

Anxiolytic and Hypnotic Drugs

Disorders involving anxiety are among the most common mental disorders. Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that arises from either a known or an 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, severe, chronic, debilitating anxiety may be treated with antianxiety drugs (anxiolytics).

Because many antianxiety drugs also cause some sedation, they may be used clinically as both anxiolytic and hypnotic (sleep-inducing) agents.

Classification of Anxiolytics and Hypnotics

(in this you must know the names of 4-5 major drugs at least)

1. BENZODIAZEPINES:

- Alprazolam
- Triazolam
- Diazepam
- Flurazepam
- Lorazepam
- Clorazepate

KEY: AT DFLC

2. BENZODIAZEPINE ANTAGONIST

- Flumazenil

3. ANXIOLYTIC DRUGS

- Antidepressants
- Buspirone
- Some Benzodiazepines are anxiolytics at low doses

KEY: AB S

4. BARBITURATES

- Amobarbital
- Pentobarbital
- Phenobarbital
- Secobarbital
- Thiopental

KEY: AP PST

5. HYPNOTIC AGENTS

PHARMACOLOGY

- Antihistamines (various like Avil)
- Doxepin
- Ramelteon (widely used these days)
- Zaleplon
- Zolpidem

KEY: AD RZZ

BENZODIAZEPINES

Benzodiazepines are widely used anxiolytic drugs. They have largely replaced barbiturates in the treatment of anxiety and insomnia, because benzodiazepines are generally considered to be safer and more effective.

Though benzodiazepines are commonly used, they are not necessarily the best choice for anxiety or insomnia.

Mechanism of action:

The targets for benzodiazepine actions are the γ -aminobutyric acid (GABA_A) receptors.

[Note: GABA is the major inhibitory neurotransmitter in the central nervous system (CNS).]

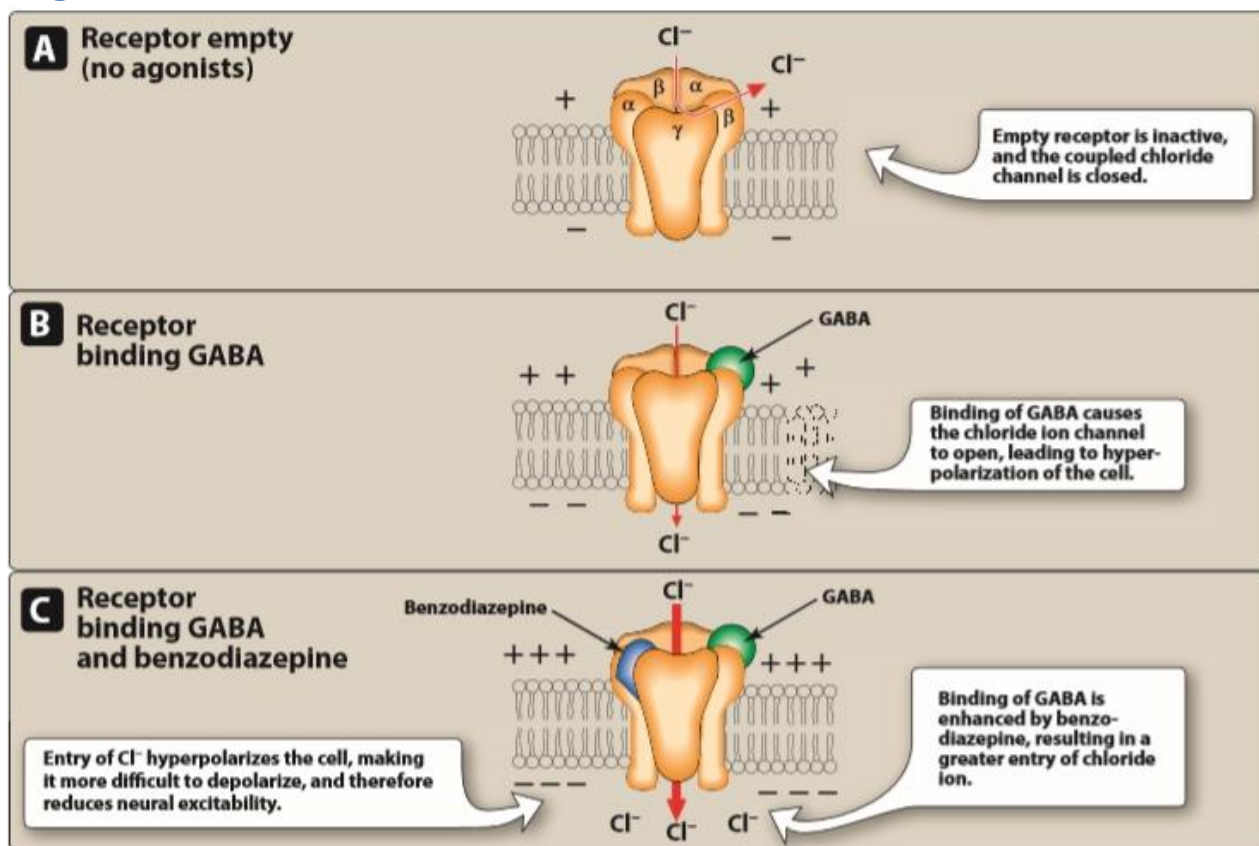
GABA is a pentameric transmembrane ion channel gated structure). The GABA_A receptors are composed of a combination of five $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$ and γ subunits.

- 1- During anxiety, Chloride channels are closed and there is no Cl^- influx.
- 2- The channels for Cl^- influx remain close until GABA binds to its receptor.
- 3- GABA neurotransmitter attaches at GABA receptor.
- 4- Chloride channel opens and Cl^- influx increases.
- 5- If Benzodiazepine is given, it attaches to GABA receptor along with GABA neurotransmitter in result to which Cl^- influx further increases causing "hyper-polarization"

GABA (neurotransmitter) attaches to GABA (receptor) = Cl^- influx increases

GABA (neurotransmitter) + Benzodiazepines attaches on GABA (receptor) = Cl^- influx further increases (hyperpolarization)

Diagrammatic view:



Major Pharmacological and Therapeutic Actions of Anxiolytics:

1. Reduction of anxiety:

At low doses, the benzodiazepines are anxiolytic. They are thought to reduce anxiety by selectively enhancing transmission in neurons having the α_2 sub-unit in their GABA_A receptors. E.g. Generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, posttraumatic stress disorder, obsessive-compulsive disorder, and extreme anxiety associated with phobias, such as fear of flying.

The benzodiazepines are also useful in treating anxiety related to depression and schizophrenia. These drugs should be reserved for severe anxiety only and not used to manage the stress of everyday life.

Because of their addiction potential, they should only be used for short periods of time. The longer-acting agents, such as diazepam are often preferred in those patients with anxiety that may require prolonged treatment.

The antianxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects.

PHARMACOLOGY

Tolerance is, decreased responsiveness to repeated doses of the drug or Reduction in drug effect requiring an increased dose to maintain same response.

Tolerance develops if Benzodiazepine is taken for a long time.

2. Amnesia (temporary loss of memory):

The shorter-acting agents are often employed as pre-medication for anxiety-provoking and unpleasant procedures, such as endoscopy, dental procedures, and angioplasty. They cause a form of conscious sedation, allowing the person to be receptive to instructions during these procedures. **Midazolam** is used to facilitate Amnesia while causing sedation prior to anesthesia.

3. Seizures:

Diazepam, lorazepam, and oxazepam are useful in the acute treatment of alcohol withdrawal and reduce the risk of withdrawal-related seizures.

4. Muscle relaxant:

At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord, where the $\alpha 2$ -GABAA receptors are largely located.

Diazepam is useful in the treatment of skeletal muscle spasms.

5. Sleep disorders:

A few of the benzodiazepines are useful as hypnotic agents.

Benzodiazepines increase Non-rapid eye movement sleep and decrease Rapid eye movement sleep (slow wave sleep).

Examples may include **Temazepam** used in frequent waking and **Triazolam** used for insomnia.

Dependence:

Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given for a prolonged period.

Comprises of

1- Physical dependence

2- Physiological dependence

1- Physical dependence:

The state of response to a drug whereby the removal of drug evokes unpleasant symptoms usually opposite of drug effect.

Mortality rate of Physical dependence is more.

2- Physiological dependence:

The state of response of a drug whereby a drug user feels compelled to use the drug and suffer anxiety when separated from the drug in which repeated use of the drug induces reliance for a state of well-being and contentment but there are no physical withdrawal symptoms e.g. Nicotine (soft drug).

Classification of Benzodiazepine (regarding duration of action)

1- Long acting (1-3 days)

- decrease Sleep Induction time
- decrease No of Wakening
- Increase duration of Sleep

Examples: Clorazepate, Chlordiazepoxide, Diazepam, Flurazepam, Quazepam

2- Intermediate Acting (10-20 hours)

- decrease frequent wakening
- peak sedative effect in 1-3 hours
- 1-2 hours before going to sleep

Examples: Alprazolam, Estazolam, Lorazepam, Temazepam

3- Short Acting (3-8 hours)

Examples: Oxazepam, Triazolam

Benzodiazepine Antagonist

We give it to patients who have been taking Benzodiazepines from a long time.

In Benzodiazepine toxicity we may also do Gastric lavage, use activated charcoal, induce emesis, may do alkalization of urine and even dialysis.

- It reverses the effect of Benzodiazepine e.g. Flumazenil is a GABA receptor antagonist that can rapidly reverse the effects of benzodiazepines
- Intra- venous (IV) administration only
- Onset is rapid
- duration is short, with a half-life of about 1 hour
- Frequent administration may be necessary
- If given to patients of seizures, the seizures increase
- In patients of depression using Tricyclic antidepressants if we use Flumazenil it will cause sedation.

PHARMACOLOGY

Barbiturates

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep.

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

They induce drug metabolizing enzymes like Cytochrome P450.