone, hydroxyzine, antidepressants.
4. Other hypnotic agents: antihistamine, chloral hydrate, ethanol, ramelteon, zolpidem.

**Barbiturates**

They have been largely replaced by the benzodiazepines, because Barbiturates:

1. Low therapeutic index.
2. Induce tolerance, Physical dependence, Very severe withdrawal symptoms
3. Induce drug-metabolizing enzymes.
4. Ability to cause coma in toxic doses.
5. When used as hypnotics, they suppress REM sleep more than other stages.

Certain barbiturates, such as the very short-acting thiopental, are still used to induce anesthesia

**Barbiturates are classified according to their duration of action into:**

- **Ultra-short acting:** thiopental (20 minutes)
- **Short acting:** pentobarbital, secobarbital, amobarbital(3-8)hours
- **Long acting:** phenobarbital(1-2 days)

**Mechanism of action**

The sedative-hypnotic action of the barbiturates is due to their interaction with GABA<sub>A</sub> receptors, which enhances GABAergic transmission. The binding site is distinct from that of the benzodiazepines.

- Barbiturates potentiate GABA( the major inhibitory neurotransmitter in the central nervous system )action on chloride entry into the neuron by prolonging the duration of the chloride channel openings.
• In addition, barbiturates can block excitatory glutamate receptors.
• Anesthetic concentrations of pentobarbital also block high-frequency sodium channels. All of these molecular actions lead to decreased neuronal activity.

**Actions:**

**Depression of CNS:**

- At low doses, the barbiturates produce sedation (calming effect, reducing excitement).
- At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and finally, coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose. Barbiturates do not raise the pain threshold and have no analgesic properties. They may even exacerbate pain. Chronic use leads to tolerance.

**Respiratory depression:** Respiratory depression and death may occur in overdose.

**Enzyme induction:** Barbiturates induce P450 microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are dependent on p450 metabolism to reduce their concentration as phenytoin, anticoagulants.

**Therapeutic uses of barbiturates:**

**Anesthesia:** The ultra short-acting barbiturates, such as thiopental, are used intravenously to induce anesthesia.

**Anticonvulsant:** Phenobarbital is used in:

- long-term management of tonic-clonic seizures
- status epilepticus,
- Phenobarbital has been regarded as the drug of choice for treatment of young children with recurrent febrile seizures.

**Anxiety:** Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. When used as hypnotics, they suppress REM sleep more than other stages. However, most have been replaced by the benzodiazepines.
Pharmacokinetics:
Barbiturates are absorbed orally and distributed widely throughout the body. Barbiturates are metabolized in the liver, and inactive metabolites are excreted in the urine. They cross the placenta and can depress the fetus.

Adverse effect of barbiturates:
1) CNS: Barbiturates cause drowsiness, impaired concentration, The CNS depressant effects of barbiturates synergize with those of ethanol.
2) Drug hangover
3) Induce the P450 system and may decrease the duration of action of drugs that are metabolized by these hepatic enzymes.
4) Increase porphyrin synthesis, and are contraindicated in patients with acute intermittent porphyria.
5) Physical dependence: Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, nausea and vomiting, seizures, delirium, and cardiac arrest.
6) Poisoning: death resulting from drug overdoses because of severe depression of respiration and central cardiovascular depression.

Note: No specific barbiturate antagonist is available

Treatment of patient with barbiturates poisoning
- Artificial respiration
- Purging the stomach of its contents if the drug has been recently taken
- Hemodialysis may be necessary if large quantities have been taken.
- Alkalization of the urine often aids in the elimination of phenobarbital.
Benzodiazepines
They are the most widely used anxiolytic drugs. They have largely replaced barbiturates because:
1. The benzodiazepines are safer (have a wide therapeutic index) and more effective.
2. Not cause drug-drug interaction (not induce hepatic microsomal enzyme)
3. Produce tolerance and psychological dependence but physical dependence and withdrawal symptom are less marked
4. Benzodiazepine antagonist is available

Benzodiazepines are classified according to their duration of action into:
- **Short-acting**: Oxazepam, Triazolam (3-8) hours
- **Intermediate-acting**: Alprazolam, Lorazepam, Temazepam (10-20) hours
- **Long-acting**: Chlordiazepoxide, Diazepam, Flurazepam

**ANXIOLYTIC**: Alprazolam, chlordiazepoxide, clonazepam, diazepam, lorazepam
**Hypnotic**: Triazolam, temazepam, flurazepam

**Mechanism of action:**
Binding of GABA to its receptor triggers an opening of a chloride channel, which leads to an increase in chloride conductance.
Benzodiazepines increase the frequency of channel openings produced by GABA. The influx of chloride ions causes a small hyperpolarization, inhibits the formation of action potentials.

**Actions:**
The benzodiazepines have neither antipsychotic activity nor analgesic action, and they do not affect the autonomic nervous system. All benzodiazepines exhibit the following actions to a greater or lesser extent:
1. **Reduction of anxiety**: At low doses, the benzodiazepines are anxiolytic. They are thought to reduce anxiety by selectively inhibiting neuronal circuits in the limbic system of the brain.
2. **Sedative and hypnotic actions:** All of the benzodiazepines used to treat anxiety have some sedative properties, and some can produce hypnosis at higher doses.

3. **Anticonvulsant:** some are used to treat epilepsy (status epilepticus) and other seizure disorders.

4. **Muscle relaxant:** At high doses, the benzodiazepines relax the spasticity of skeletal muscle

**Therapeutic uses:**

1. Benzodiazepines are effective for the treatment of the anxiety symptoms secondary to panic disorder, generalized anxiety disorder, specific phobias, such as fear of flying.

2. Diazepam is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain, and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

3. The shorter-acting agents are often employed as premedication for anxiety-provoking and unpleasant procedures, such as endoscopic, bronchoscopic, and certain dental procedures as well as angioplasty. They also cause a form of conscious sedation, allowing the person to be receptive to instructions during these procedures.

4. Midazolam is an injectable-only benzodiazepine also used for the induction of anesthesia.

5. **Seizures:**
   - Clonazepam is occasionally used in the treatment of certain types of epilepsy.
   - Diazepam and lorazepam are the drugs of choice in terminating grand mal epileptic seizures and status epilepticus.
   - Due to cross-tolerance, chlordiazepoxide, diazepam, and oxazepam are useful in the acute treatment of alcohol withdrawal and reducing the risk of withdrawal-related seizures.

6. **Sleep disorders:**
   - **Flurazepam:** has a long-acting effect and causes little rebound insomnia.
   - **Temazepam:** This drug is useful in patients who experience frequent wakening (insomnia caused by the inability to stay asleep). However, the
peak sedative effect occurs 1 to 3 hours after an oral dose; therefore, it should be given 1 to 2 hours before the desired bedtime.

**Triazolam:** short duration of action and, therefore, is used to induce sleep in patients with recurring insomnia (difficulty in going to sleep)

**Pharmacokinetics**
- The benzodiazepines are lipophilic, and they are rapidly and completely absorbed after oral administration and distribute throughout the body.
- The half-lives of the benzodiazepines are very important clinically, because the duration of action may determine the therapeutic usefulness.
- The longer-acting agents form active metabolites with long half-lives.
- Most benzodiazepines, including chlordiazepoxide and diazepam, are metabolized by the hepatic microsomal system to compounds that are also active.
- The drug’s effects are terminated not only by excretion but also by redistribution.
- The benzodiazepines are excreted in the urine as glucuronides or oxidized metabolites.
- All the benzodiazepines cross the placental barrier and may depress the CNS of the newborn if given before birth. Nursing infants may also become exposed to the drugs in breast milk.

**Adverse effects**
1. Drowsiness and confusion: Ataxia occurs at high doses
2. Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given over a prolonged period. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and rarely, seizures. Because of the long half-lives of some benzodiazepines, withdrawal symptoms may occur slowly and last a number of days after discontinuation of therapy.

**Note:** Benzodiazepines with a short elimination half-life, such as triazolam, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated, such as flurazepam
Precautions:
- In treating patients with liver disease.
- In patients with acute narrow-angle glaucoma.
- Alcohol and other CNS depressants enhance the sedative-hypnotic effects of the benzodiazepines.

Benzodiazepine Antagonist
Flumazenil (is a GABA-receptor antagonist) that can rapidly reverse the effects of benzodiazepines (competitively occupies a GABA-receptor without causing a functional change in CL channel). The drug is available for intravenous administration only. Onset is rapid but duration is short, with a half-life of about 1 hour. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine

Side effects:
1. Dizziness, nausea, vomiting, and agitation are the most common.
2. Withdrawal in dependent patients
3. Seizures
   - If a benzodiazepine is used to control seizure activity
   - If the patient ingests tricyclic antidepressants.
Anxiolytic, Sedative and Hypnotic Drugs

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A Receptor empty (no agonists)

B Receptor binding GABA

C Receptor binding GABA and benzodiazepine

Entry of Cl⁻ hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.

Binding of GABA causes the chloride ion channel to open, leading to hyperpolarization of the cell.

Binding of GABA is enhanced by benzodiazepine, resulting in a greater entry of chloride ions.

Empty receptor is inactive, and the coupled chloride channel is closed.
Other anxiolytic drugs:

**Buspirone:**
It is useful in the treatment of generalized anxiety disorder and has an efficacy comparable to that of the benzodiazepines.
Mode of action differs from that of the benzodiazepines because the actions of buspirone appear to be mediated by:
- Serotonin (5-HT<sub>1A</sub>) receptors
- buspirone displays some affinity for DA<sub>2</sub> dopamine receptors and 5-HT<sub>2A</sub> serotonin receptors

Buspirone has the slow onset of action, it undergoes metabolism by CYP3A4; thus, its half-life is *shortened if taken with rifampin (an inducer of the enzyme),* *lengthened if taken with erythromycin (an inhibitor of the enzyme)*

Adverse effects: headaches, dizziness, nervousness.

**Hydroxyzine:** Is an antihistamine with antiemetic activity. It has a low tendency for habituation and, thus, is useful for patients with anxiety who have a history of drug abuse. It is also often used for sedation prior to dental procedures or surgery. Drowsiness is a possible adverse effect.

**Antidepressants:** Many antidepressants have proven efficacy in managing the long-term symptoms of chronic anxiety disorders and should be considered as first-line agents, especially in patients with concerns for addiction or dependence or a history of addiction or dependence to other substances. The SSRIs, TCAs, venlafaxine, duloxetine and MAOIs all have potential usefulness in treating anxiety.

**Other Hypnotic Agents:**

**Zolpidem:** The hypnotic zolpidem is not a benzodiazepine in structure, but it acts on a subset of the benzodiazepine receptor family, BZ<sub>1</sub>.
Zolpidem has no anticonvulsant or muscle-relaxing properties.
It shows few withdrawal effects, and minimal rebound insomnia, and little or no tolerance occurs with prolonged use.
Zolpidem is rapidly absorbed from the gastrointestinal tract, and it has a rapid onset of action and short elimination half-life (about 2 to 3 hours). Zolpidem undergoes hepatic oxidation by the cytochrome P450 system to inactive products. Thus, drugs such as rifampin, which induce this enzyme system, shorten the half-life of zolpidem, and drugs that inhibit the CYP3A4 isoenzyme may increase the half-life this drug.

**Adverse effects of zolpidem:** include nightmares, agitation, headache, gastrointestinal upset, dizziness, and daytime drowsiness.

**Ramelteon:** Is a selective agonist at the MT<sub>1</sub> and MT<sub>2</sub> subtypes of melatonin receptors. Stimulation of MT<sub>1</sub> and MT<sub>2</sub> receptors by melatonin in the hypothalamus is able to induce and promote sleep. Ramelteon is indicated for the treatment of insomnia in which falling asleep (increased sleep latency) is the primary complaint.

The potential for abuse of Ramelteon is believed to be minimal, and no evidence of dependence or withdrawal effects has been observed. Therefore, ramelteon can be administered long-term.

**Adverse effects of ramelteon:**
- Dizziness, fatigue
- Ramelteon may also increase prolactin levels.

**Chloral hydrate:** Is a trichlorinated derivative of acetaldehyde that is converted to the active metabolite, trichloroethanol, in the body. The drug is an effective sedative and hypnotic that induces sleep in about 30 minutes and the duration of sleep is about 6 hours. Chloral hydrate is irritating to the gastrointestinal tract and causes epigastric distress. It also produces an unusual, unpleasant taste sensation. It synergizes with ethanol.

**Antihistamines:** Nonprescription antihistamines with sedating properties, such as diphenhydramine, they are effective in treating mild types of insomnia. They have numerous undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines.