# DRUGS THAT ACT IN THE CNS

## Anxiolytic and Hypnotic Drugs

**Dr Karamallah S. Mahmood**

**PhD Clinical Pharmacology**

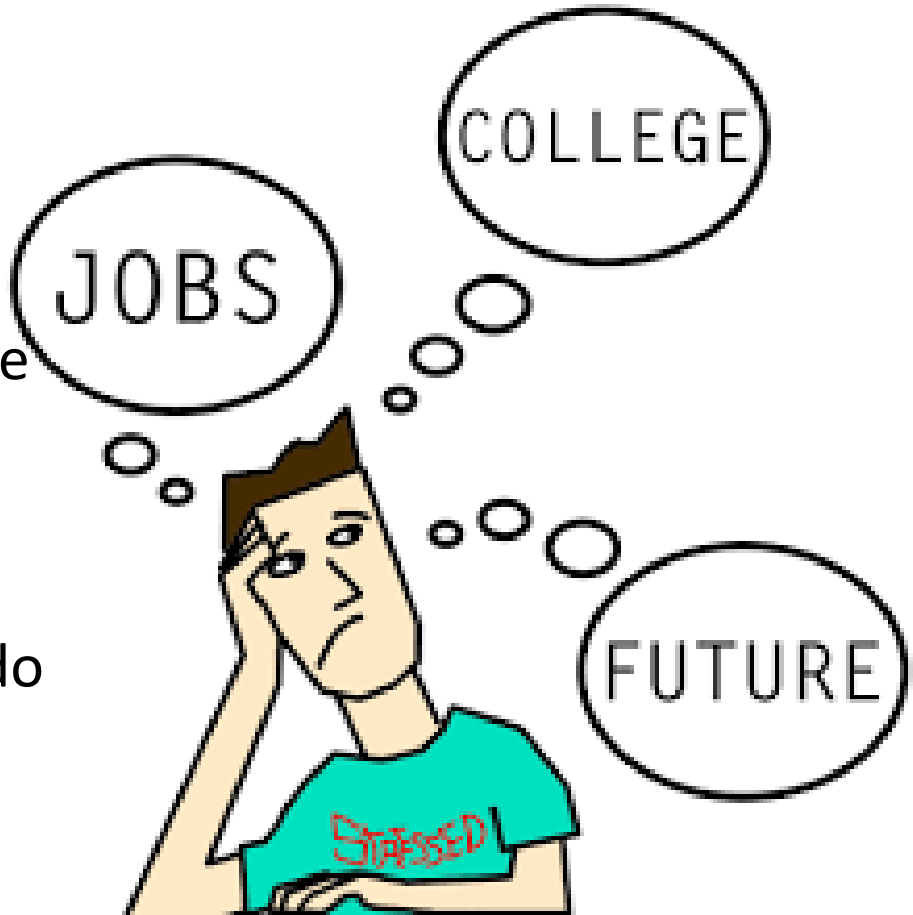
# Anxiety Disorders

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.

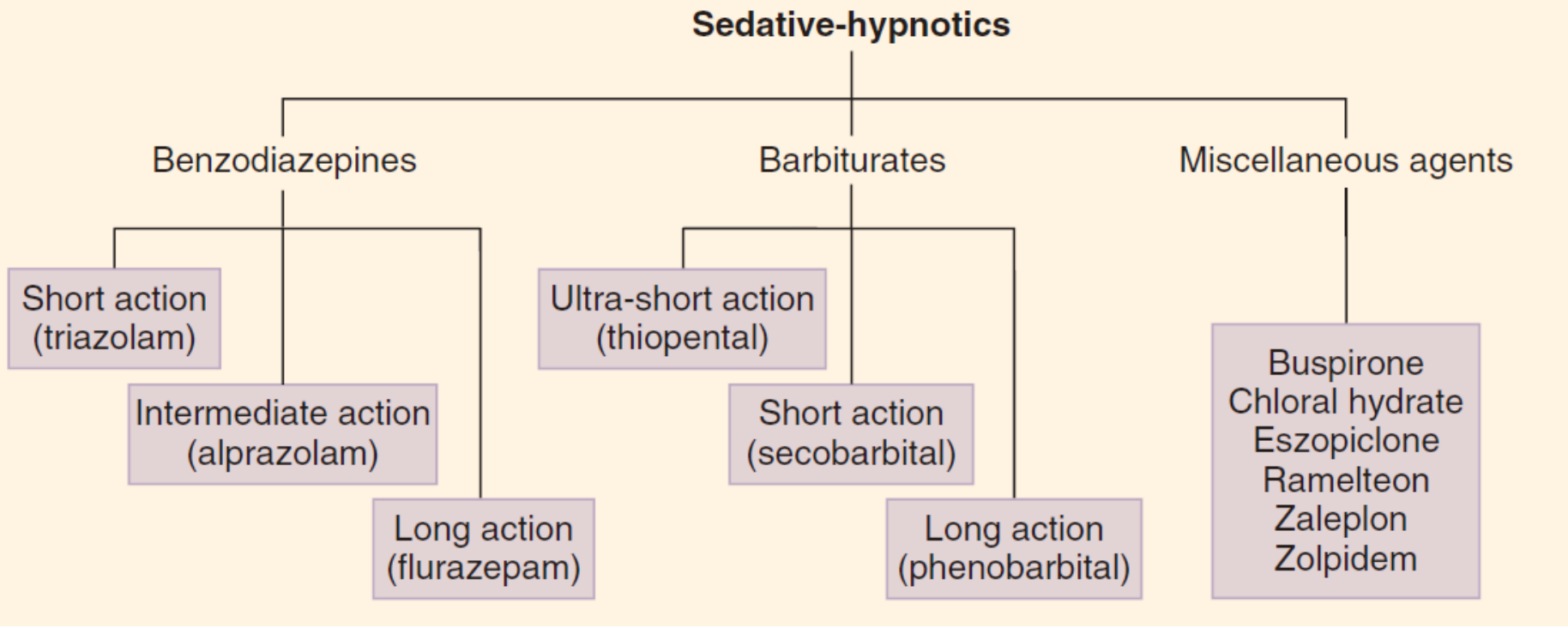


# Anxiety Disorders

However, **severe, chronic, debilitating anxiety** may be treated with antianxiety drugs (sometimes called **anxiolytics**) and/or some form of psychotherapy.

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

# Anxiety Disorders / BENZODIAZEPINES




**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**

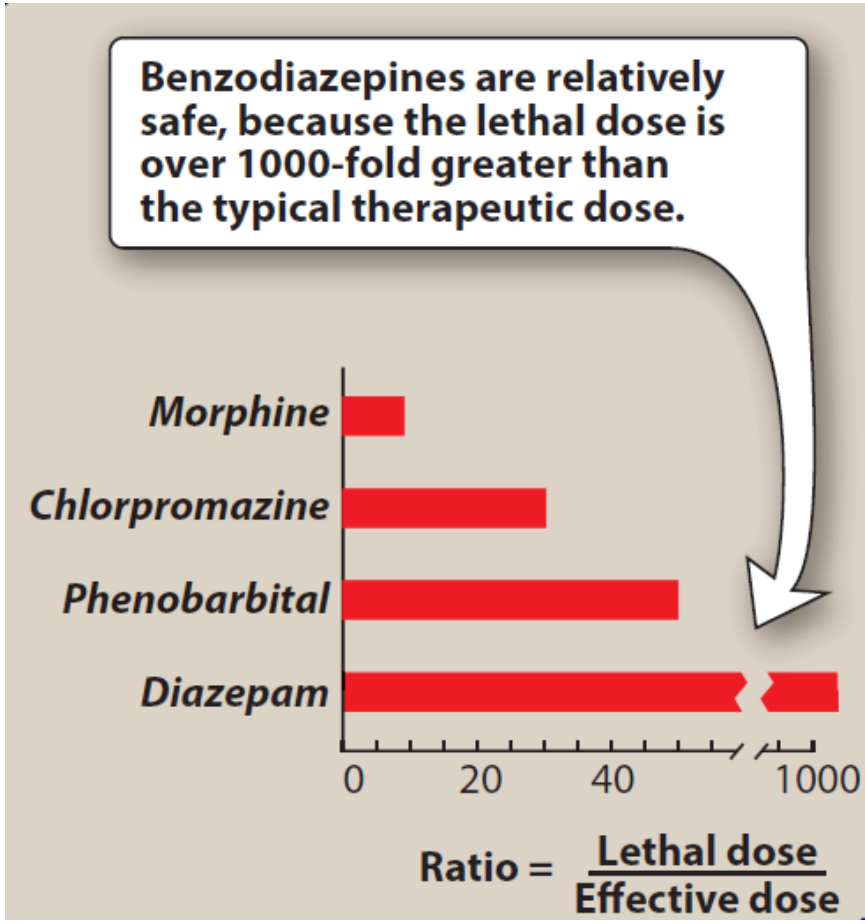
*Amobarbital* AMYTAL
*Pentobarbital* NEMBUTAL
*Phenobarbital* LUMINAL SODIUM
*Secobarbital* SECONAL
*Thiopental* PENTOTHAL

**OTHER HYPNOTIC AGENTS**

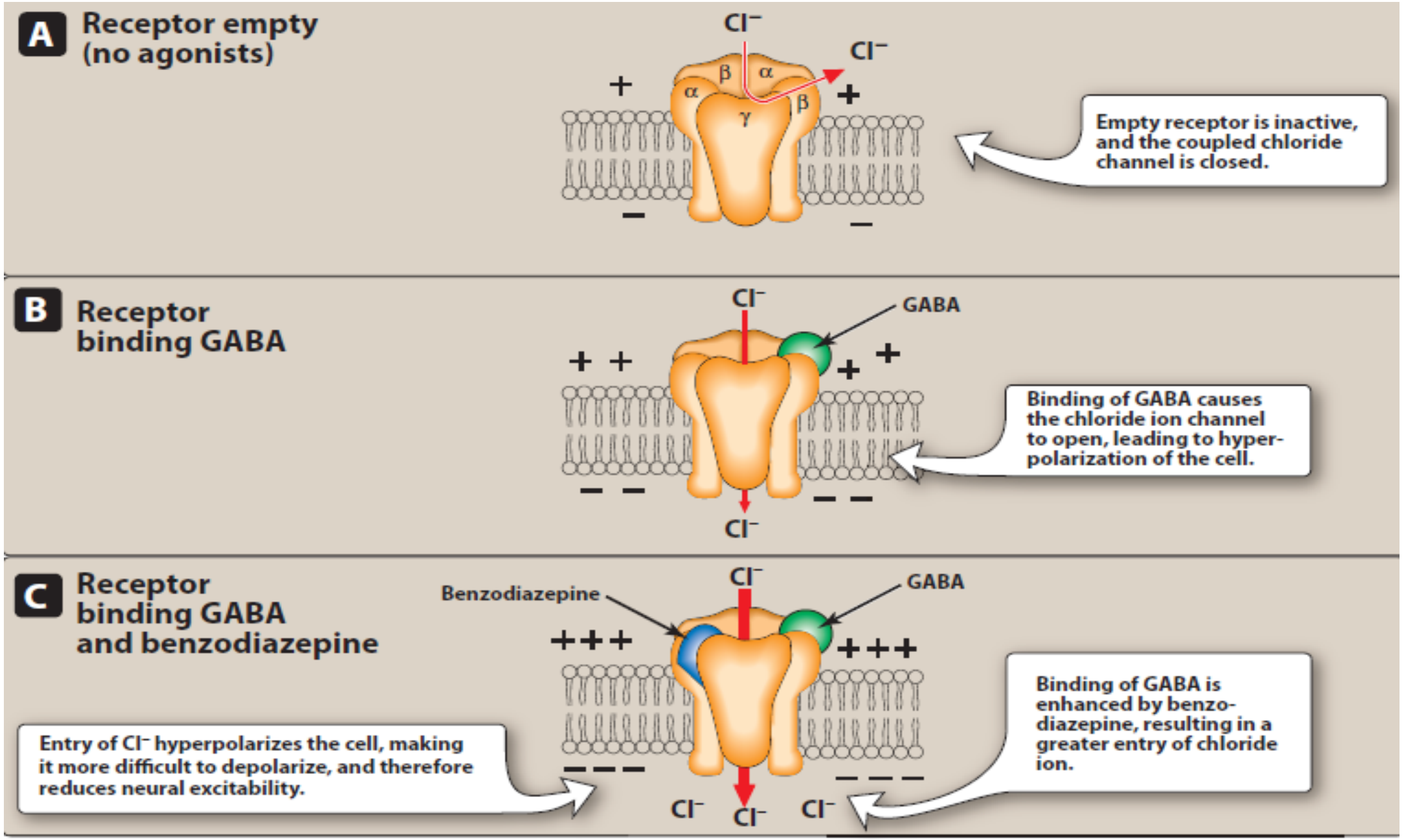
Antihistamines VARIOUS (SEE CHAPTER 30)
*Doxepin* SILENOR
*Eszopiclone* LUNESTA
*Ramelteon* ROZEREM
*Zaleplon* SONATA
*Zolpidem* AMBIEN, INTERMEZZO, ZOLPIMIST

# BENZODIAZEPINES

- ✓ Benzodiazepines are **widely used** anxiolytic drugs.
- ✓ They have largely replaced barbiturates and meprobamate 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.
- ✓ Certain antidepressants with anxiolytic action, such as the **SSRI**, are preferred in many cases, and **nonbenzodiazepine** hypnotics and antihistamines may be preferable for insomnia.



# BENZODIAZEPINES/ Mechanism of Action



# BENZODIAZEPINES/ 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).
- ✓ The GABAA receptors are composed of a combination of five α, β, and γ subunits that span the postsynaptic membrane.
- ✓ For each subunit, many subtypes exist (for example, there are six subtypes of the α subunit).
- ✓ Binding of GABA to its receptor triggers an **opening** of the central ion channel, allowing **chloride** through the pore.
- ✓ The influx of chloride ions causes **hyperpolarization** of the neuron and decreases neurotransmission by inhibiting the formation of action potentials.

# BENZODIAZEPINES/ Mechanism of Action

- ✓ Benzodiazepines modulate GABA effects by binding to a specific, high-affinity site (distinct from the GABA-binding site) located at the interface of the α subunit and the γ subunit on the GABAA receptor.

- ✓ Note: These binding sites are sometimes labeled "**benzodiazepine (BZ) receptors**." Common BZ receptor subtypes in the CNS are designated as **BZ1 or BZ2** depending on whether the binding site includes an α1 or α2 subunit, respectively.

- ✓ Benzodiazepines increase the frequency of channel openings produced by GABA.
- ✓ Note: Binding of a benzodiazepine to its receptor site increases the **affinity of GABA** for the GABA-binding site (and vice versa).

- ✓ The clinical effects of the various benzodiazepines correlate well with the binding affinity of each drug for the GABA receptor–**chloride ion** channel complex.

# BENZODIAZEPINES/ Action

## 1. Reduction of anxiety:

At **low doses**, the benzodiazepines are anxiolytic. They are thought to reduce anxiety by selectively enhancing **GABAergic** transmission in neurons having the **α2 subunit** in their $GABA_A$ receptors, thereby inhibiting neuronal circuits in the limbic system of the brain.

## 2. Sedative/hypnotic:

All benzodiazepines have sedative and calming properties, and some can produce hypnosis (artificially produced sleep) at **higher doses**. The hypnotic effects are mediated by the **α1-$GABA_A$** receptors.

# BENZODIAZEPINES/ Action

### 3. Anterograde amnesia:

Temporary impairment of memory with use of the benzodiazepines is also mediated by the **α1-GABA$_A$ receptors**. The ability to learn and form new memories is also impaired.

### 4. Anticonvulsant:

Several benzodiazepines have anticonvulsant activity. This effect is partially, although not completely, mediated by **α1-GABA$_A$** receptors.

### 5. Muscle relaxant:

**At high doses**, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord, where the **α2-GABA$_A$** receptors are largely located.

# BENZODIAZEPINES/ Therapeutic Uses

**1. Anxiety disorders:**

Benzodiazepines are effective for the treatment of the anxiety symptoms secondary to panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, post-traumatic 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.

## 1. Anxiety disorders:

The longer-acting agents, such as **clonazepam, lorazepam, and 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.

For panic disorders, **alprazolam** is effective for short- and long-term treatment, although it may cause withdrawal reactions in about 30% of patients.

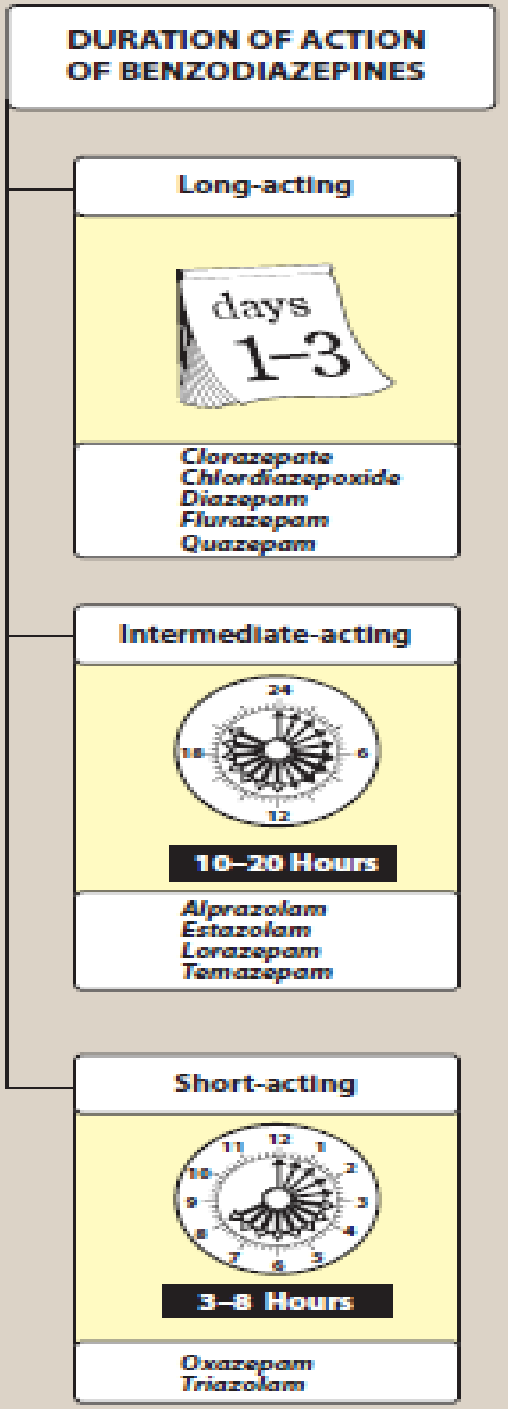
# BENZODIAZEPINES/ Therapeutic Uses

## 2. Sleep disorders:

Commonly prescribed benzodiazepines for sleep disorders include **intermediate-acting** temazepam and **short-acting** triazolam.

Long-acting flurazepam is rarely used, due to its extended half-life, which may result in excessive daytime sedation and accumulation of the drug, especially in the elderly.

Estazolam and quazepam are considered intermediate- and long-acting agents, respectively.



# BENZODIAZEPINES/ Therapeutic Uses

**3. Amnesia:**

The shorter-acting agents are often employed as **premedication** 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 a benzodiazepine used to facilitate amnesia while causing sedation prior to anesthesia.

# BENZODIAZEPINES/ Therapeutic Uses

## 4. Seizures:

**Clonazepam** is occasionally used as an adjunctive therapy for certain types of seizures, whereas **lorazepam and diazepam** are the drugs of choice in terminating status epilepticus .

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

## 5. Muscular disorders:

**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.

# BENZODIAZEPINES/ Pharmacokinetics

**Absorption and distribution:**

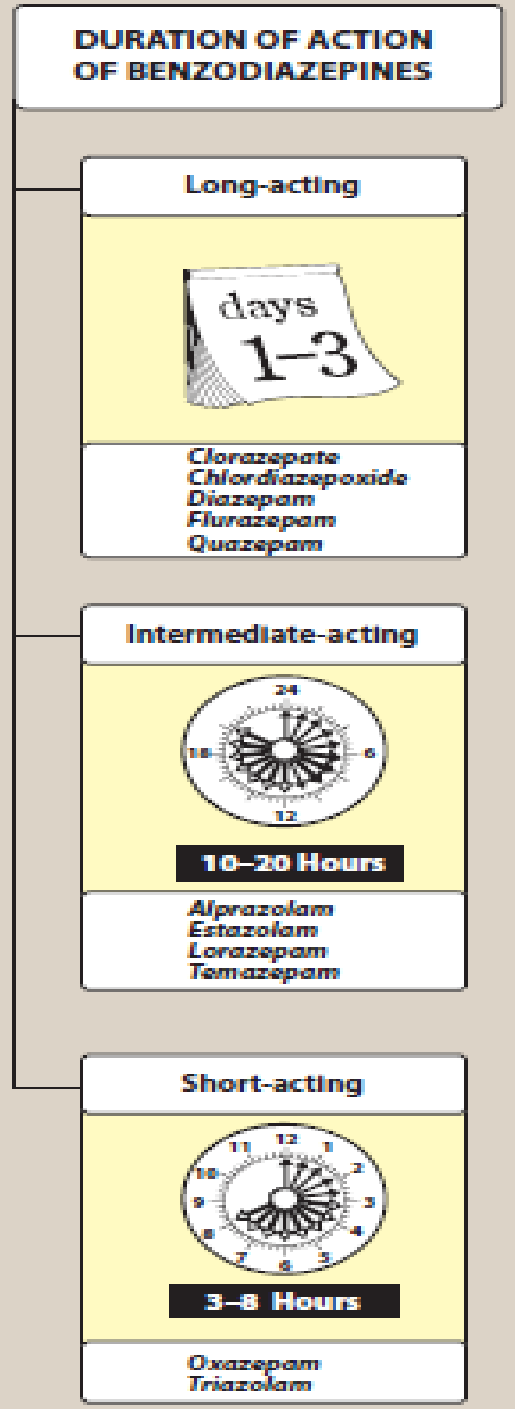
The benzodiazepines are **lipophilic**.

**Duration of action:**

The benzodiazepines can be roughly divided into short-, intermediate-, and long-acting groups.

The longer-acting agents form **active metabolites** with long half-lives.

However, with some benzodiazepines, the clinical duration of action does not correlate with the actual half-life



# BENZODIAZEPINES/ Pharmacokinetics

**Fate:**

Most benzodiazepines, including **chlordiazepoxide and diazepam**, are metabolized by the hepatic microsomal system to compounds that are also active.

All benzodiazepines cross the **placenta** and may depress the CNS of the newborn if given before birth.

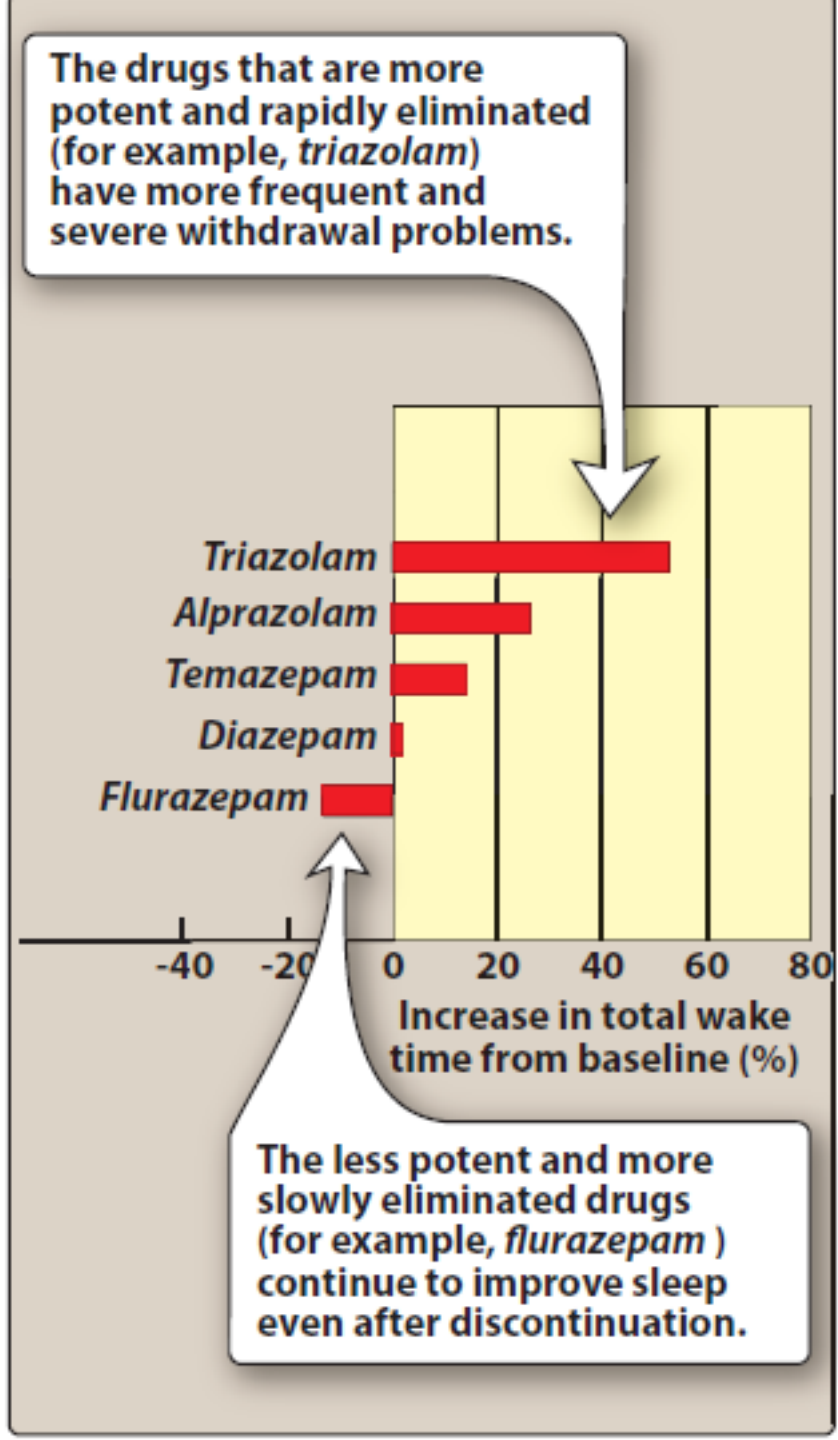
The benzodiazepines are not recommended for use during **pregnancy**.

Nursing infants may also be exposed to the drugs in breast milk.

# BENZODIAZEPINES/ Dependence

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

Abrupt discontinuation of the benzodiazepines results in **withdrawal symptoms**, including confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures. .



# BENZODIAZEPINES/ Adverse effects

**Drowsiness and confusion** are the most common side effects of the benzodiazepines.

**Ataxia** occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile.

**Cognitive impairment** (decreased long-term recall and retention of new knowledge) can occur with use of benzodiazepines.

These drugs should be avoided in patients with **acute angle-closure 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.

Administration of flumazenil may **precipitate withdrawal** in dependent patients or cause seizures if a benzodiazepine is used to control seizure activity.

Seizures may also result if the patient has a mixed ingestion with tricyclic antidepressants or antipsychotics.

Dizziness, nausea, vomiting, and agitation are the most common side effects.