

ANXIOLYTICS AND HYPNOTIC DRUGS

BENZODIAZEPINES

Alprazolam **XANAX**
Chlordiazepoxide **LIBRIUM**
Clonazepam **KLONOPIN**
Clorazepate **TRANXENE**
Diazepam **VALIUM, DIASTAT**
Estazolam
Flurazepam **DALMANE**
Lorazepam **ATIVAN**
Midazolam **VERSED**
Oxazepam
Quazepam **DORAL**
Temazepam **RESTORIL**
Triazolam **HALCION**

BENZODIAZEPINE ANTAGONIST

Flumazenil **ROMAZICON**

OTHER ANXIOLYTIC DRUGS

Antidepressants **VARIOUS (SEE CHAPTER 10)**
Buspirone **BUSPAR**

BARBITURATES

Amobarbital **AMYTAL**
Pentobarbital **NEMBUTAL**
Phenobarbital **LUMINAL SODIUM**
Secobarbital **SECONAL**
Thiopental **PENTOTHAL**

OTHER HYPNOTIC AGENTS

Antihistamines **VARIOUS (SEE CHAPTER 30)**
Doxepin **SILENOR**
Eszopiclone **LUNESTA**
Ramelteon **ROZEREM**
Zaleplon **SONATA**
Zolpidem **AMBIEN, INTERMEZZO, ZOLPIMIST**

• Anxiety is an unpleasant state of tension, apprehension, or uneasiness, a fear that seems to arise from a sometimes unknown source.

• The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation.

• Episodes of mild anxiety are common life experiences and do not warrant treatment.

• However, the symptoms of severe, chronic, debilitating anxiety may be treated with anti-anxiety drugs (sometimes called anxiolytic or minor tranquilizers) and psychotherapy.

• Because many of the anti-anxiety drugs also cause some sedation, the same drugs often function clinically as both

anxiolytic and hypnotic (sleep-inducing) agents.

- In addition, some drugs have anticonvulsant activity.

The Benzodiazepines (BDZs)

- BDZ are the most widely used anxiolytic drugs.
- The BDZ are safe and effective.

Mechanism of action

- The targets for benzodiazepine actions are the γ -aminobutyric acid (GABA_A) receptors.
- GABAergic neurons are distributed widely in the CNS.
- GABA is the major inhibitory neurotransmitter in the CNS.
- GABA controls the state of excitability in all brain areas.

- When GABA binds with the GABA_A-benzodiazepine receptor complex, the permeability of the receptor to chloride ions increases, allowing more ions to enter into the neuron and decreasing excitability.
- Drugs that act as agonists at this receptor are used in sleep and anxiety disorders.

Actions

- BDZs have hypnotic, sedative, anxiolytic, anticonvulsant and (central) muscle relaxant actions.

All BDZs exhibit the following actions to a greater or lesser extent:

- 1- Reduction of anxiety:** At low doses, the BDZ are anxiolytic.
- 2- Sedative and hypnotic actions:** All BDZ have some sedative properties, and some can produce hypnosis (artificially produced sleep) at higher doses.
- 3- Anticonvulsant:** Several of the BDZ have anticonvulsant activity and some are used to treat epilepsy .
- 4- Muscle relaxant:** At high doses, the BDZ relax the spasticity of skeletal muscle.

Therapeutic uses:-

- 1. Anxiety disorders:** BDZ are effective for the treatment of the anxiety symptoms secondary to panic disorder, generalized anxiety disorder, social anxiety disorder, performance anxiety, posttraumatic stress disorder, obsessive-compulsive disorder, and the extreme anxiety sometimes encountered with specific phobias, such as fear of flying. *These drugs should not be used to alleviate the normal stress of everyday life.* The longer-acting agents, such as *clonazepam, lorazepam, and diazepam*, are often preferred in

those patients with anxiety that may require treatment for prolonged periods of time.

2. Muscular disorders: *Diazepam* is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain.

3. Amnesia: 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. *Midazolam* is used for this purpose.

4. Seizures:

Clonazepam is occasionally used in the treatment of certain types of epilepsy, whereas *diazepam* and *lorazepam* are the drugs of choice in terminating grand mal epileptic seizures.

Due to cross-tolerance, **chlordiazepoxide, clorazepate diazepam, and oxazepam** are useful in the acute treatment of alcohol withdrawal and reducing the risk of withdrawal-related seizures.

5. sleep disorders: some BDZ are useful as hypnotic agents. It is important to balance the sedative effect needed at bedtime. The drugs used are: *flurazepam (long-acting), temazepam, Triazolam*.

Pharmacokinetics

1. Absorption and distribution: The BDZs are lipophilic, and they are rapidly and completely absorbed after oral administration and distribute throughout the body.

Duration of actions: The half-lives of the BDZs are very important clinically, because the duration of action may determine the therapeutic usefulness. The BDZs can be roughly divided into short-, intermediate-, and long-acting groups. The longer-acting agents form active metabolites with long half-lives.

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.

Other Anxiolytic Drugs

A. Buspirone

Buspirone is as effective as BDZ in treating anxiety disorders..The actions of *buspirone* appear to be mediated by serotonin (5-HT_{1A}) receptors, Thus, its mode of action differs from that of the benzodiazepines. It lacks the anticonvulsant and muscle-relaxant properties of the BDZs and causes only minimal sedation.

B- Hydroxyzine

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.

Barbiturates

- The barbiturates were formerly the mainstay of treatment to sedate the patient or to induce and maintain sleep.
- Today, they have been largely replaced by the BDZs, primarily because barbiturates induce tolerance, drug-metabolizing enzymes, physical dependence, and are associated with very severe withdrawal symptoms.
- They can cause coma in toxic doses.
- Certain barbiturates, such as the very short-acting *thiopental*, are still used to induce anesthesia.

Mechanism of action

- The sedative-hypnotic action of the barbiturates is due to their interaction with GABA_A receptors, which enhances GABAergic transmission.
- Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings.

Therapeutic uses

Anesthesia: Selection of a barbiturate is strongly influenced by the desired duration of action. *thiopental*, are used intravenously to induce anesthesia.

Anticonvulsant: *Phenobarbital* is used in long-term management of tonic-clonic seizures, status epilepticus, and eclampsia.

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.

Adverse effects

CNS: Barbiturates cause drowsiness, impaired concentration.

Drug hangover: Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient wakes. Occasionally, nausea and dizziness occur.

Physical dependence: Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opiates and can result in death.

Poisoning: Barbiturate poisoning has been a leading cause of death resulting from drug overdoses for many decades. Severe depression of respiration is coupled with central cardiovascular depression.

Non-benzodiazepines hypnotics

These drugs act on the same receptors as BDZs, GABA_A, although they are structurally unrelated to BDZs.

1. *Zolpidem*

This drug acts on a subset of the BDZ receptor family, BZ1. *Zolpidem* has no anticonvulsant or muscle-relaxing properties. It shows few withdrawal effects. Has 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).

2. *Zaleplon*

Zaleplon is very similar to *zolpidem* in its hypnotic actions.

3. *Eszopiclone*

This drug acts also at BZ1 receptor, used to treat insomnia. It is rapidly absorbed (time to peak, 1 hour).

4. *Ramelteon*

Ramelteon is a selective agonist at the MT1 and MT2 subtypes of melatonin receptors.

Ramelteon is indicated for the treatment of insomnia. 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.

Chloral hydrate

Chloral hydrate 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*.