# Sedative and hypnotics

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# Central nervous system (CNS) depressants

- Central nervous system (CNS) depressants are used to relieve anxiety (anxiolytic), to produce sedation (sedative), or to induce sleep (hypnotic).
- They are also anticonvulsants, centrally acting muscle relaxants, and drugs that produce amnesia.
- Physical and psychological dependence develops with prolonged use of these agents.

# Anxiolytic and Hypnotic Drugs

- 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.
- 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.

## BENZODIAZEPINES

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

## BENZODIAZEPINE ANTAGONIST

*Flumazenil* GENERIC ONLY

## OTHER ANXIOLYTIC DRUGS

Antidepressants VARIOUS (SEE CHAPTER 10)
*Buspirone* GENERIC ONLY
*Meprobamate* GENERIC ONLY

## BARBITURATES

*Amobarbital* AMYTAL
*Pentobarbital* NEMBUTAL
*Phenobarbital* GENERIC ONLY
*Secobarbital* SECONAL

## OTHER HYPNOTIC AGENTS

**Antihistamines** VARIOUS (SEE CHAPTER 37)

***Doxepin*** SILENOR

***Eszopiclone*** LUNESTA

***Ramelteon*** ROZEREM

***Suvorexant*** BELSOMRA

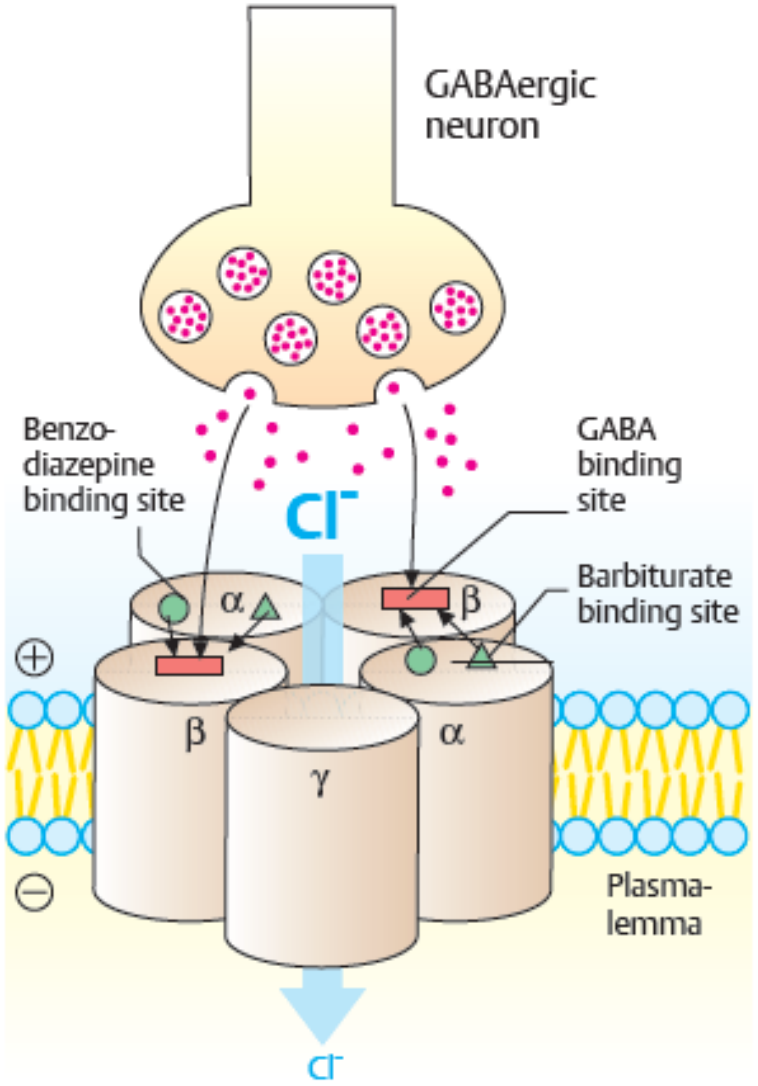
***Tasimelteon*** HETLIOZ

***Zaleplon*** SONATA

***Zolpidem*** AMBIEN, INTERMEZZO, ZOLPIMIST

# Mechanism of action of benzodiazepines and barbiturates.

- Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system (CNS).
- When GABA is released from GABAergic neurons, it binds to the β subunit of the pentameric GABA receptor, leading to opening of the chlorine channel, Cl– influx, neuronal hyperpolarization, and decreased excitability.
- **Benzodiazepines** bind to the α subunits of the GABAA receptor, enhancing the binding and effects of GABA.
- **Barbiturates** also bind to the α subunits of the GABAA receptor. They increase the length of time that the chlorine channel is open when acted upon by GABA



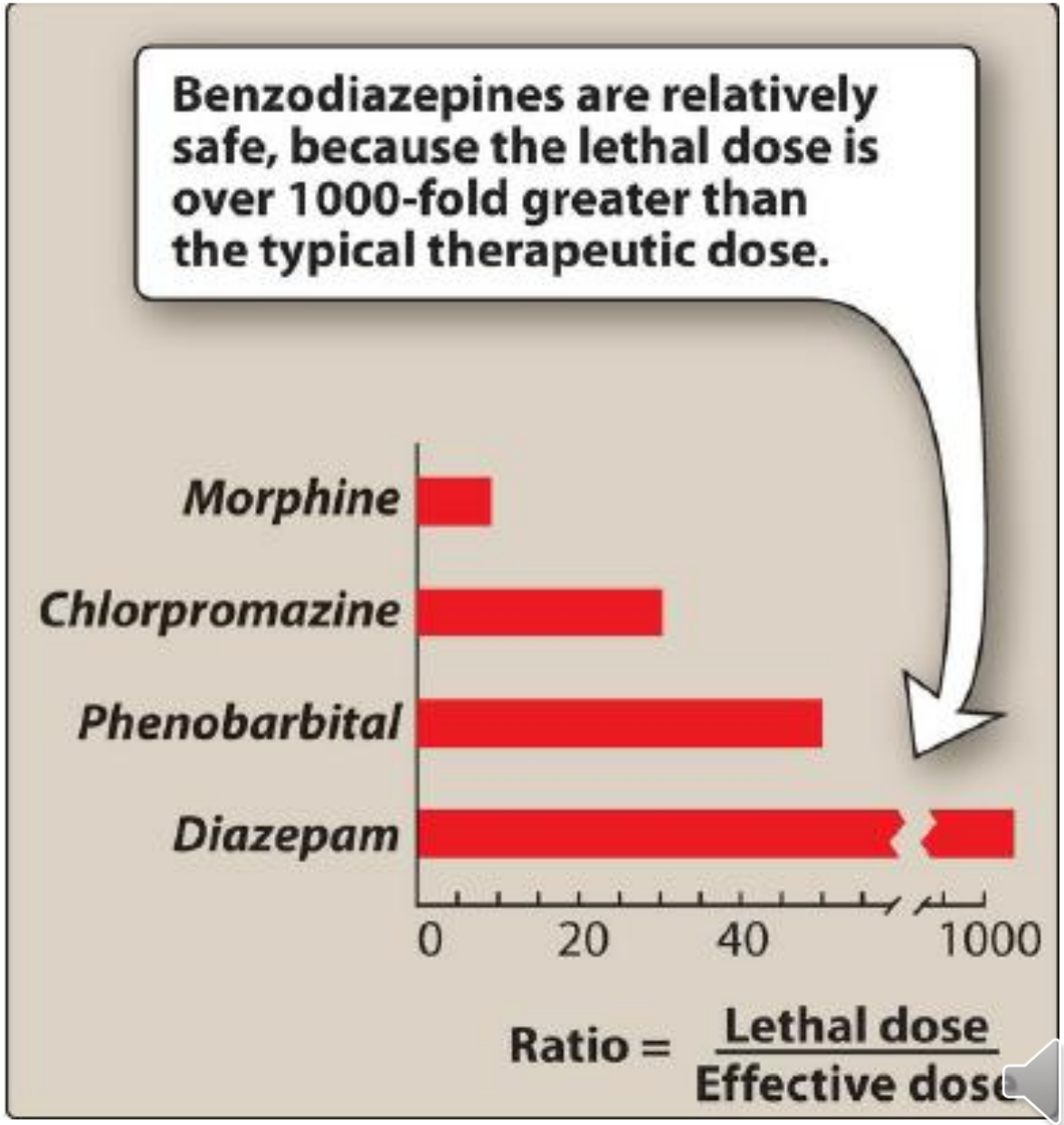
# Benzodiazepines

- There are many benzodiazepines in use, varying mainly in **potency** and **pharmacokinetics** (i.e., onset and duration of action).
- Depending on these properties, specific agents are used to treat **insomnia**, **anxiety**, **epilepsy**, and for **anesthetic induction**.
- Diazepam, Midazolam, Temazepam, Triazolam, Flurazepam, Clonazepam, Oxazepam, Lorazepam, and Alprazolam
- **Mechanism of action.**
- The benzodiazepines potentiate the actions of gamma-aminobutyric acid (GABA) by increasing the flow of Cl– ions through the GABAA receptor.

# Benzodiazepines

- *Note:* Benzodiazepines have a higher therapeutic index than barbiturates. This is because benzodiazepines act by facilitating the effects of endogenous GABA, whereas barbiturates facilitate the effects of endogenous GABA and have direct GABA-like effects, thus producing more CNS depression.
- — Diazepam has a direct muscle relaxant effect in addition to CNS actions.
- — Alprazolam has an additional antidepressant effect.
- — Triazolam may result in rebound anxiety following cessation of administration.

Ratio of lethal dose to effective dose for *morphine* (an opioid,), *chlorpromazine* (an antipsychotic), and the anxiolytic, hypnotic drugs, *phenobarbital* and *diazepam*.



# Benzodiazepines

- Many benzodiazepines have active metabolites. Effects. Benzodiazepines act almost exclusively in the CNS. The only peripheral effects are coronary vasodilation after certain benzodiazepines are injected intravenously (IV) and neuromuscular block after very high doses.

# Summary of Benzodiazepine Uses

Table 9.1 ▶ Summary of Benzodiazepine Uses

| Benzodiazepine Agent | Duration of Action | Use(s) |
|---|---|---|
| Midazolam | Short | Anesthetic induction |
| Triazolam | | Insomnia |
| Temazepam | Intermediate | Insomnia |
| Clonazepam | | Anticonvulsant |
| Oxazepam | | Anxiolysis |
| Lorazepam | | Anxiolysis |
| Alprazolam | | Anxiolysis |
| Diazepam | Long | Anxiolysis |
| Flurazepam | | Insomnia |

# DURATION OF ACTION OF BENZODIAZEPINES

## Long half-life


*Clorazepate*
*Chlordiazepoxide*
*Diazepam*
*Flurazepam*
*Quazepam*

## Intermediate half-life


**10–20 Hours**

*Estazolam*
*Lorazepam*
*Temazepam*

## Short half-life


**3–8 Hours**

*Alprazolam*
*Midazolam*
*Oxazepam*
*Triazolam*

# Benzodiazepines

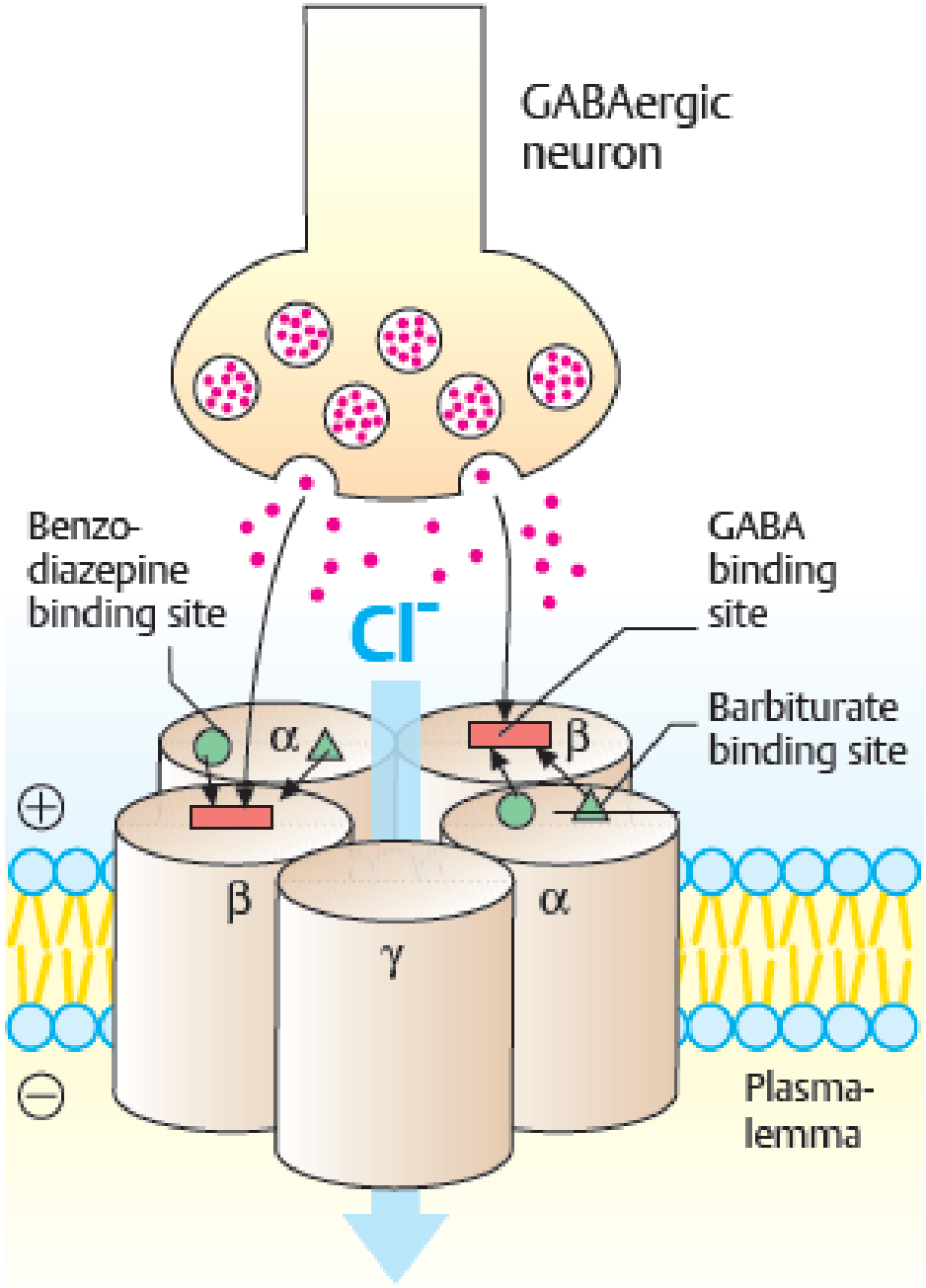
- **Side effects**
- Incoordination, dizziness, drowsiness, and decreased cognitive function
- Fatal overdose can occur when combined with ethanol.
- **Flumazenil**
- Mechanism of action. Flumazenil is a relatively specific competitive antagonist at benzodiazepine receptors.
- Uses of **Flumazenil**
- Overdose or poisoning with benzodiazepines

# Nonbenzodiazepine Benzodiazepine Receptor Agonists

- **Eszopiclone**, **Zaleplon**, and **Zolpidem**
- **Mechanism of action**. These agents are structurally unrelated to the benzodiazepines but bind to a specific subclass of benzodiazepine receptor found in the brain. They have poor muscle- relaxing or anticonvulsant activity.
- **Uses**: They are used exclusively to treat insomnia.
- **Tolerance, Dependence, and Withdrawal**
- Tolerance develops to the effects of these agents.
- Physical dependence can occur.
- Withdrawal symptoms are generally opposite to the effects of the drugs: anxiety, insomnia, and convulsions in severe withdrawal.

# Barbiturates

- Thiopental, Phenobarbital, Thiomylal, Methohexital, Amobarbital, Pentobarbital, and Secobarbital
- **Mechanism of action.** Barbiturates increase the chloride conductance of the GABAA receptor by facilitating the action of GABA. They also have direct GABA-like effects



# Barbiturates

- Thiopental, Phenobarbital, Thiomylal, Methohexital, Amobarbital, Pentobarbital, and Secobarbital
- **Pharmacokinetics**
- — Barbiturates have a low therapeutic index, so overdose (accidental or deliberate) is a problem with these agents
- — These agents induce cytochrome P-450 microsomal enzyme activity, which increases the rate of their own metabolism, as well as other drugs metabolized by this system.
- — They also induce δ-aminolevulinic acid (δ-ALA) synthetase, the rate-limiting step in heme biosynthesis. Thus, barbiturates are contraindicated in patients with acute intermittent porphyria, porphyria variegata, or a positive family history of these porphyrias.

# This table summarizes the use of each of the barbiturate drugs.

Table 9.2 ► **Summary of Barbiturate Uses**

| Barbiturate Drug | Duration of Action | Use(s) |
|---|---|---|
| Thiopental<br>Methohexital<br>Thiomylal | Ultra-short acting | Anesthetic induction |
| Amobarbital<br>Pentobarbital<br>Secobarbital | Intermediate* | Insomnia |
| Phenobarbital | Long | Anticonvulsant |

* Intermediate-acting drugs are more prone to abuse.

# Barbiturates

- **Side effects**
- — Incoordination, dizziness, drowsiness, and decreased cognitive function occur with intensity proportional to potency and dose.
- — Fatal overdose may occur by suppression of the neurogenic and hypoxic drive for respiration.