Anxiolytics and Hypnotics

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

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Anxiety

- Anxiety is an unpleasant state of tension, apprehension or uneasiness (a fear that arises from either a known or an unknown source).
- Physical symptoms of anxiety are a result of sympathetic activation: tachycardia, sweating, trembling and palpitations).
- Anxiety disorders include: Generalized anxiety disorder, panic disorder, obsessive compulsive disorder, phobias, etc.

Anxiolytics: Classes of 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

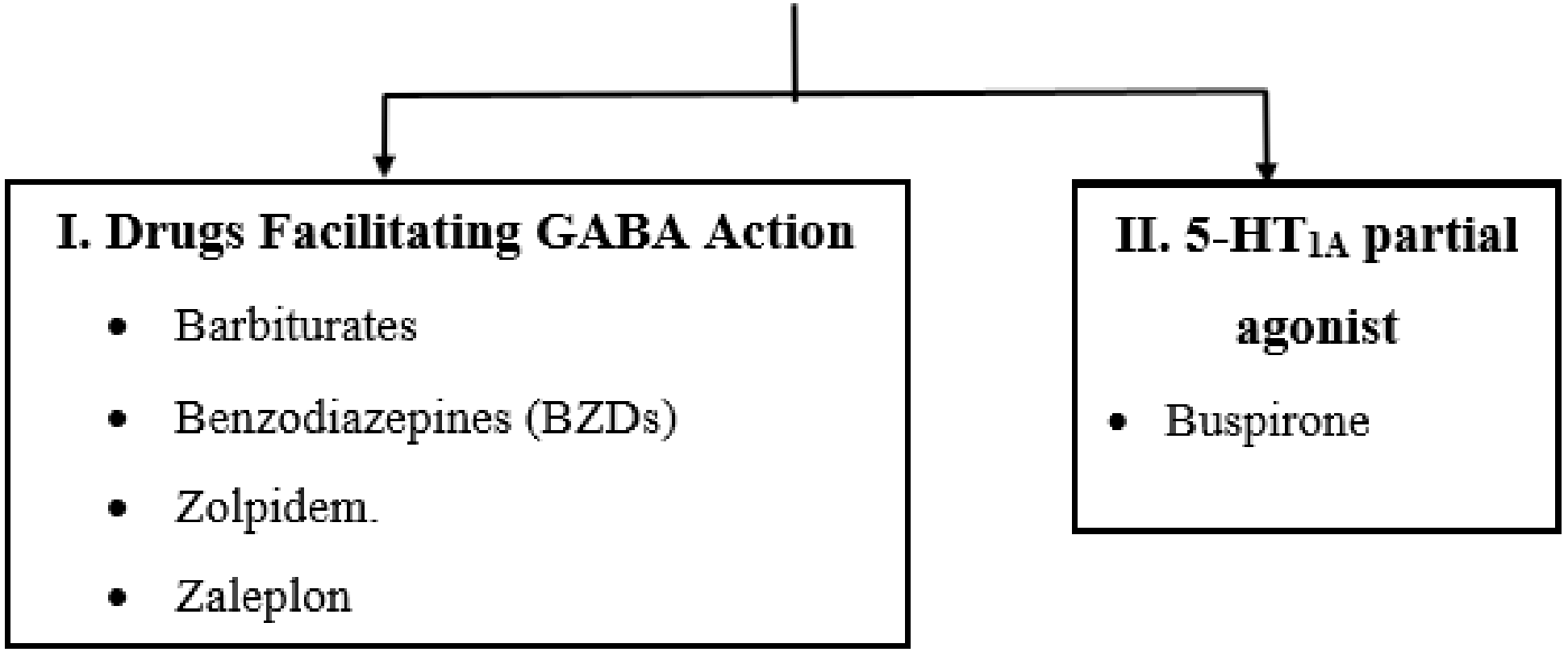
BARBITURATES

Amobarbital AMYTAL
Pentobarbital NEMBUTAL
Phenobarbital LUMINAL SODIUM
Secobarbital SECONAL
Thiopental PENTOTHAL

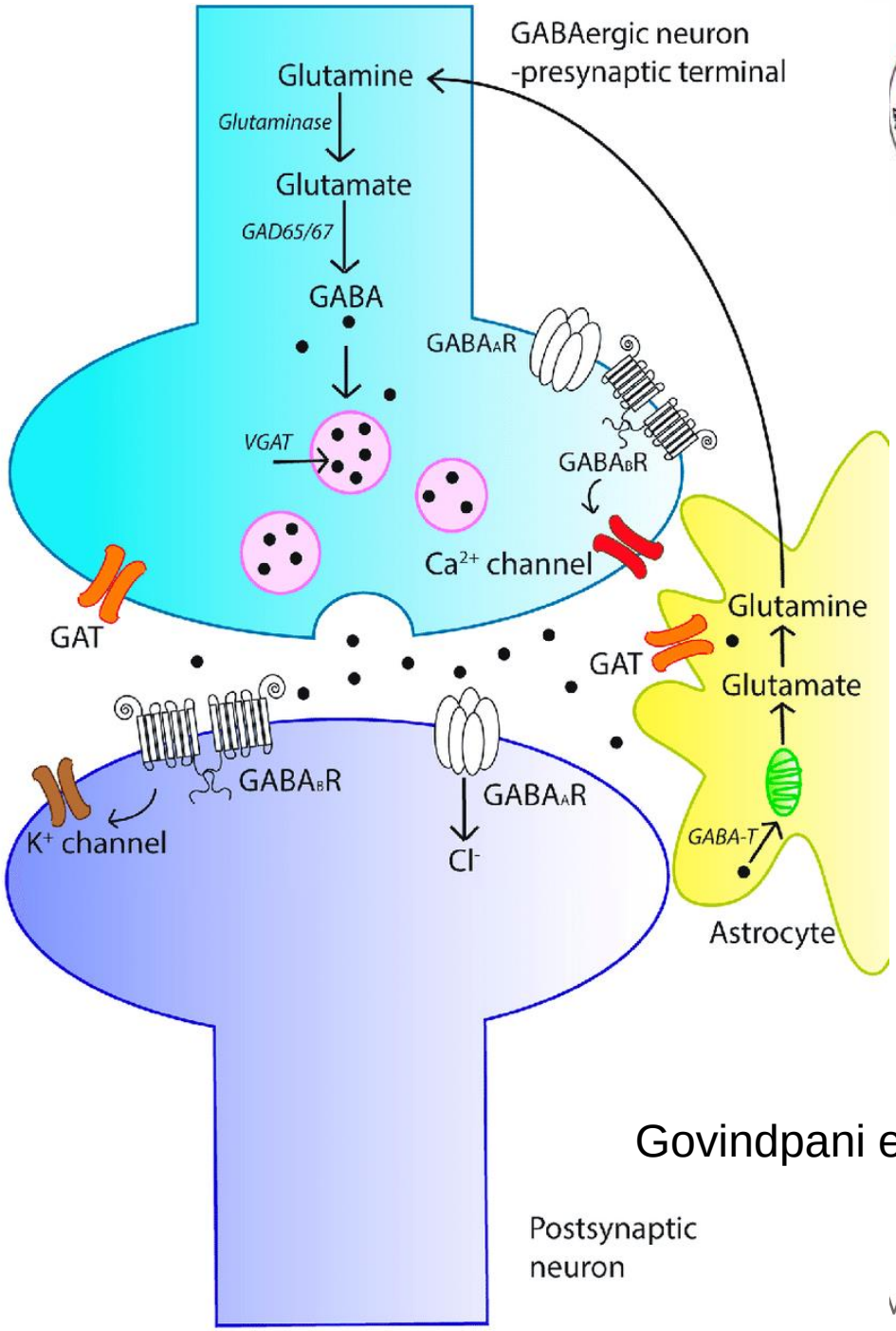
OTHER HYPNOTIC AGENTS

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

Classification According to Mechanism of Action



The GABAergic Synapse



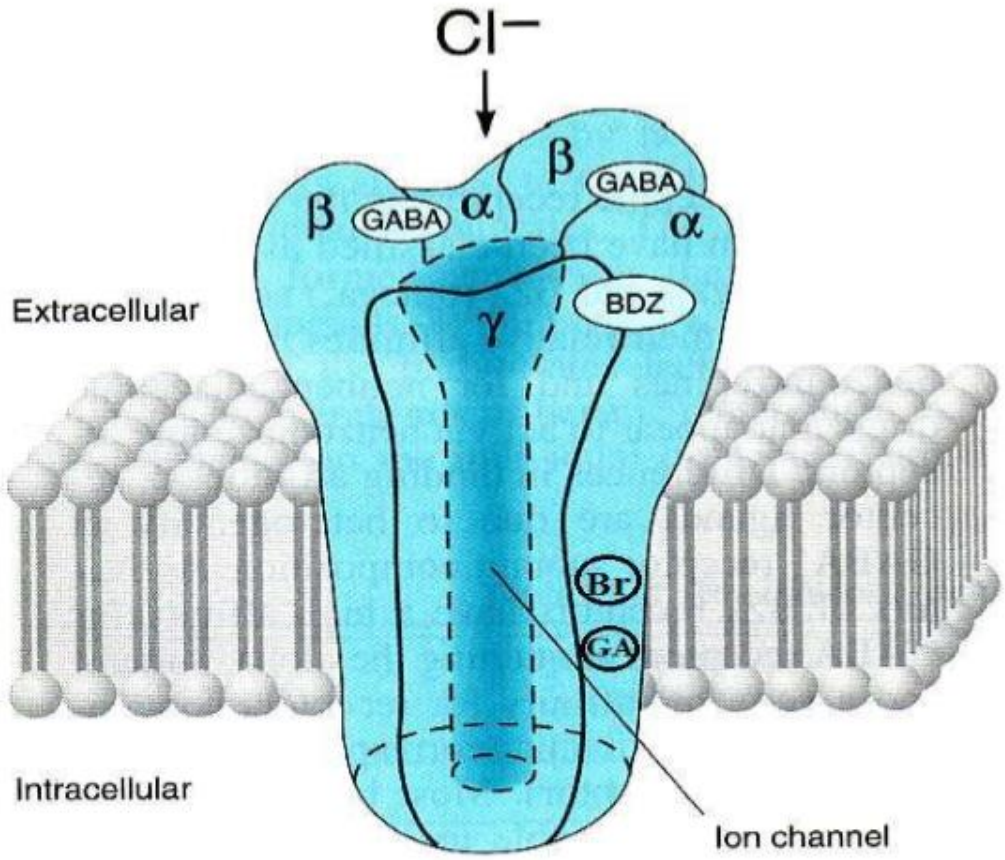
Govindpani et al, 2017

GABA Receptors

- Receptors for the inhibitory neurotransmitter γ-aminobutyric acid (GABA).
- Two main receptors types:

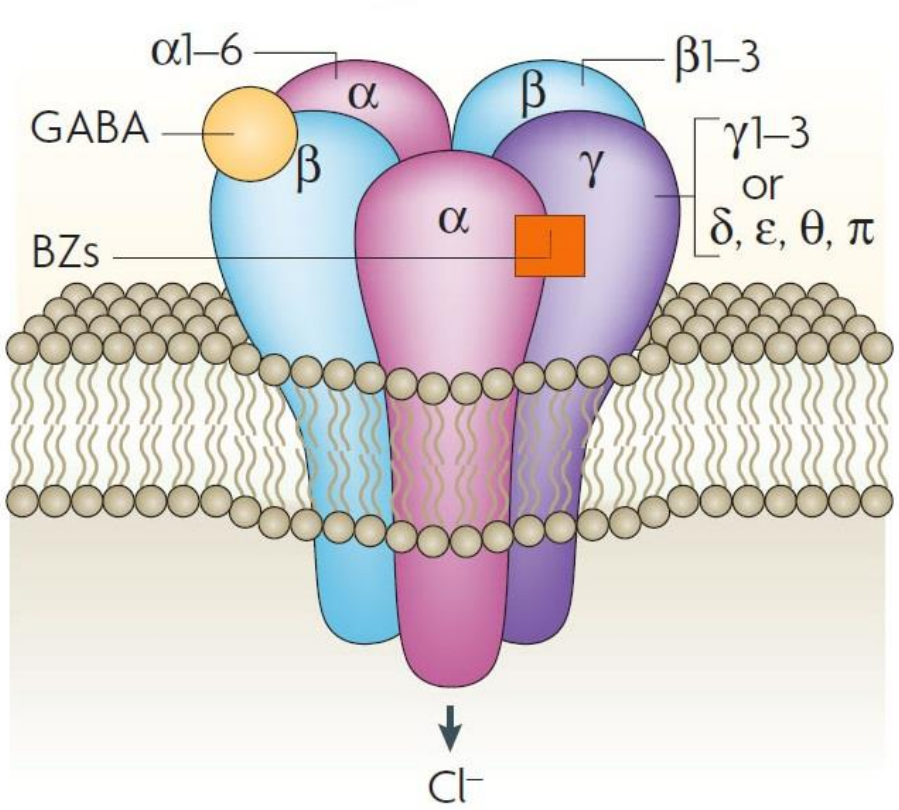
❑**$GABA_A$ receptors**: ligand-gated ion channels (*ionotropic*)

❑**$GABA_B$ receptors**: G-protein-coupled receptors (*metabotropic*)



$GABA_A$ Receptor

- *pentamer* formed of 3 different types of subunits (two α, two β and one γ) surrounding a Cl^- ion channel.
- The GABA binding site is at the <u>interface between α and β subunits</u>.
- Binding of 2 GABA molecules triggers the opening Of the central ion channel allowing for chloride influx.
- The influx of chloride → hyperpolarization → decreases action potentials (neurotransmission).



Benzodiazepines

Benzodiazepines

Mechanism of action:

- Benzodiazepines are allosteric modulators of $GABA_A$ receptors.
- They bind to distinct, high-affinity site from the GABA-binding site located at the interface between the α and γ subunits.
- These binding sites are labeled as benzodiazepine (BZ) receptors.
- CNS BZ receptors:

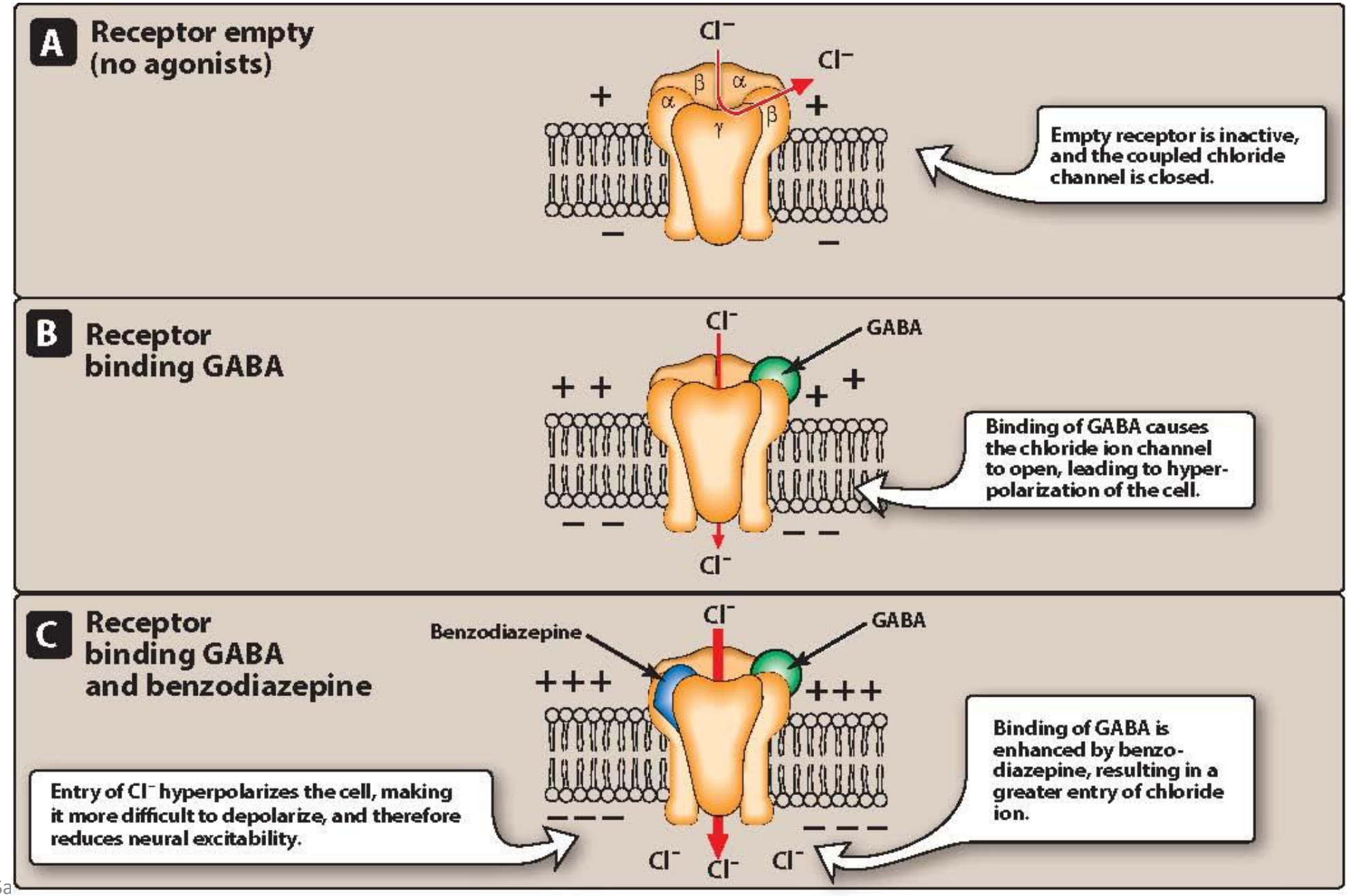
❑ **BZ_1** includes α_1 subunits (mediate sedation, hypnosis, amnesia and antiepileptic effects)

❑ **BZ_2** includes α_2 subunits (anxiolytic and muscle relaxant effects)

Benzodiazepines

Mechanism of action:

- Binding of benzodiazepines to the BZ receptors on the $GABA_A$ receptor complex → **increases affinity** of GABA to bind to its receptors. This **increases the frequency of opening** of Cl^- channel → facilitating the inhibitory effects of GABA.

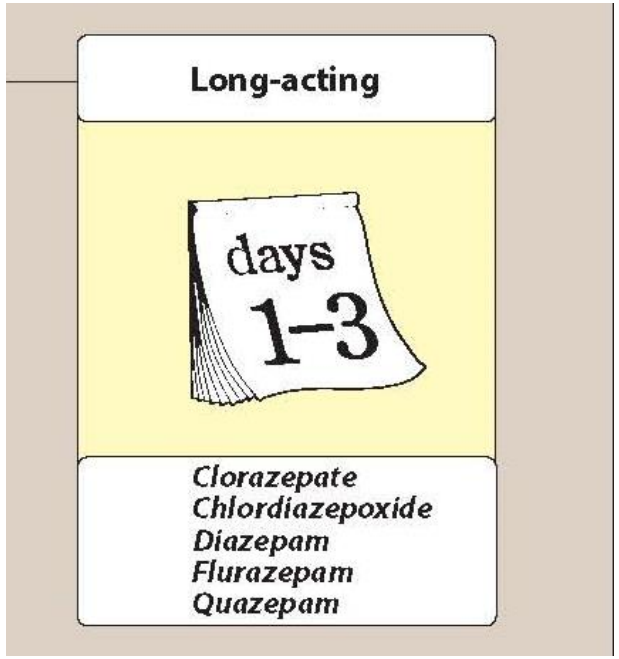


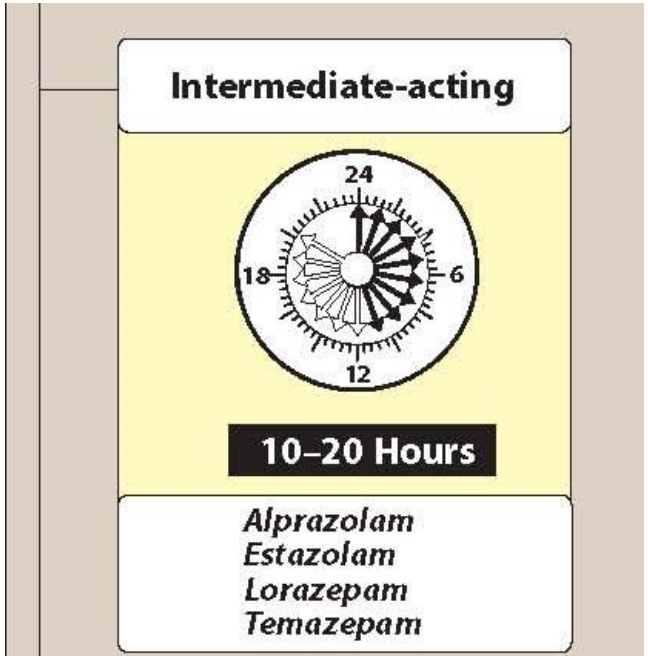
Benzodiazepines

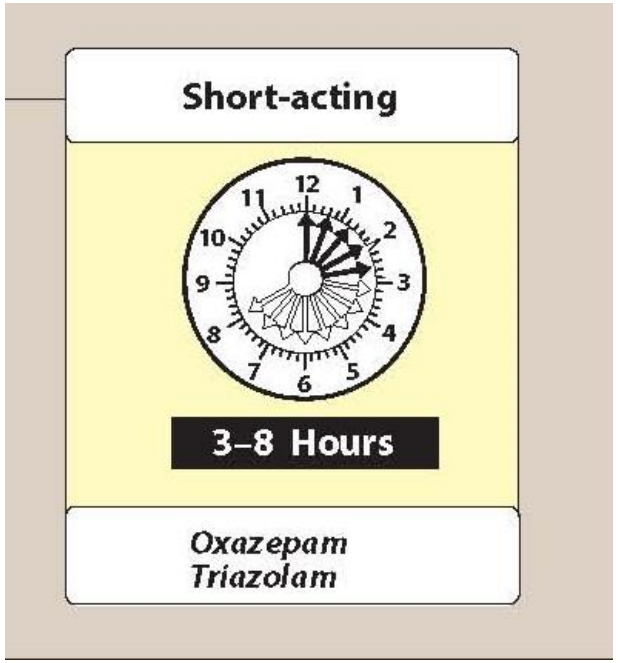
Actions:

- **Reduction of anxiety:** through α_2 subunit containing $GABA_A$ receptors.
- **Sedative/hypnotic:** through α_1 subunit containing $GABA_A$ receptors.
- **Anterograde amnesia:** through α_1 subunit containing $GABA_A$ receptors.
- **Anticonvulsant:** through α_1 subunit containing $GABA_A$ receptors.
- **Muscle relaxant:** through α_2 subunit containing $GABA_A$ receptors.

Benzodiazepines: Duration of Action







Duration of action

- determine therapeutic uses **(half-life is very important)**

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

Benzodiazepines

Therapeutic uses:

- **Anxiety disorders:**

- Panic disorder, GAD, OCD, social anxiety disorder, phobias.

- Anxiety related to depression or schizophrenia.

- ONLY for severe anxiety (NOT for the stress of everyday life).

- Longer-acting drugs are preferred: **lora**-; **clona**-; and **diazepam**.

- Tolerance: anxiolytic effects < sedative/hypnotic.

Benzodiazepines

Therapeutic uses:

- **Sleep disorders (insomnia)**

❑ Decrease latency to sleep onset AND Increase stage II of non-rapid eye movement (REM) sleep.

❑ commonly used drugs:

1. **Temazepam**: intermediate-acting – given 1-2 hours before bedtime – Best for frequent awakening.
2. **Triazolam**: short-acting – best for inability to go/stay asleep – Rebound insomnia

(using long-acting like flurazepam may result in excessive daytime sedation)

Benzodiazepines

Therapeutic uses:

- **Amnesia**

❑used as an adjunct to anesthesia: to relief unpleasant, surgery-induced anxiety

❑**midazolam** is often used for this purpose

Benzodiazepines

Therapeutic uses:

- **Seizures**

❑**Clonazepam** used as adjunctive therapy for certain types of seizures.

❑**Lora-; and diazepam** used for the treatment of *status epilepticus (given IV)* and alcohol-withdrawal associated seizures.

Benzodiazepines

Therapeutic uses:

- **Muscular disorders**

❑used for skeletal muscle spasms

❑used for spasticity associated with multiple sclerosis and cerebral palsy

Benzodiazepines

Pharmacokinetics

- **Absorption**

  - highly lipophilic

CNS distribution? Fat? Pregnancy?

- **Metabolism**

❑ metabolized by hepatic microsomal system

❑ mostly the metabolites are also active

❑ excreted in the urine

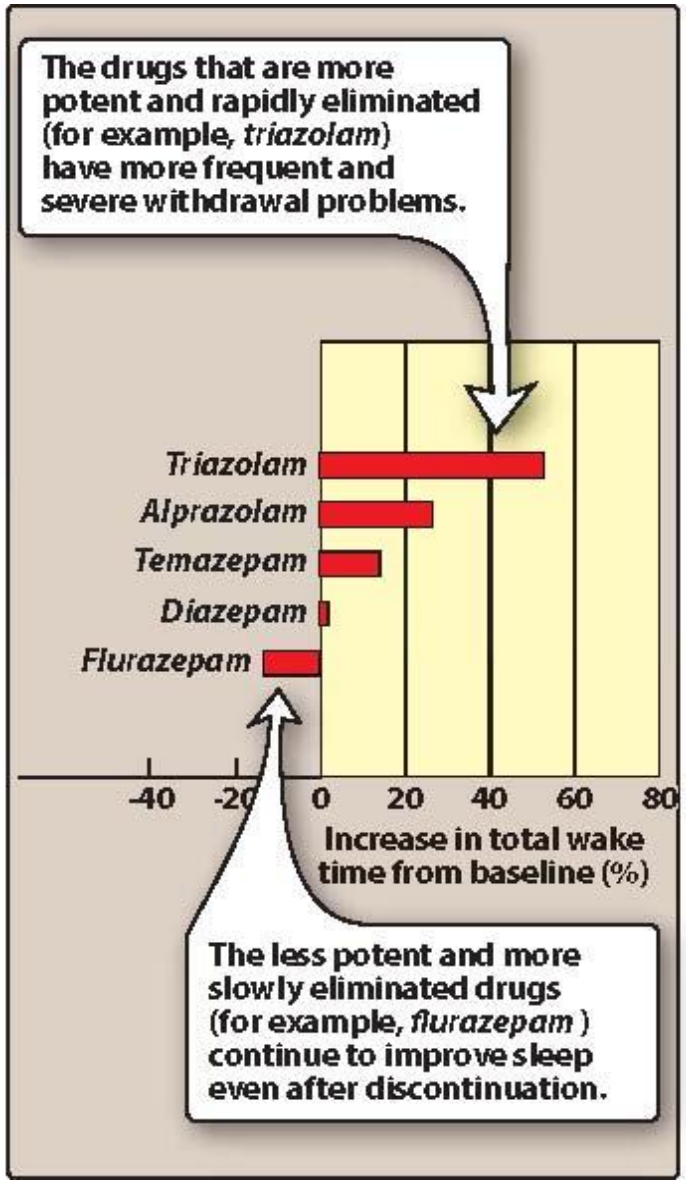
Benzodiazepines

Dependence

- Psychological and physical dependence can develop rapidly
- Used for short periods of time
- Abrupt discontinuation → <u>WITHDRAWAL:</u>

- confusion, anxiety, agitation, rebound insomnia, tension and seizures.

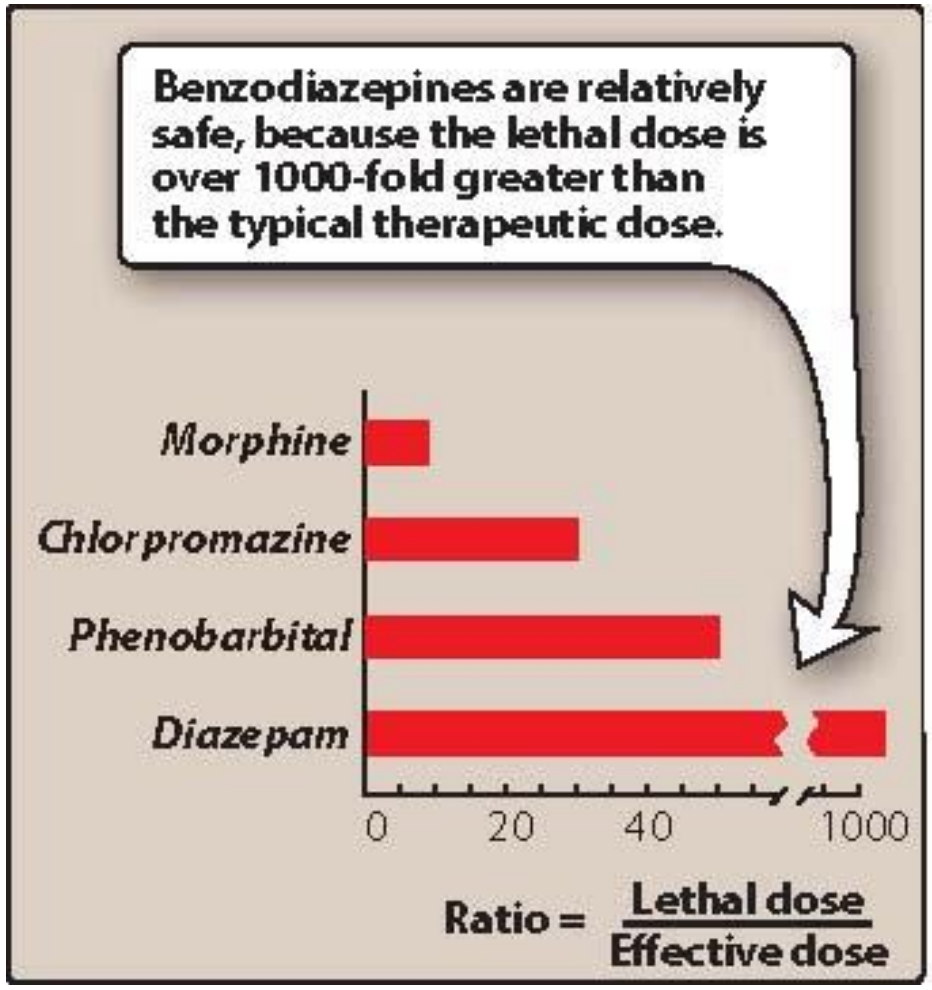
- withdrawal happens more with short-acting



Benzodiazepines

Adverse effects

- Drowsiness and sedation
  - ➢Driving
  - ➢Cognitive impairment
- Combination with other sedatives can be dangerous:
  - ➢Alcohol, barbiturates, anesthetics, …
- Anterograde amnesia
  - ➢Impaired ability to learn new information.



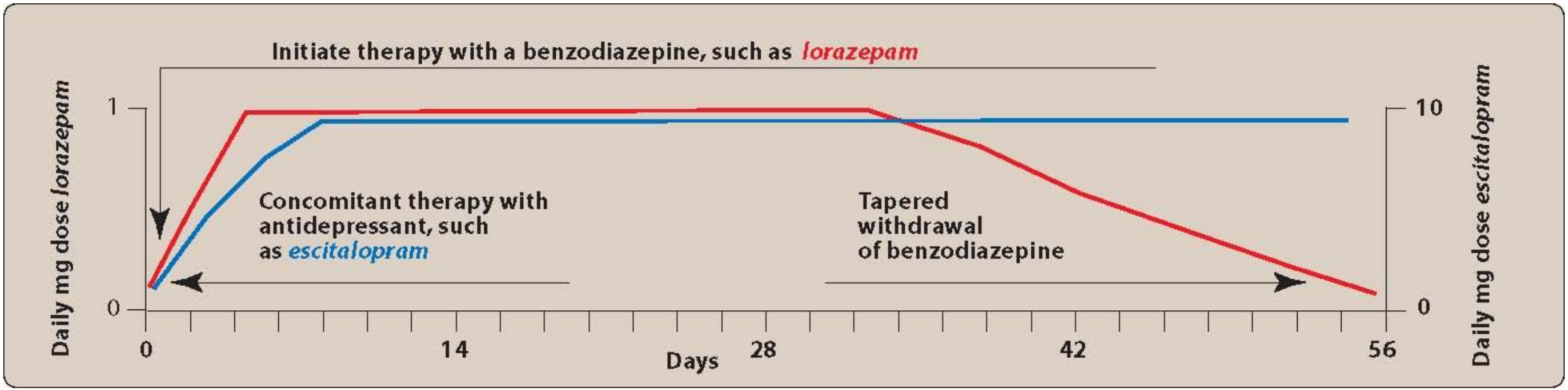
Benzodiazepine Antagonist: antidote

- **Flumazenil**
  - GABA receptor antagonist
  - used for benzodiazepine toxicity/overdose
  - IV only
  - rapid onset, short duration of action
  - may precipitate withdrawal in dependent patients

Other anxiolytics: antidepressants

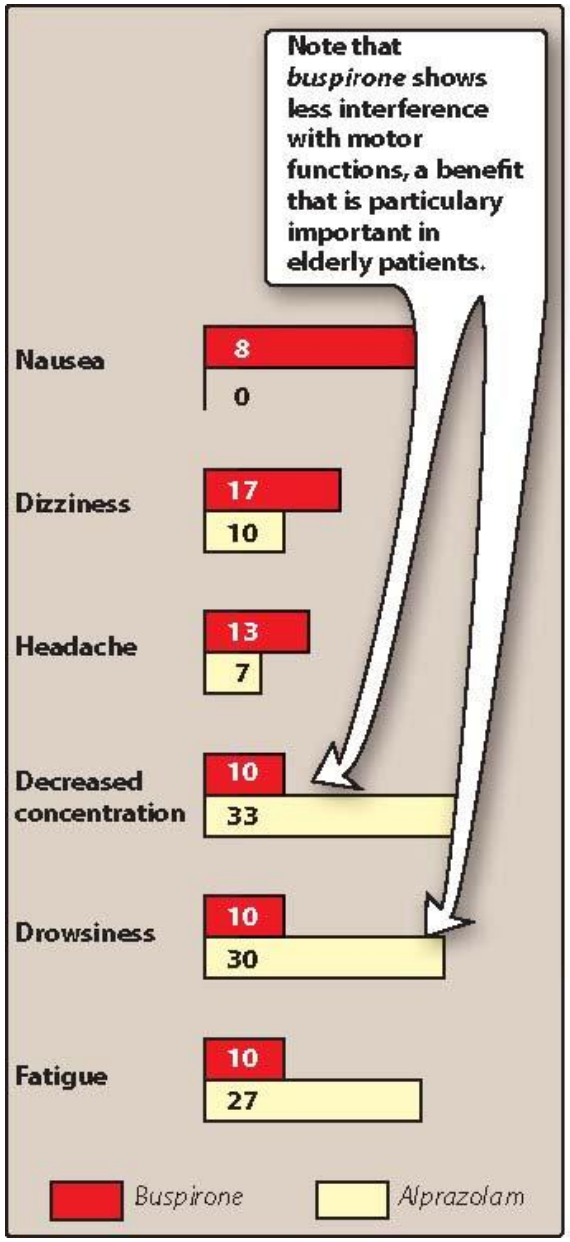
- Remember: many antidepressants are used to treat anxiety.
- **SSRIs** (escitalopram, paroxetine) and **SNRIs** (duloxetine, venlafaxine) are FIRST LINE to treat anxiety.
- Often used with a benzodiazepine initially (first 4-6 weeks)

Other anxiolytics: Antidepressants



Other anxiolytics: Buspirone

- Useful for the chronic treatment of generalized anxiety disorder.
- Ineffective for short-term "on demand" "as needed" treatment of acute anxiety: slow onset of action.
- Effect mediated by 5-HT1A receptors.
- No anti-seizure or muscle relaxant properties
- No dependence



Barbiturates

Barbiturates

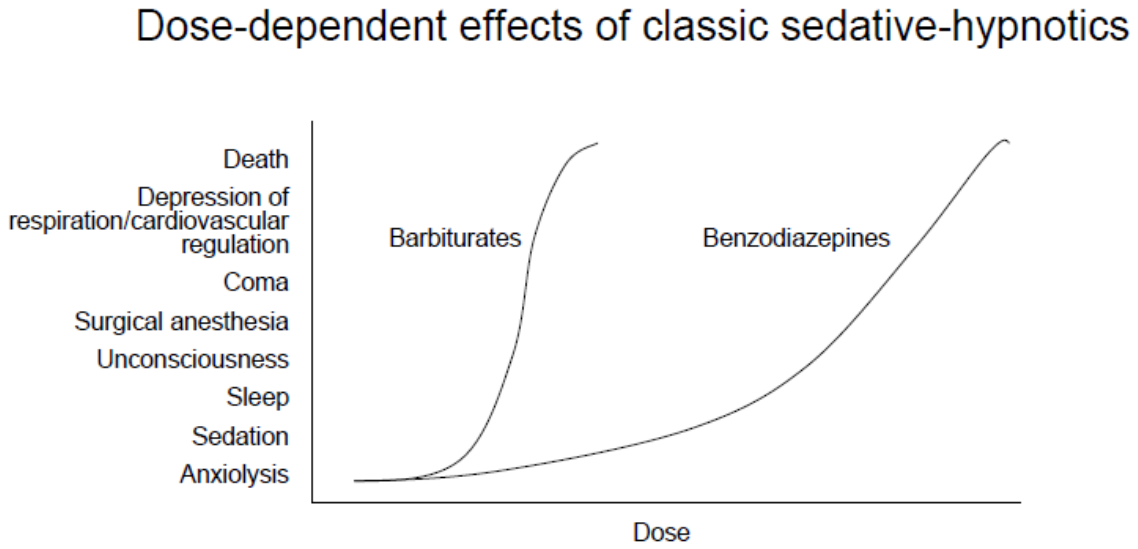
Overview:

- Old
- Largely replaced by benzodiazepines as sedative/hypnotics

❑ Induce tolerance/dependence/withdrawal/lethal overdose >>>> benzodiazepines

- Some still in use but the majority are not

- example: thiopental is a short-acting barbiturate have been used to induce anesthesia.



Barbiturates

Mechanism of action:

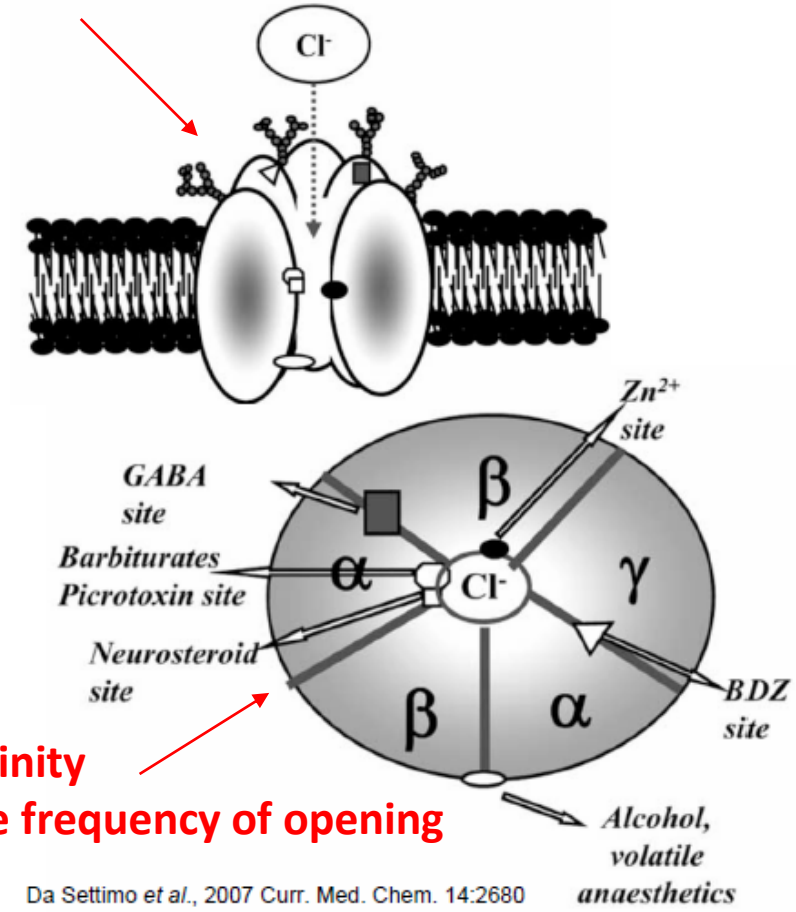
- **Site of action:** $GABA_A$ receptors.
- **Binding site**: different from benzodiazepines

❑ Barbiturates potentiate GABA action on chloride entry by **prolonging the duration** of Cl channel opening.

Barbiturates vs benzodiazepines

The γ-aminobutyric acid ($GABA_A$) receptor

prolonging the duration



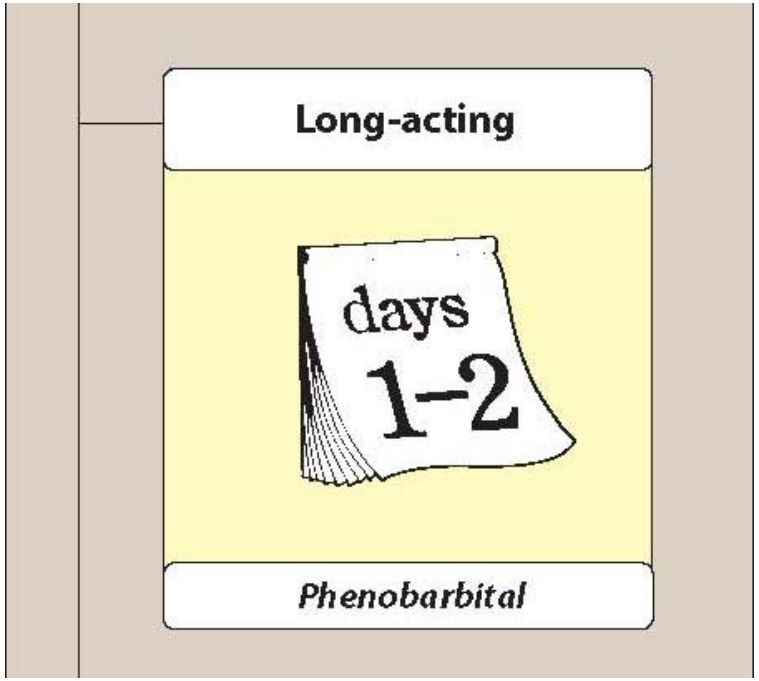
increasing affinity
increasing the frequency of opening

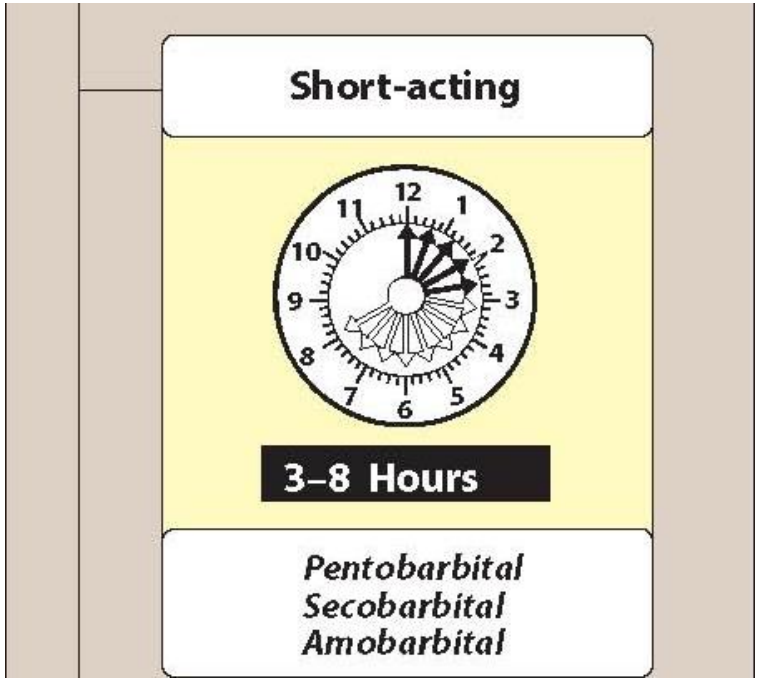
Da Settimo *et al.*, 2007 Curr. Med. Chem. 14:2680

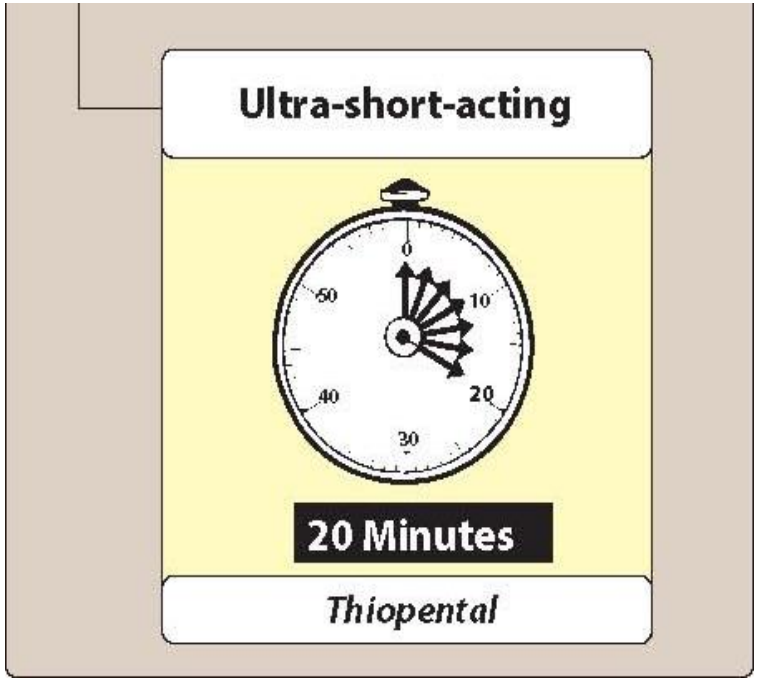
Barbiturates bind to site in ion channel, increasing Cl^- channel open time. Can activate channel at high concentrations.

Benzodiazepines increases affinity of GABA binding site for its ligand. In the absence of GABA, benzodiazepines have no detectable effect on receptor function.

Barbiturates







Barbiturates

Actions:

- **CNS depression:**

❑low doses→ sedation

❑High doses→ hypnosis >>> anesthesia

❑Higher doses → coma and DEATH!

- **Respiratory depression**

Barbiturates

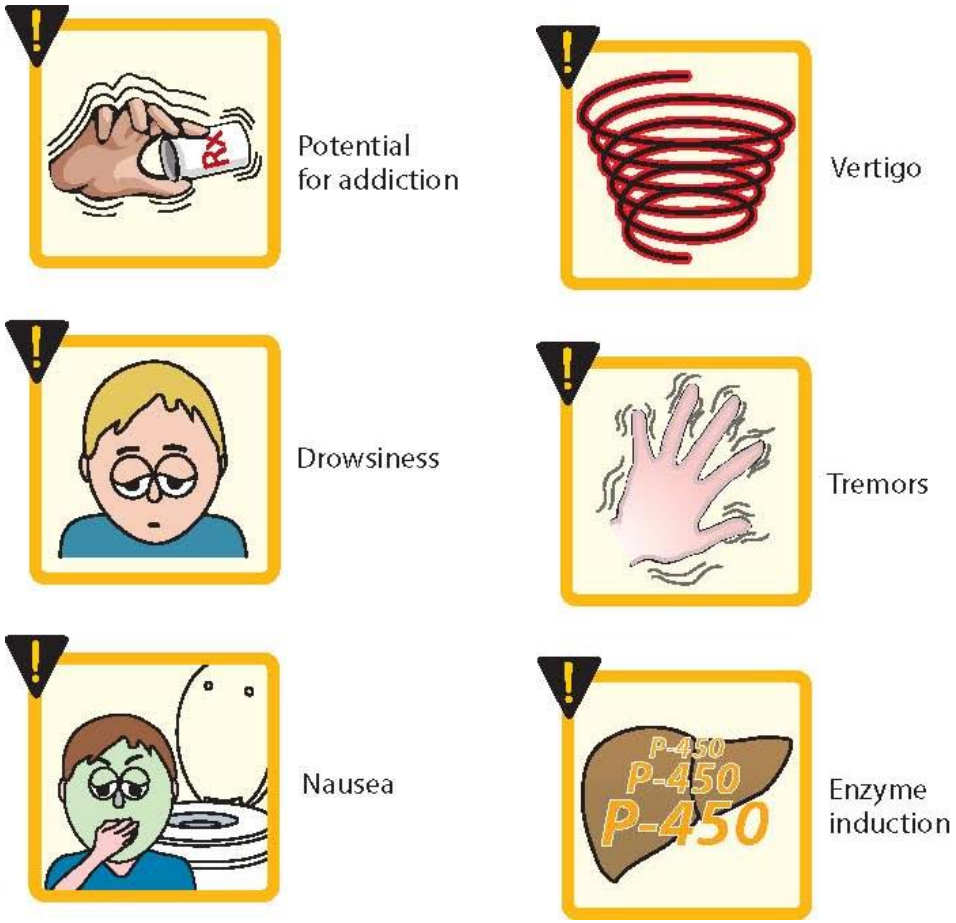
Therapeutic uses:

1. **Anesthesia:** e.g., thiopental for induction of anesthesia (not anymore).
2. **Anticonvulsant:** e.g., phenobarbital for refractory seizures.
3. **Sedative/hypnotic:** for insomnia (no longer accepted)

Barbiturates

Adverse effects:

Barbiturates are contraindicated in patients with acute intermittent porphyria



Withdrawal can result in death

Overdose can result in death

Other Hypnotics: Zolpidem

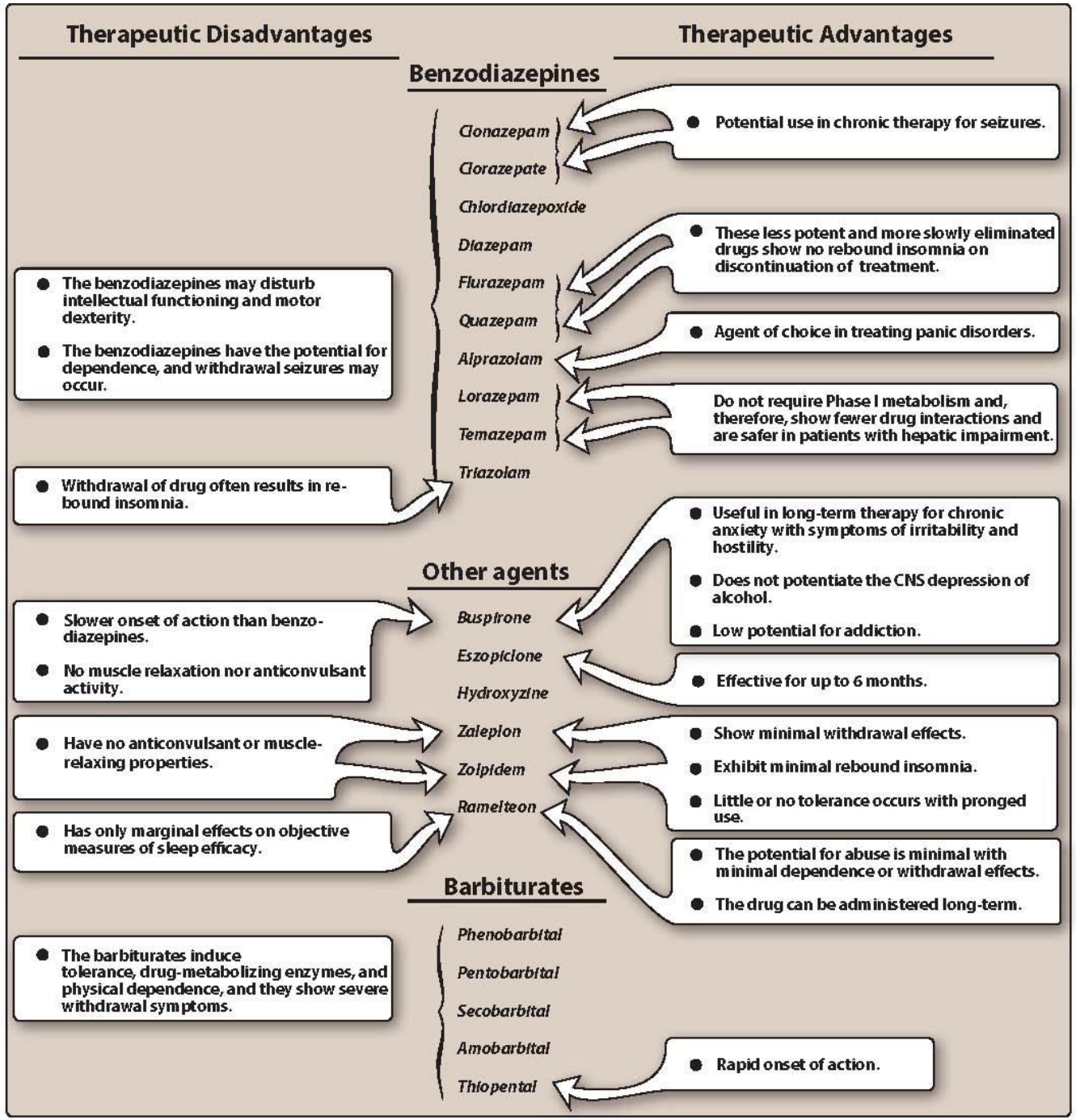
- Not a benzodiazepine, but the same mechanism of action (on BZ_1)
- short half-life (2-3 hrs), rabid onset of action.
- Most commonly prescribed drug for insomnia in the US.
- Decrease sleep latency, no effect on sleep.
- Adverse effect: impaired performance in the morning, driving, and dependence.

Other Hypnotics: Ramelteon

- Selective agonist: melatonin receptors 1 and 2
- Indicated for the treatment of insomnia (decreases sleep latency)
- No abuse potential/dependence/withdrawal

Other Hypnotics: Over-The-Counter

- **Antihistamines:**
  - Insomnia (mild).
  - Diphenhydramine.
  - Chlorphenamine (Allerfin).



Summary of Clinical Uses

- Benzodiazepines are indicated only in severe anxiety or insomnia.
- Drug therapy should be started with a small oral dose for a limited period (less than 3 weeks for insomnia) to avoid drug abuse and dependence
- Gradual termination of therapy should be done to avoid withdrawal.
- *Longer-acting* drugs are preferred as *anxiolytics* …*shorter-acting* as *hypnotics*.
- Most benzodiazepines are metabolized in liver → dose adjustment is required in liver cirrhosis to avoid accumulation to toxic levels specially of long acting agents and those metabolized to active metabolites such as diazepam.

- Thank you

- Questions?

Send me an email to tareq@hu.edu.jo