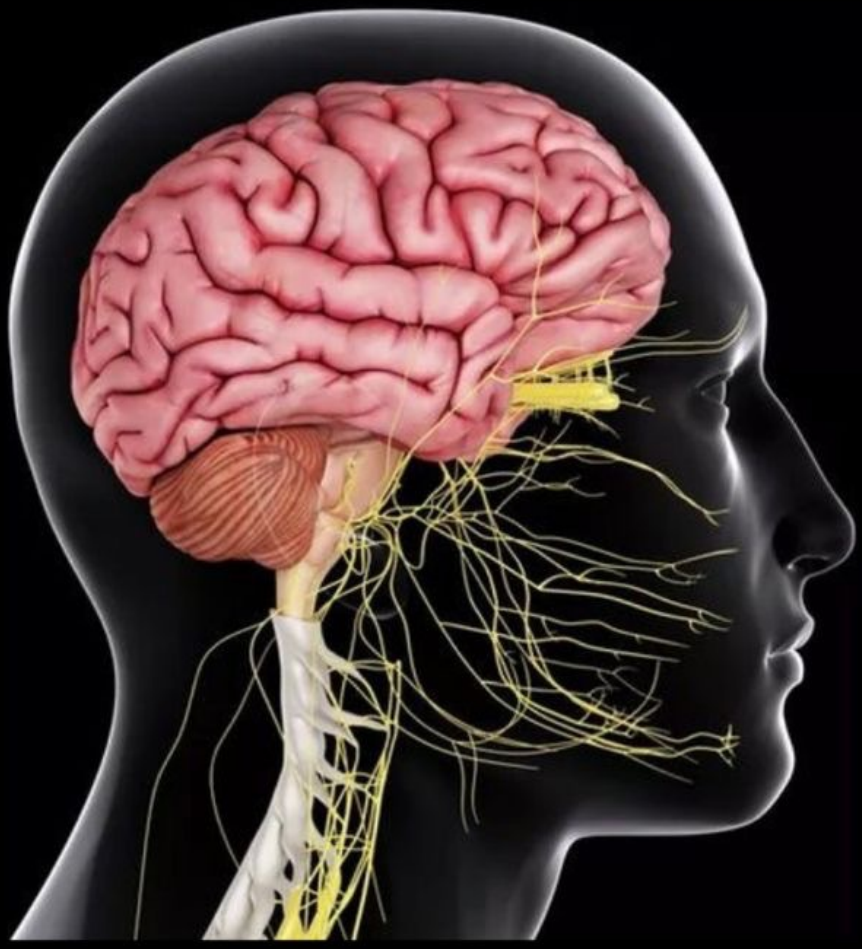
CENTRAL NERVOUS SYSTEM



SUBJECT : Pharmacology

LEC NO. : 6

DONE BY : Batool ALzubaidi

وَقُل رَّبِّ زِدْنِي عِلْمًا

Anxiolytics and Hypnotics

They're dangerous, associated with high risk of dependence, shouldn't be prescribed as first line agents

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

Tareq Saleh

Faculty of Medicine

The Hashemite University

Anxiety

Mental health / psychiatric disorder that describes the feeling of unpleasent, uncomfortable, irritable, patient usually worried about something

- 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.

Stress pathway

Generalized anxiety » constant unrelieved anxiety

Tareq Saleh ©

Wolters Kluwer

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

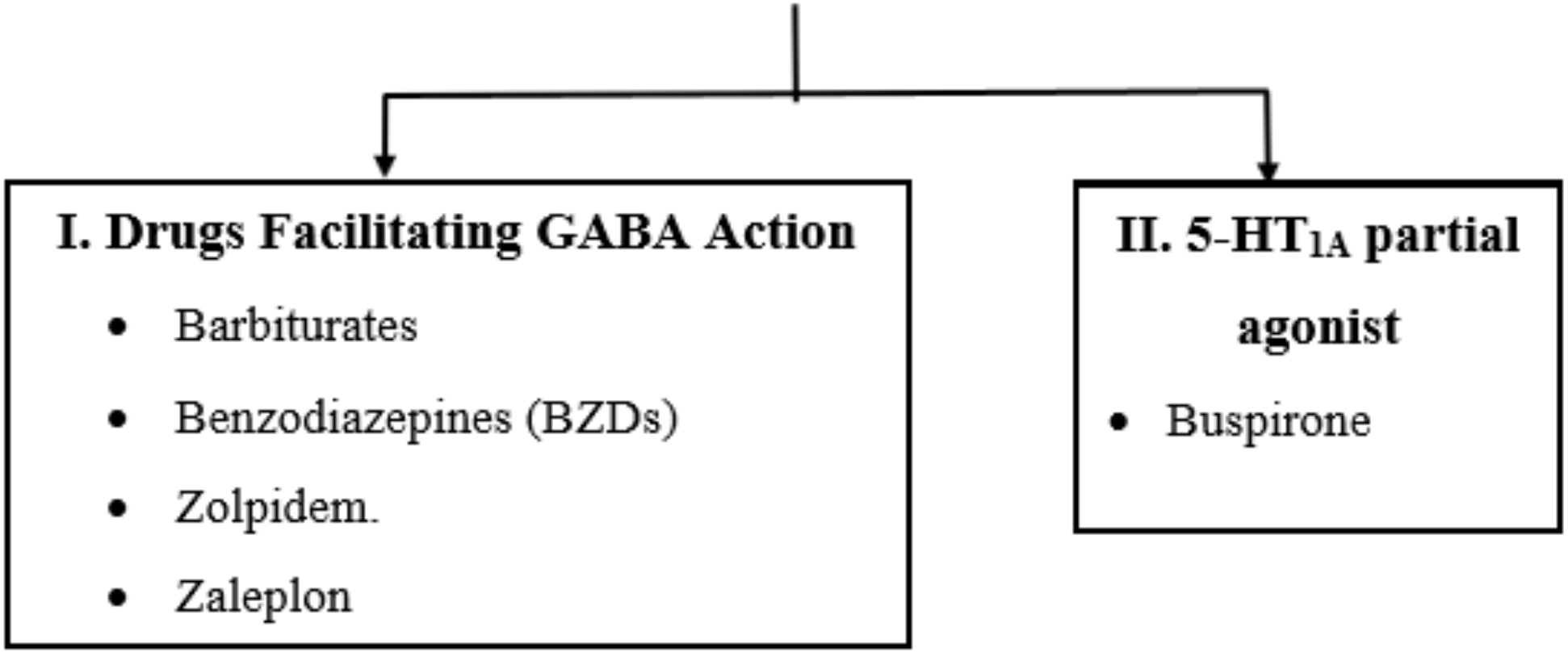
Amobarbital AMYTAL
Pentobarbital NEMBUTAL
Phenobarbital LUMINAL SODIUM
Secobarbital SECONAL
Thiopental PENTOTHAL

OTHER HYPNOTIC AGENTS

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

ماجست

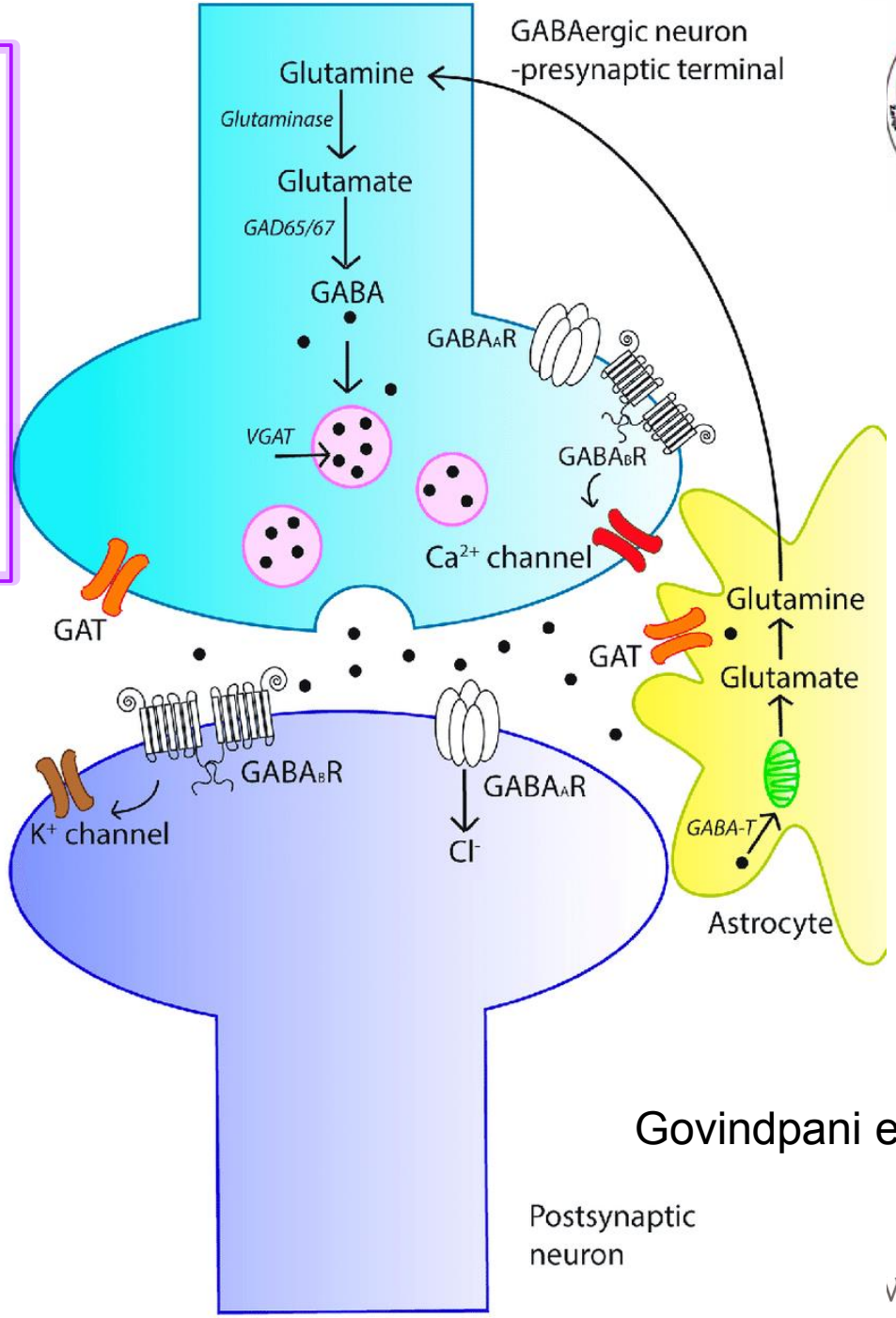
Classification According to Mechanism of Action



بالمنطق الادوية الي راح تستخدم لعلاج ال anxiety لازم تكون يشتغلوا على inhibitory pathways يعني لازم يعملوا activation to inhibitory pathways in the brain و ال main هو ال most لانه ال GABA BABAergic pathways بالدماغ هم ال inhibitory pathway زيه زي اي GABA ال.. dominant inhibitory neurotransmitter يتصنع بال neuron من glutamine يعني amino acid derivative بعدين بصيرله packaging in vesicles و الله special transporters اسمه GATA و بس يجي ال action potential that will activate its release by degranulation into the synaptic cleft

The GABAergic Synapse

و بعدها بربط بال receptor تاعه على post synaptic neuron الي هم GABA ال A عبارة عن A\B يعني بسمح بال influx of ligand gated ion channels و ال B عبارة عن metabotropic مرتبط ب Gi .. في جزء من ال GABA بصيرله reuptake by presynaptic neuron و جزء بصيرله reuptake by astrocytes و جزء من ال metabolism بصير جواهم برجع بتجول ال glutamate ل glutamine و برجع ل presynaptic neuron، هلا عشان نعمل ال inhibitory effect لازم اعمل activation of GABA receptor so it can exert its function



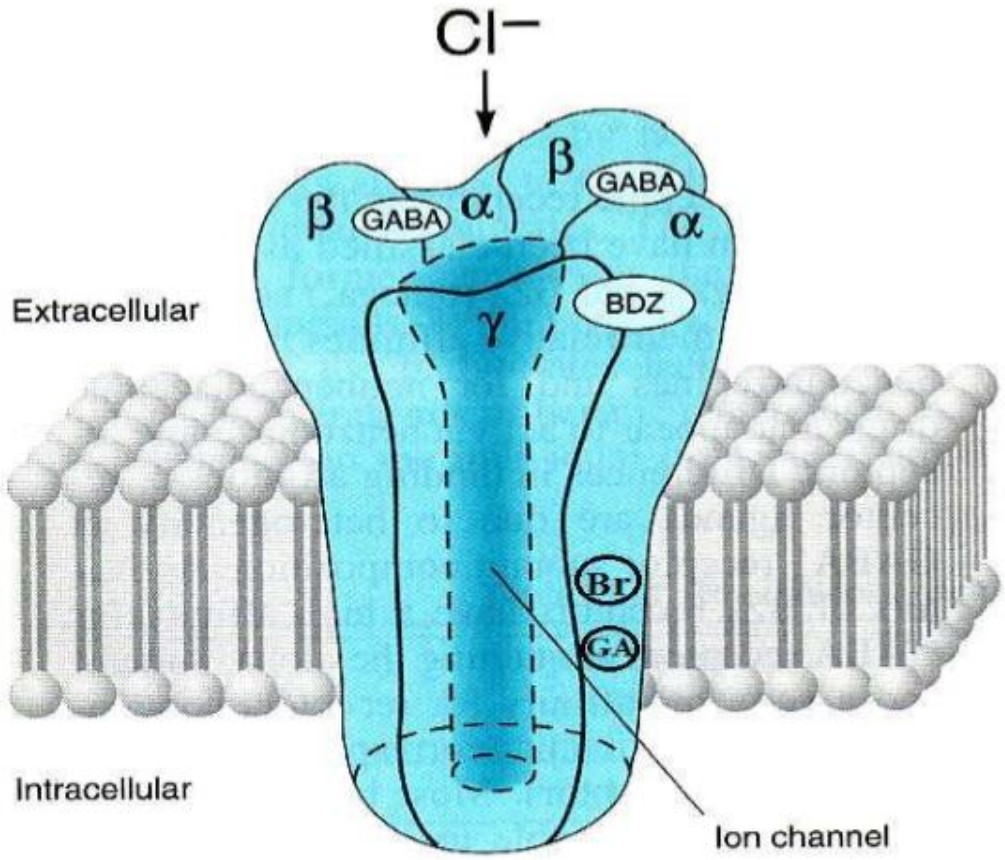
Govindpani et al, 2017

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

و كل وحدة منهم الها انواع مثلا في ٦ انواع ل alpha و ٣ انواع ل beta snd gamma و هاد الاشي بسمح انه بكون في انواع كتيرة ل GABAa receptor نفسه و كانهم subtypes و فعلا عنا بالدماغ multiple a subtypes و باختلاف ال subtype بختلف ال binding site اللي برتبط فيه ال GABA

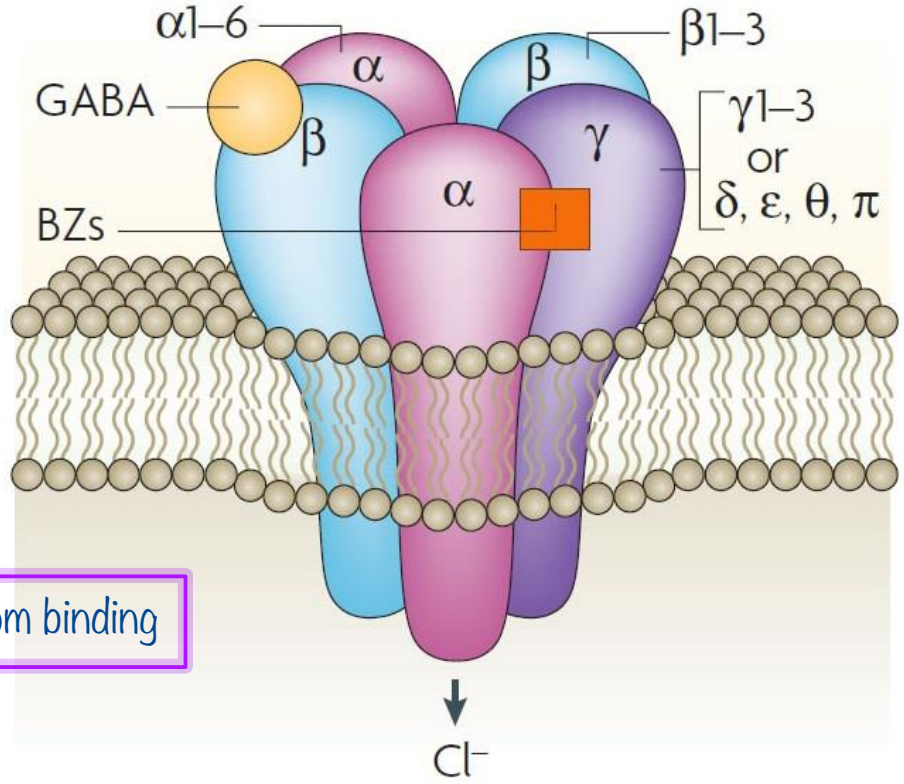
5 subunits

- *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 interface between α and β subunits.
- Binding of 2 GABA molecules triggers the opening Of the central ion channel allowing for chloride influx.

In response to conformational changes resulting from binding

- The influx of chloride → hyperpolarization → decreases action potentials (neurotransmission).

Becomes more difficult to activate the neuron



ال benzodiazepines بربطوا على ال GABA receptor على site different than the site of the original ligand بين alpha and gamma، هل هاد يعني انهم agonists على ال receptor اذا حكينا انه ارتباطهم enhances chloride influx ؟

قبل الجواب سال سؤال شو الفرق بين ال agonist and positive allosteric modulator ؟ال positive allosteric راح يعمل activation لل receptor بس بشرط اولا only in the presence of original agonist ثانيا binding to a site different than original binding site of the original ligand

و ال benzodiazepines by definition بعمل ا زي ال positive allosteric modulators ف GABA their binding results with enhancement of effect allowing for more chloride enflux to happen which means further inhibition for neurotransmition through this pathway

لـ بتشمل سلايد 13+8

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:

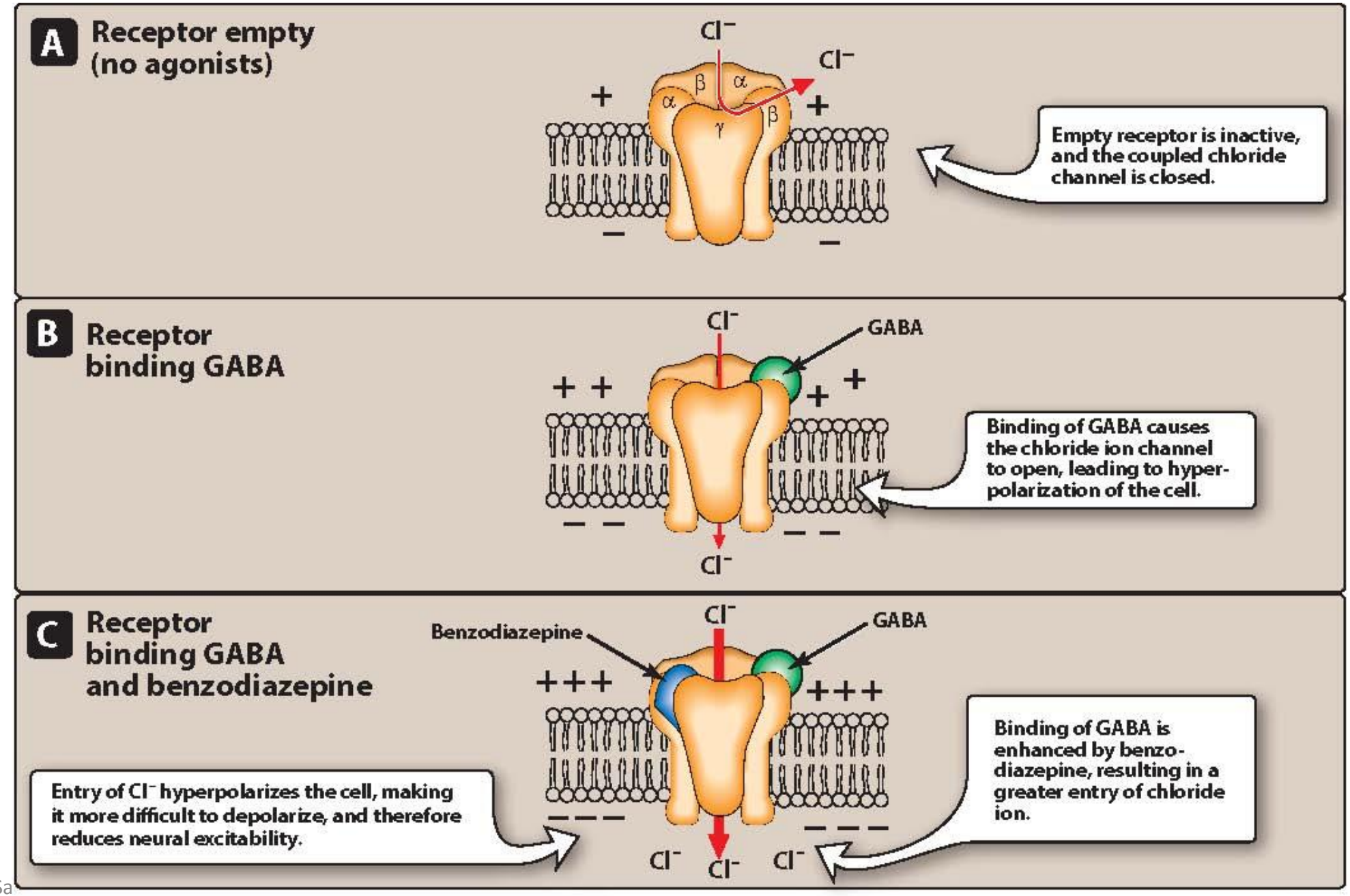
❑ **BZ_1** includes α_1 subunits (mediate sedation, hypnosis, amnesia and antiepileptic effects)

❑ **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.

Anti-seizure

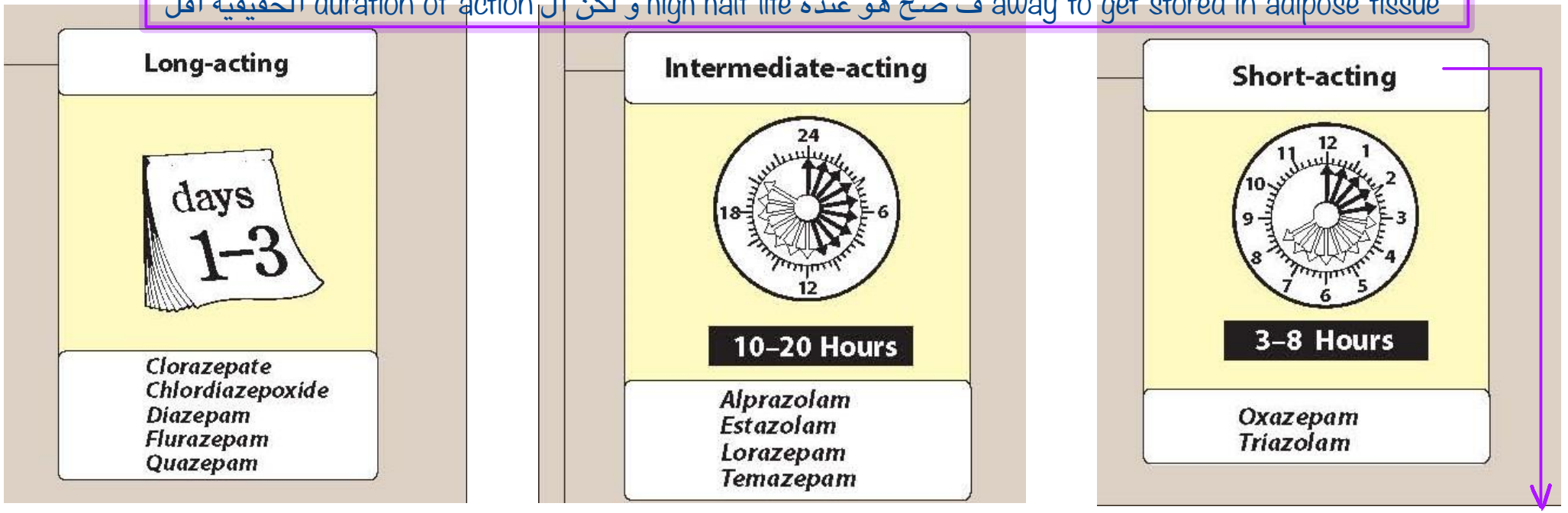
Amnesia » short temporary memory loss

Spastic muscle disorders » cerebral palsy, multiple sclerosis

كلهم عندهم نفس ال mechanism of action بس بختلفوا بال duration of action، لا تنخدعوا بال consistency بين ال duration of action و ال receptor disassociation لانه الها علاقة بال fake duration of action بعطيه مرة كل ٣ ايام و هاي مثلا diazepam action and half life

Benzodiazepines: Duration of Action

و مع انه ال drug is present in the blood it disassociates from GABAa receptor in the brain and diffuses away to get stored in adipose tissue ف صح هو عنده high half life و لكن ال duration of action الحقيقية اقل



هدول بنستخدمهم بحالات ال insomnia

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**

ال anxiety disorder بستخدملهم long acting

Only for short term treatment not beyond 2 weeks, after that dependence and all other complications increases, and they're associated with high risk of dependence and tolerance for these drugs develop so fast

Benzodiazepines

ما حكينا انه ال euphoria وحدة من ال could they although effects، في feeling between euphoria و بالعادة is which alcohol with abused they're anxiolytic بس of one they're definitely symptoms drug explains which anxiolytic the most abused drugs on the street very dangerous because both of them have the same inhibitory effect on CNS

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.

withdrawal symptoms ال عكس ال effect راح يعملوا insomnia, anxiety و غيرها عشان هيك لازم ال gradual be disease the of stopping

Benzodiazepines

If your have a chance to never expose your patient to benzodiazepines you shouldn't expose them, because we can't expect what will happen upon ascending exposure, some of them could exert neuroblastic changes in the brain

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.

Only case where there usage as first line treatment

كان شائع استخدامهم لل epilepsy اما حاليا لا هم 3rd or 4th line حاليا ما بستخدمهم الا بحالة status epileticus which is an emergency of acute continuous epileptic effect

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

Distributes everywhere in the body, absorbed and stored in the adipose tissue, crosses the placental barrier

CNS distribution? Fat? Pregnancy?

- **Metabolism**

If you described it to a pregnant lady the fetus will be born dependent, will suffer from withdrawl offer birth

- ❑ metabolized by hepatic microsomal system
- ❑ mostly the metabolites are also active
- ❑ excreted in the urine

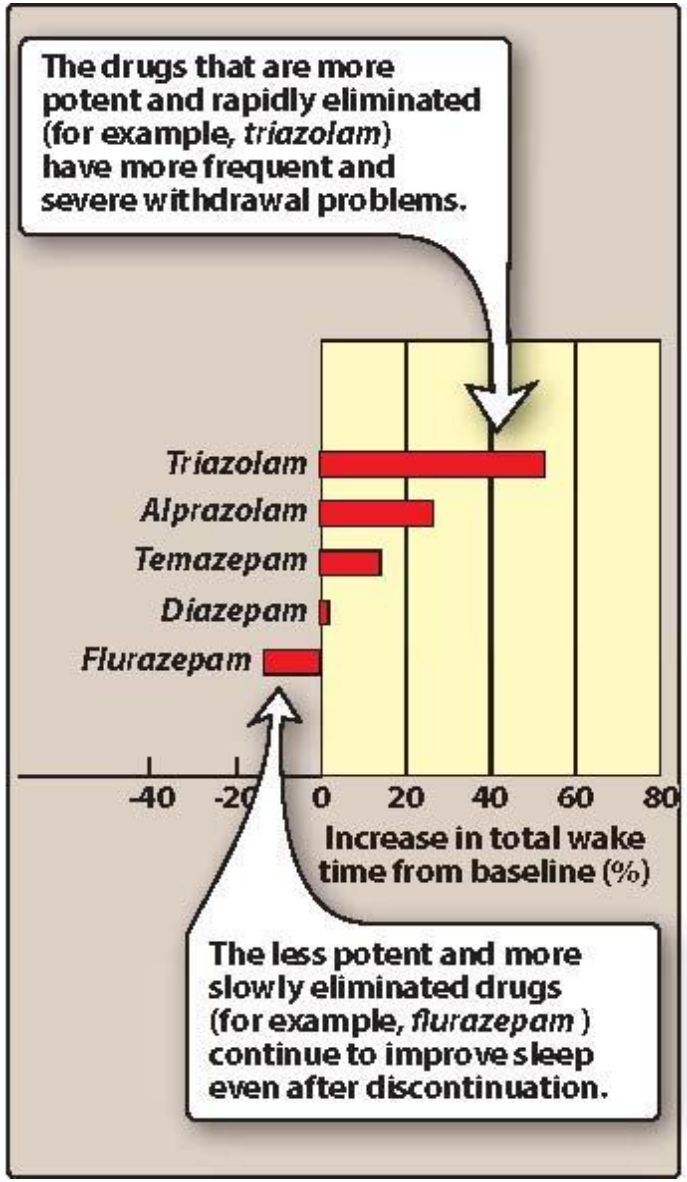
Benzodiazepines

Dependence

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

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

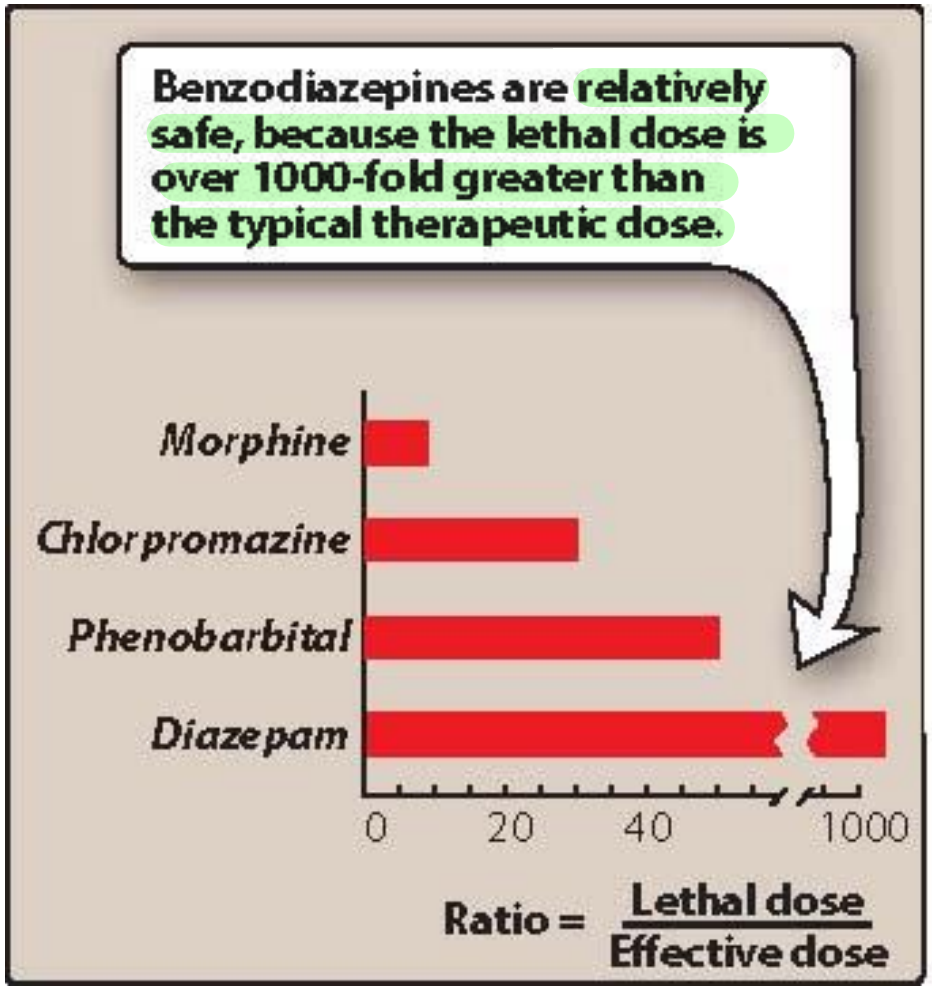
 - withdrawal happens more with short-acting



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.



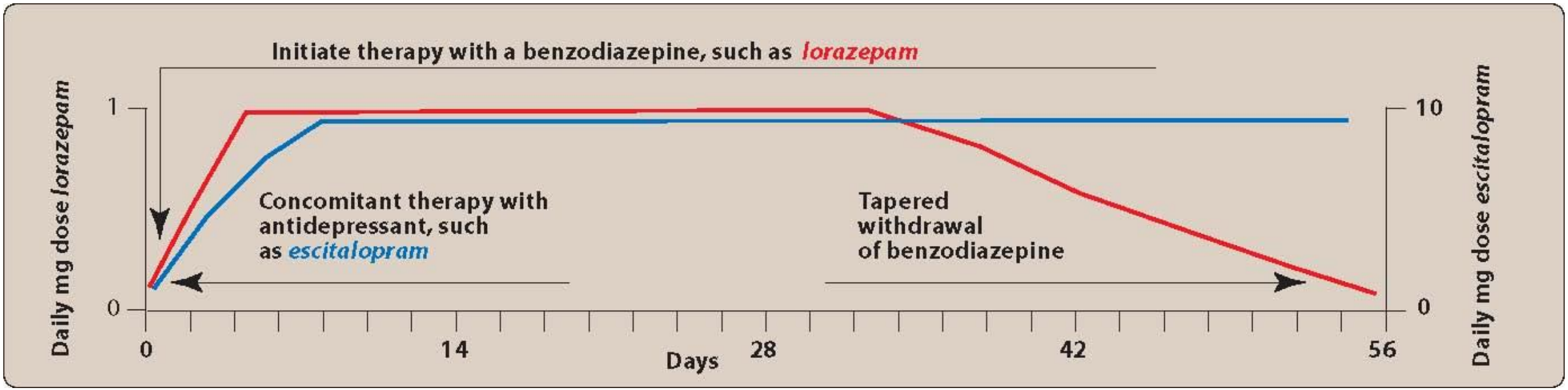
Benzodiazepine Antagonist: antidote

- **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

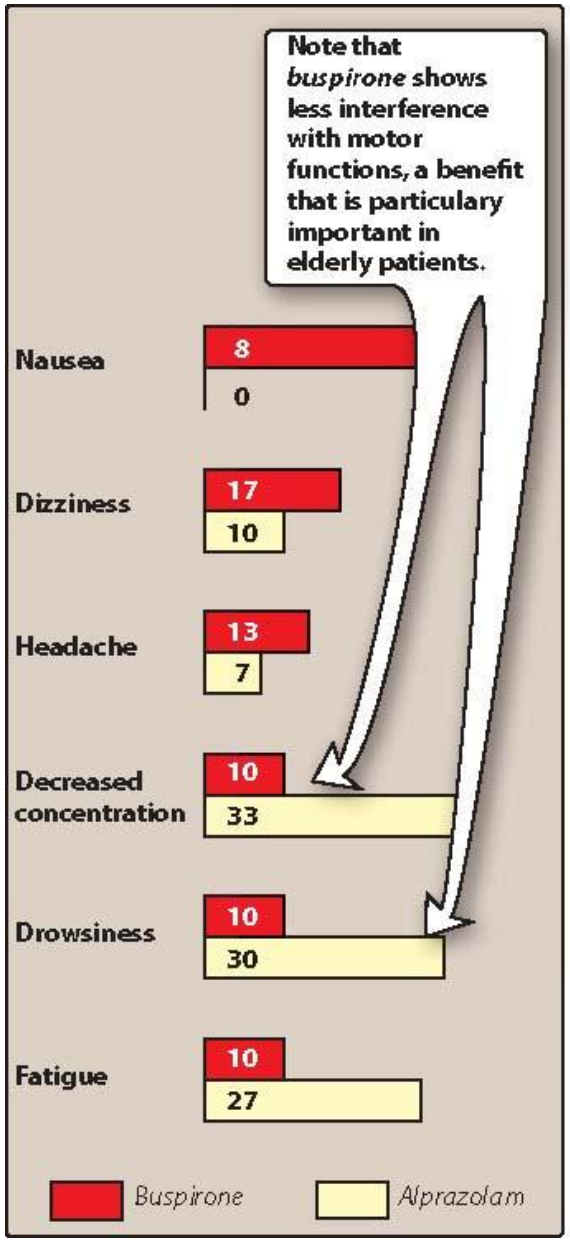
- Remember: many antidepressants are used to treat anxiety.
- **SSRIs** (escitalopram, paroxetine) and **SNRIs** (duloxetine, venlafaxine) are FIRST LINE to treat anxiety.
- Often used with a benzodiazepine initially (first 4-6 weeks)

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

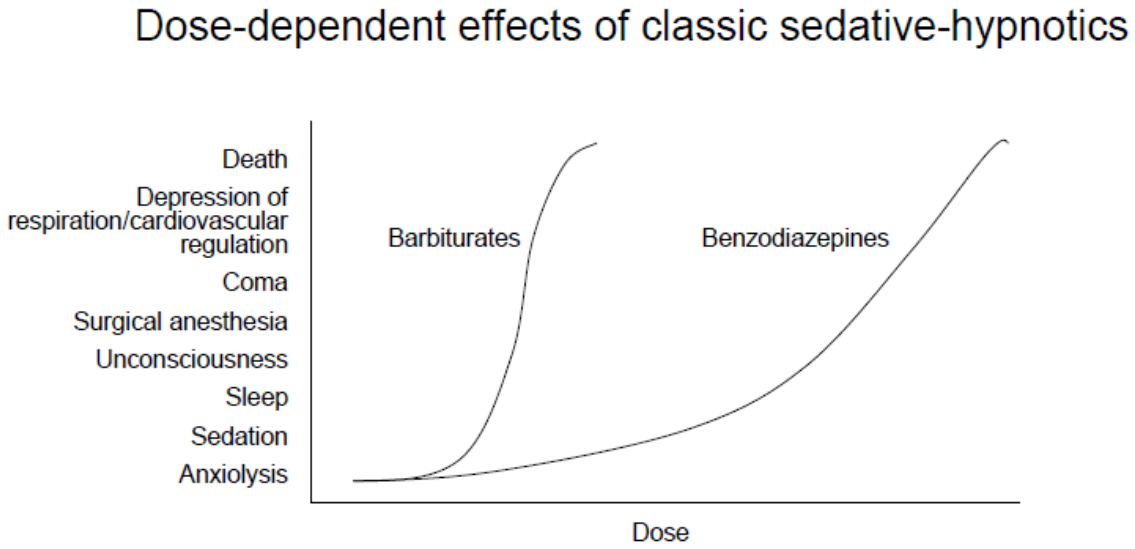
Overview:

- 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:

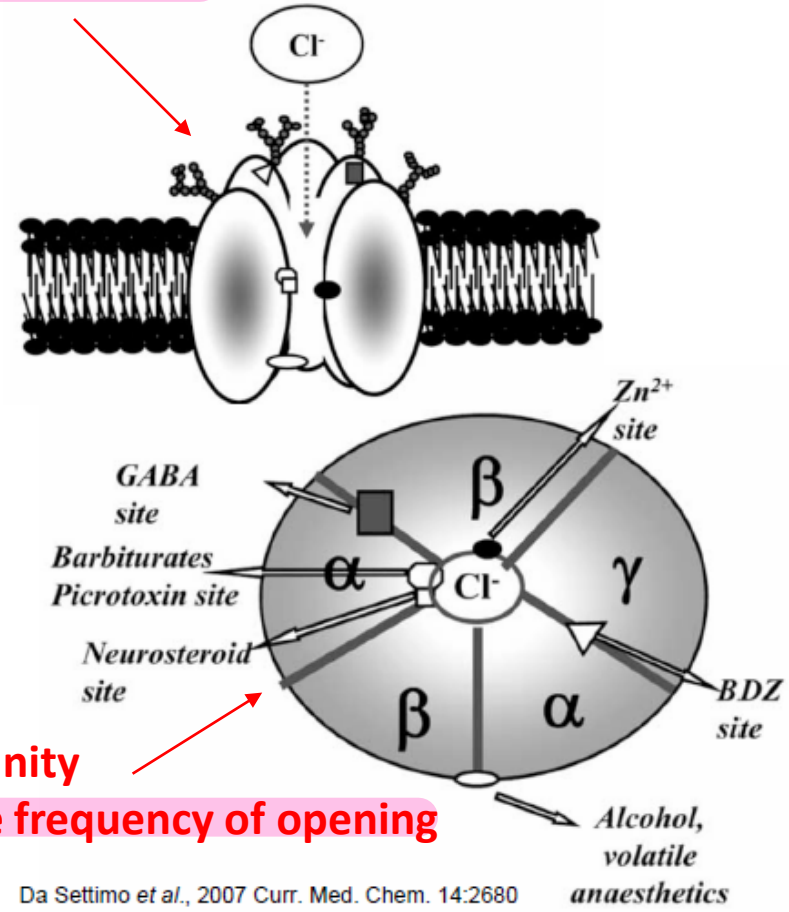
- **Site of action:** $GABA_A$ receptors.
- **Binding site**: different from benzodiazepines

❑ 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

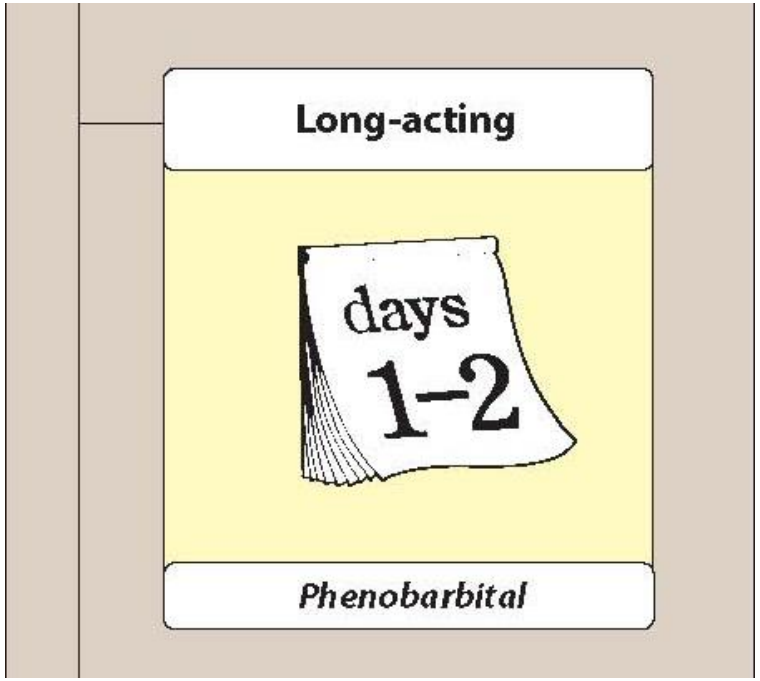
Da Settimo *et al.*, 2007 Curr. Med. Chem. 14:2680

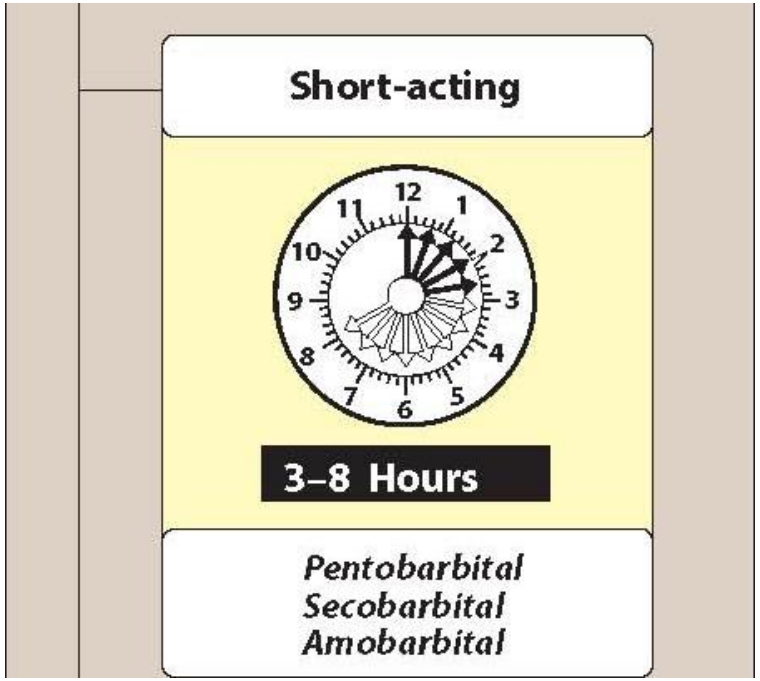
Barbiturates bind to site in ion channel, increasing Cl^- channel open time. Can activate channel at high concentrations.

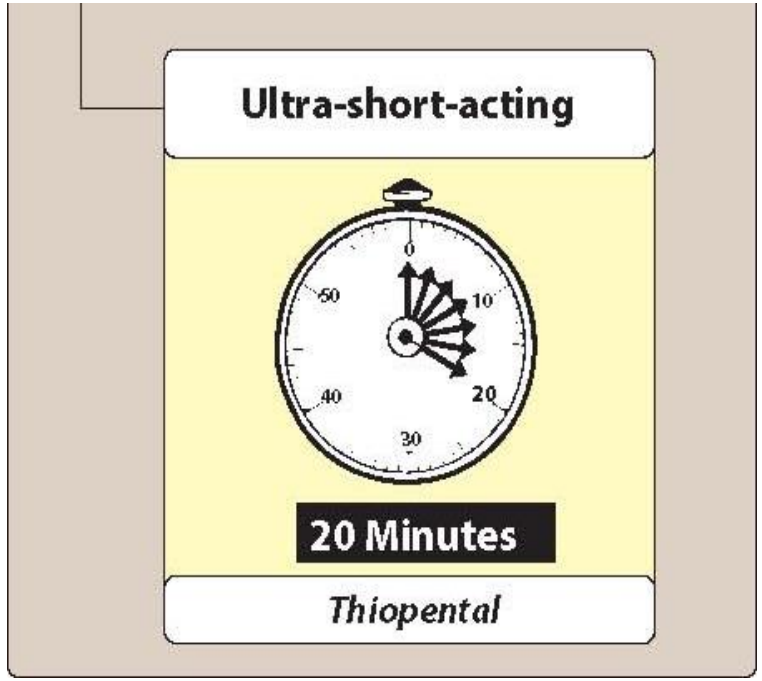
Benzodiazepines increases affinity of GABA binding site for its ligand. In the absence of GABA, benzodiazepines have no detectable effect on receptor function.

Barbiturates

Still used for induction of anesthesia







Barbiturates

Actions:

- **CNS depression:**

❑low doses→ sedation

❑High doses→ hypnosis >>> anesthesia

❑Higher doses → coma and DEATH!

- **Respiratory depression**

Barbiturates

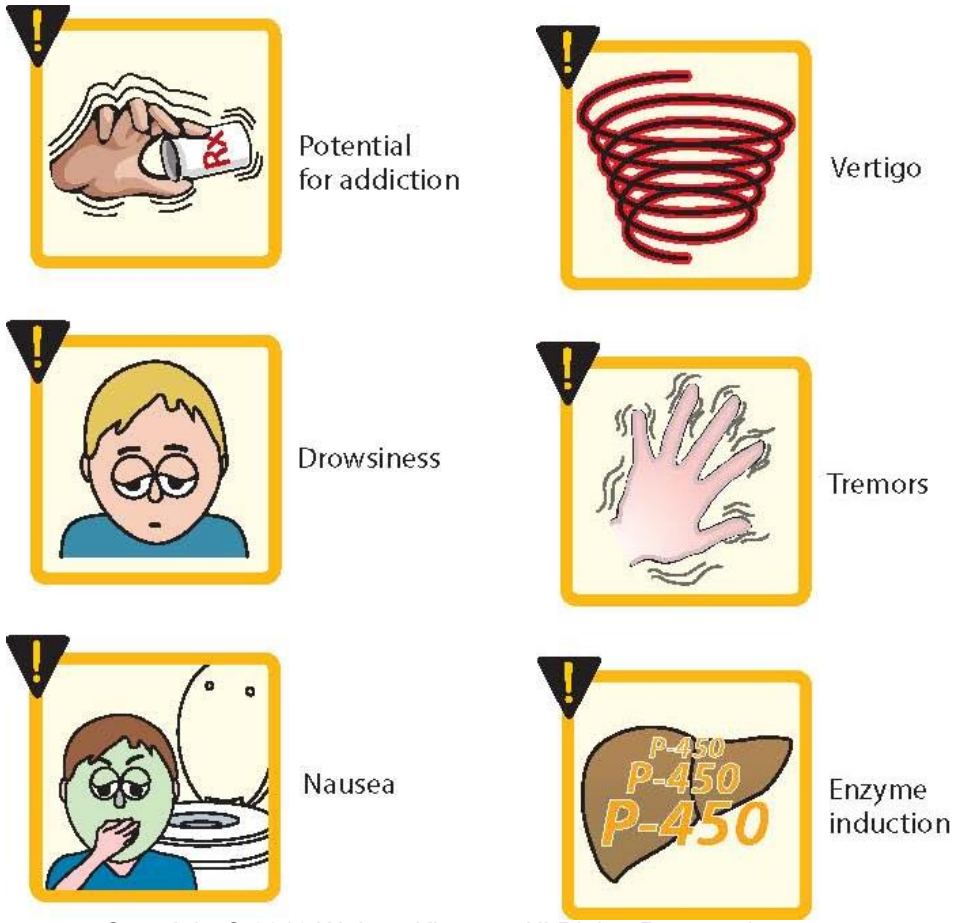
Therapeutic uses:

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.

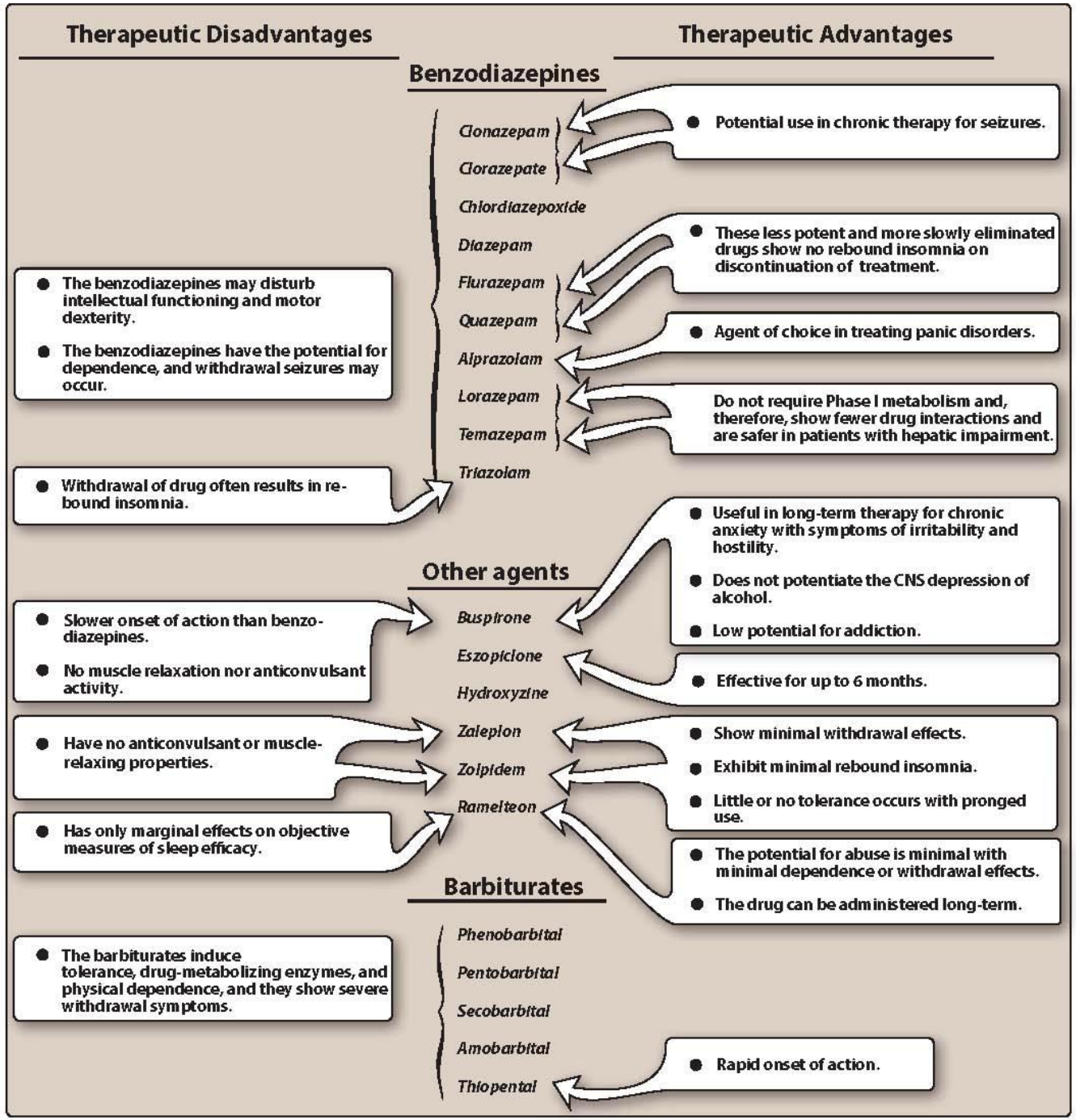
Other Hypnotics: Ramelteon

- 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).

Safer as sedatives for insomnia



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.