Al-Mustaqbal University College

Pharmacology II 4th stage

Anxiolytic and Hypnotic Drugs

Dr. Hasanain Owadh

Anxiolytic and Hypnotic Drugs

Anxiolytic agent (also antianxiety and antipanic): Is a medication that reduces anxiety.

Anxiety is an unpleasant state of tension and a feeling of uneasiness (a fear that arises from either a known or an unknown source).

Hypnotic (from Greek Hypnos, sleep). Hypnotic drugs are intended to induce sedation and promote sleep.

The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, and trembling) and involve sympathetic activation.

Anxiety types

1- Mild Anxiety : Episodes of mild anxiety are common life experiences and do not warrant treatment.

2- Sever , chronic, debilitating anxiety may be treated with anti anxiety drugs

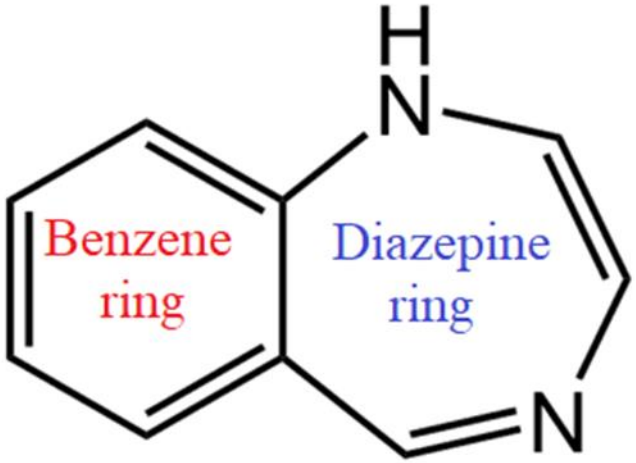
Because many antianxiety drugs also cause some sedation, they may be used clinically as both anxiolytic and hypnotic (sleep-inducing) agents.

Anxiolytic drugs

1- Benzodiazepines
2- Antidepressants
3- Buspirone

1- Benzodiazepines

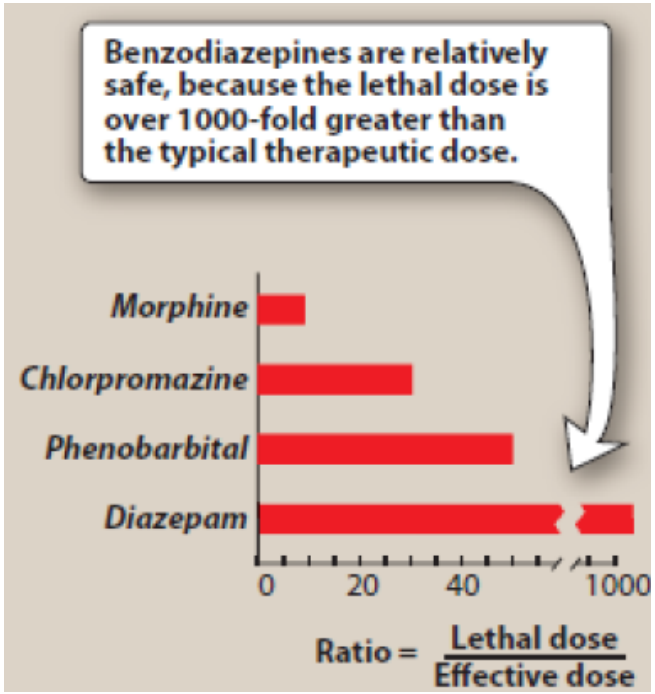
Benzodiazepines are widely used anxiolytic drugs.
whose core chemical structure is the fusion of a benzene ring and a diazepine ring.



Benzodiazepines

Benzodiazepines are widely used anxiolytic drugs.

Benzodiazepines are commonly used, because benzodiazepines are generally considered to be safer and more effective than barbiturates.



I- Mechanism of action

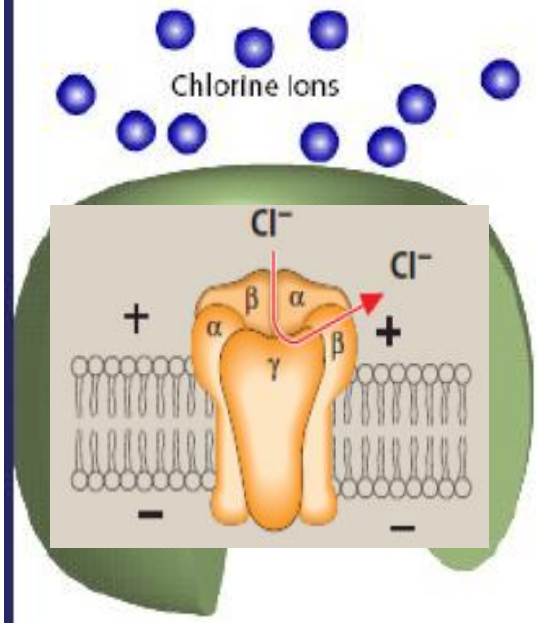
Benzodiazepines modulate GABA (γ-aminobutyric acid GABA is the major inhibitory NT in the CNS) effects by binding to a specific, high-affinity site (distinct from the GABA-binding site) located at the interface of the α subunit and the γ subunit on the $GABA_A$ receptor

Binding of GABA to its receptor triggers an opening of the central ion channel, allowing chloride through the pore and causes hyperpolarization of the neuron and decreases neurotransmission by inhibiting the formation of action potentials.

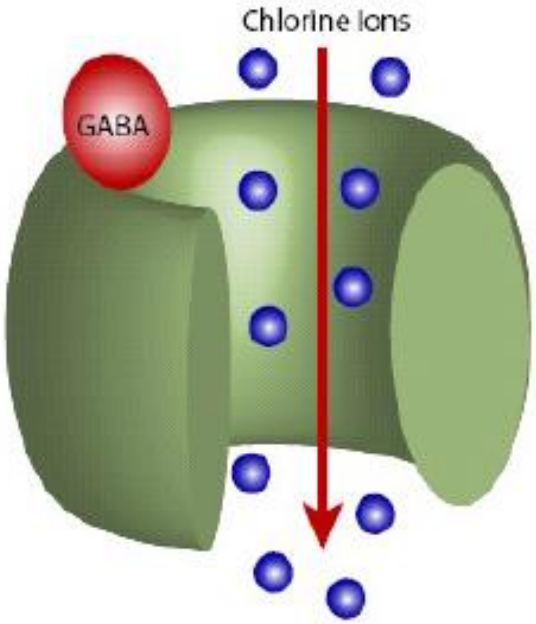
Benzodiazepine has two binding site or receptors on GABA receptor BZ1 & BZ2.

Binding of benzodiazepine to its receptors leads to increase the frequency of channel openings produced by GABA.

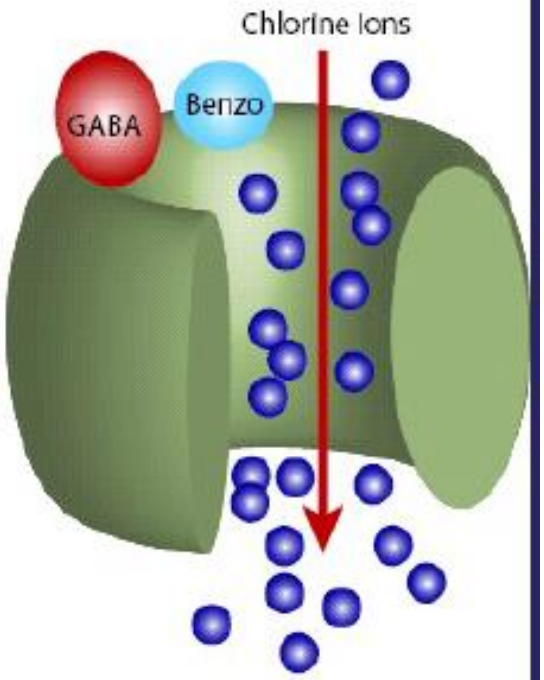
Extracellular Side of $GABA_A$ Receptor



1. No chlorine influx because GABA has not bound to receptor



2. Normal chlorine influx resulting from GABA binding to receptor



3. Increased chlorine influx resulting from both GABA and benzodiazepine binding to receptor

II- Actions

All benzodiazepines exhibit the following actions to some extent:

1. Reduction of anxiety: At low doses, the benzodiazepines are anxiolytic. (Through α_2 subunit in their $GABA_A$ receptors , in limbic system of the brain).

2. Sedative/hypnotic:

- All benzodiazepines have sedative and calming properties,
- and some can produce hypnosis (by α_1-$GABA_A$ receptors) at higher doses.

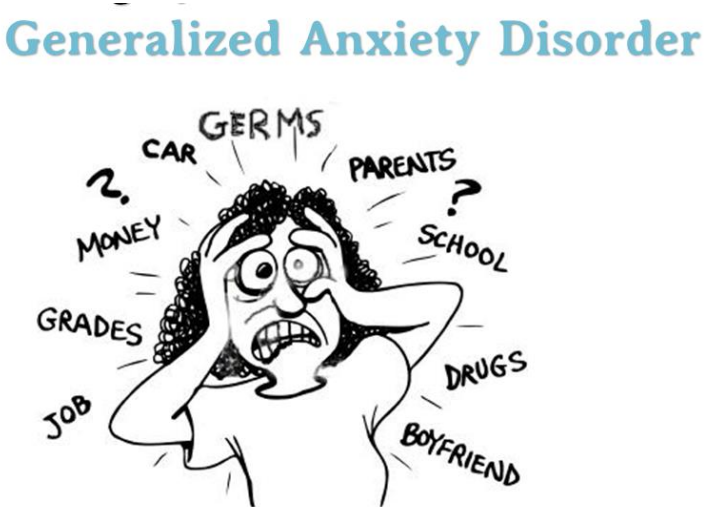
3. Anterograde amnesia: Temporary impairment of memory with the use of the benzodiazepines (α_1-$GABA_A$, receptors.

4. Anticonvulsant: This effect is partially, although not completely, mediated by α_1-$GABA_A$, receptors.

5. Muscle relaxant: At high doses, the benzodiazepines relax the spasticity of skeletal muscle, (presynaptic inhibition in the spinal cord, α_2-$GABA_A$).

III- Therapeutic uses:

1. Anxiety disorders.
2. Sleep disorders.
3. Amnesia.
4. Seizures.
5. Muscular disorders.



1- Anxiety disorders:

like panic disorder,
generalized anxiety disorder (GAD),
social anxiety disorder.

Q / These drugs should be reserved for severe anxiety only and not used to manage the stress of everyday life, why ?
- Because of their addiction potential, they should only be used for short periods of time.

The longer-acting agents, are often preferred in patients with anxiety that 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 approximately 30% of patients.

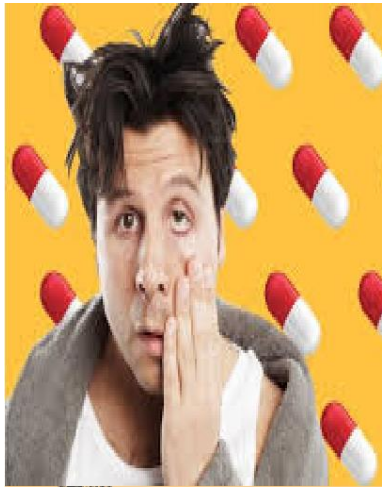
[Note: Tolerance is decreased responsiveness to repeated doses of the drug that occurs when used for more than 1 to 2 weeks.]

Tolerance happens when two biological events occur:

- Pharmacokinetic tolerance (drug not reaching the brain's receptors)
- Pharmacodynamic tolerance (receptors are damaged or lost)

2. Sleep disorders: Benzodiazepine hypnotics decrease the latency to sleep onset and increase stage II of non-rapid eye movement (REM) sleep.

it is important to balance the sedative effect needed at bedtime with the residual sedation ("hangover") upon awakening.



Q- In general, hypnotics should be used for only a limited time, usually 1 to 3 weeks and also used intermittently, Why?
To avoid Tolerance development and withdrawal symptoms.

Short-acting triazolam is effective in treating individuals who have problems falling asleep.

The risk of withdrawal and rebound insomnia is higher with triazolam than with other agents.

Intermediate-acting temazepam is useful for patients who experience frequent awakenings and it should be administered 1 to 2 hours before the desired bedtime.

3. Amnesia: The shorter-acting agent like **Midazolam** is often employed as premedication for anxiety-provoking and unpleasant procedures, such as :

Endoscopy , dental procedures, and angioplasty.

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 (epilepsy).

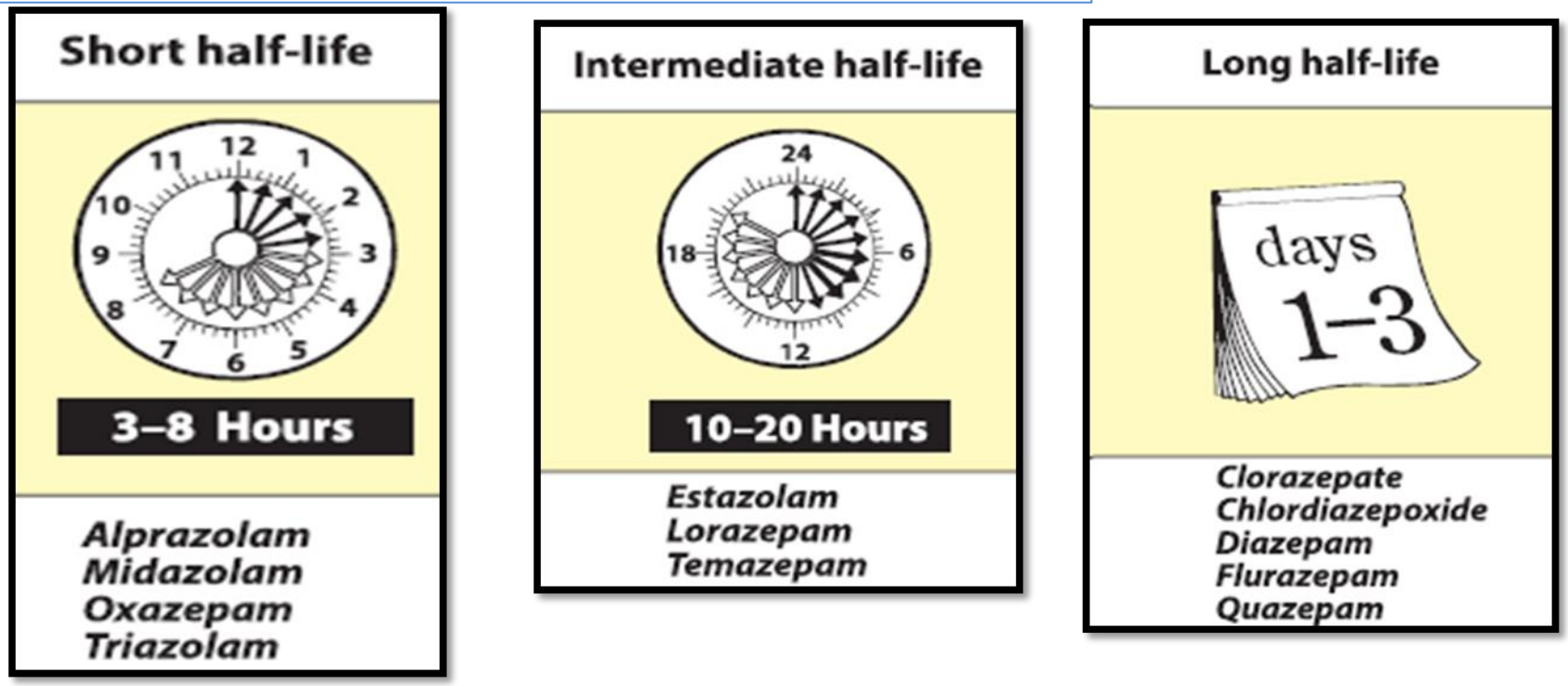
5. Muscular disorders: **Diazepam** is useful in the treatment of skeletal Muscle spasms.

IV- Pharmacokinetics

1. Absorption and distribution:

The benzodiazepines are lipophilic. They are rapidly and completely absorbed after oral administration, distribute throughout the body, and penetrate into the CNS.

2. Duration of Action of Benzodiazepines



Q. Classify benzodiazepines drugs according to duration of action?

3. Fate (Metabolism & elimination): Most benzodiazepines are metabolized by the hepatic microsomal system and the apparent half-life of the drug represents the combined actions of the parent drug and its active metabolites.

Drug effects are terminated not only by excretion but also by redistribution.
The benzodiazepines are excreted in the urine as glucuronides or oxidized metabolites.

Q/ The benzodiazepines are not recommended for use during pregnancy & during breast feeding, **why?**

Because All benzodiazepines cross the placenta and secreate in breast milk and may depress the CNS of the newborn or infant.

V. Dependence

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

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

VI. Adverse effects

Drowsiness and confusion (common).

Ataxia occurs at high doses

Cognitive impairment

Benzodiazepines should be used cautiously in patients with liver disease.

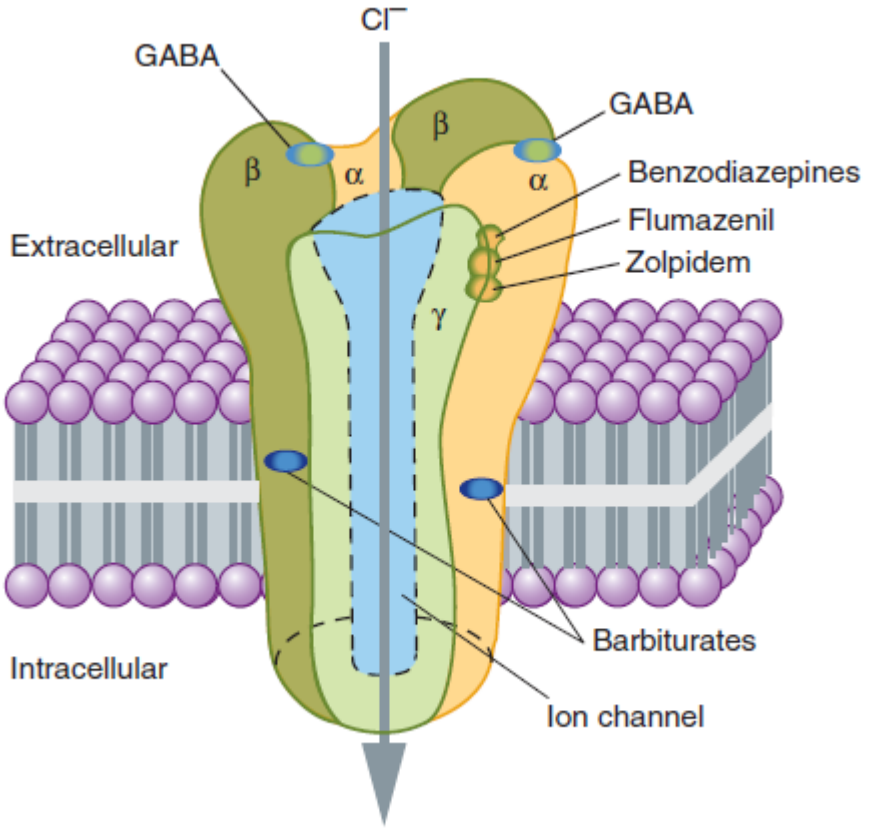
A drug overdose is seldom lethal unless other central depressants, such as alcohol or opioids, are taken concurrently.

VII- BENZODIAZEPINE ANTAGONIST

Flumazenil is a GABA receptor antagonist that rapidly reverses the effects of benzodiazepines.
It is (IV) administration only.

Onset is rapid, but the duration is short, with a half-life of about 1 hour.

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



2- Antidepressants

Many antidepressants are considered as first-line agents in the treatment of chronic anxiety disorders.

SSRis (such as escitalopram or paroxetine) or serotonin /norepinephrine reuptake inhibitors (SNRis, such as venlafaxine or duloxetine) may be used alone or prescribed in combination with a benzodiazepine during the first week of treatment.

After 4 to 6 weeks, when the antidepressant begins to produce an anxiolytic effect, the benzodiazepine dose can be tapered.

3- Buspirone

Buspirone is useful for the chronic treatment of GAD and has an efficacy comparable to that of benzodiazepines and not use for treatment of acute anxiety.

The actions of buspirone appear to be mediated by serotonin (5-HT_{1A}) receptors, although it also displays some affinity for D_2 dopamine receptors and 5-HT_{2A} serotonin receptors.

Adverse effects:

Headache, dizziness, nervousness, nausea, and light-headedness are most common.

Sedation and psychomotor and cognitive dysfunction are minimal.

Dependence is unlikely.

Q- What are the most common adverse effects of buspirone**?**

Hypnotic Drugs

1-Benzodiazepines

2- Barbiturates

3- Zaleplon

4- Zolpidem

5- Eszopiclone

6- Melatonin receptor agonists

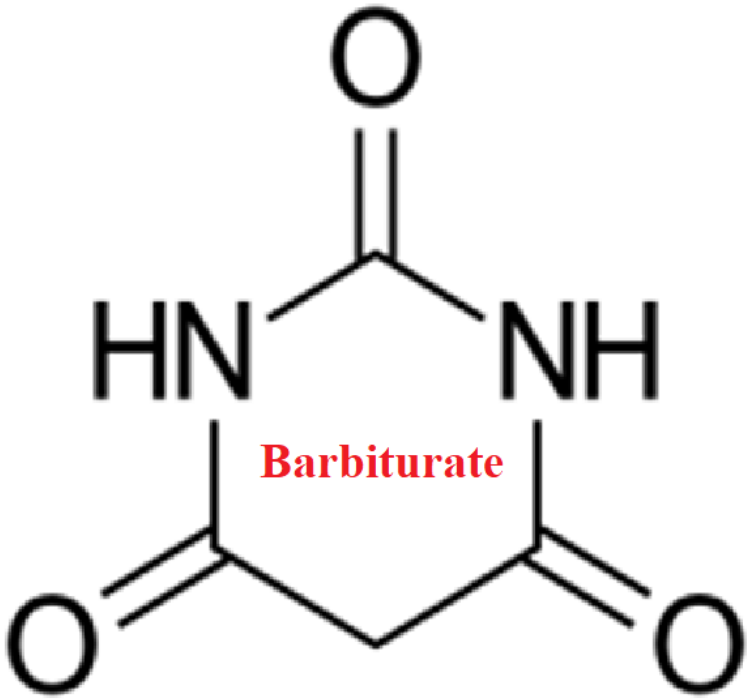
7- Antihistamines

8- Antidepressants

9- Suvorexant

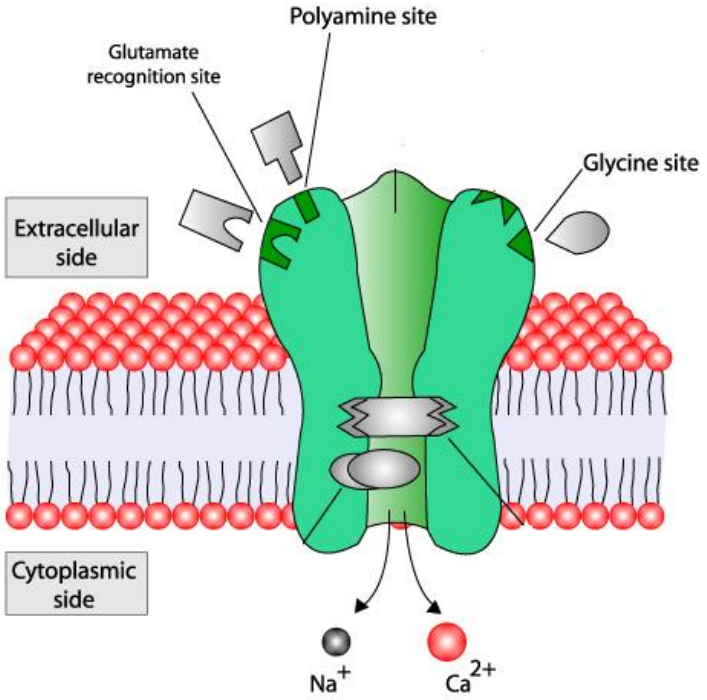
2- Barbiturates

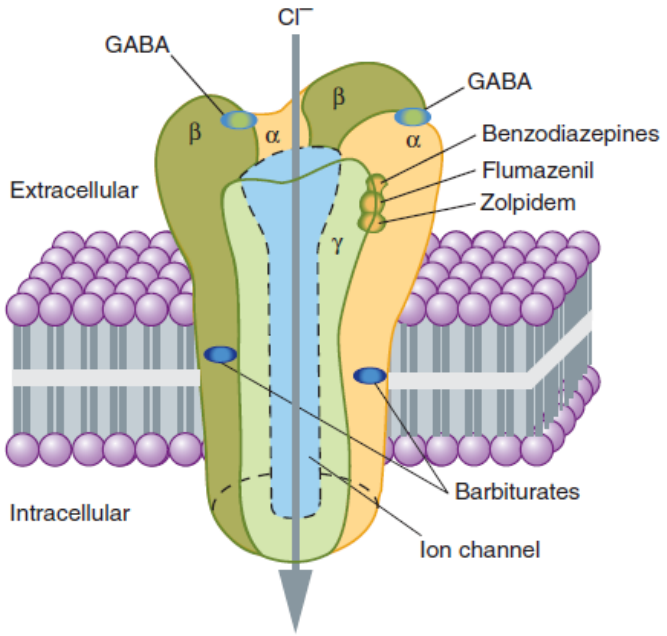
They have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance and physical dependence, are lethal in overdose, and are associated with severe withdrawal symptoms.



I. Mechanism of action The sedative-hypnotic action of the barbiturates is due to their interaction with GABAA receptors, which enhances GABAergic transmission.

In addition, barbiturates can block excitatory glutamate receptors. These molecular actions lead to decreased neuronal activity.

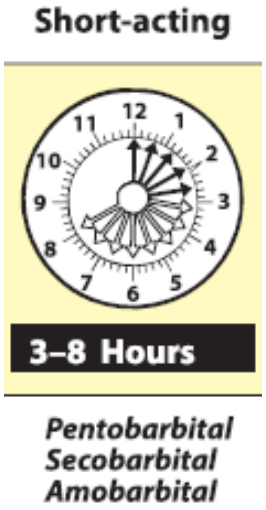




II. Actions

Barbiturates are classified according to their duration of action

Ultra–short-acting thiopental



1. Depression of CNS: At low doses, the barbiturates produce sedation (have a calming effect and reduce excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and, finally, coma and death.

Chronic use leads to tolerance.

2. Respiratory depression: Barbiturates suppress the hypoxic and chemoreceptor response to $C0_2$, and overdose is followed by respiratory depression and death.

III- Therapeutic Uses of Barbiturates

1. **Anesthesia:** previously used intravenously to induce anesthesia.
2. **Anticonvulsant:** Phenobarbital has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.

Q- Phenobarbital should be used for treatment of seizures and refractory status epilepticus only if other therapies have failed, why?
Answer: Because it can depress cognitive development in children and decrease cognitive performance in adults.

3. **Sedative/hypnotic**:
The use of barbiturates for insomnia is no longer generally accepted.

Butalbital is commonly used with (acetaminophen or aspirin) and caffeine as a sedative to assist in the management of tension or migraine headaches.

IV. Pharmacokinetics

Barbiturates are well absorbed after oral administration and distribute throughout the body.

All barbiturates redistribute from the brain to the splanchnic areas, to skeletal muscle, and, finally, to adipose tissue.

Barbiturates readily cross the placenta and can depress the fetus.

These agents are metabolized in the liver, and inactive metabolites are excreted in urine.

V. Adverse effects

drowsiness,
impaired concentration,
Mental and psychomotor impairment.
The CNS depressant (synergize with ethanol).
drug "hangover

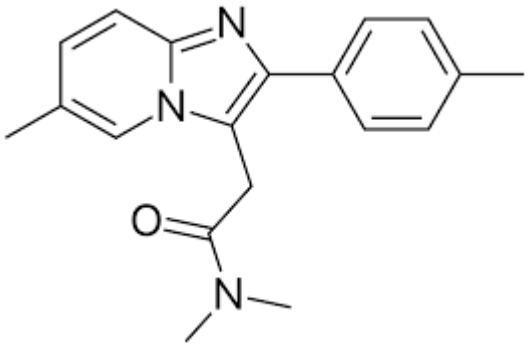
Occasionally, nausea and dizziness occur.
Barbiturates induce cytochrome P450 (CYP450)

Barbiturates are contraindicated in patients with acute intermittent porphyria.

Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness restlessness, nausea and vomiting, seizures, delirium, cardiac arrest, Severe cardiovascular and respiratory depression and death.

OTHER HYPNOTIC AGENTS

3- Zolpidem



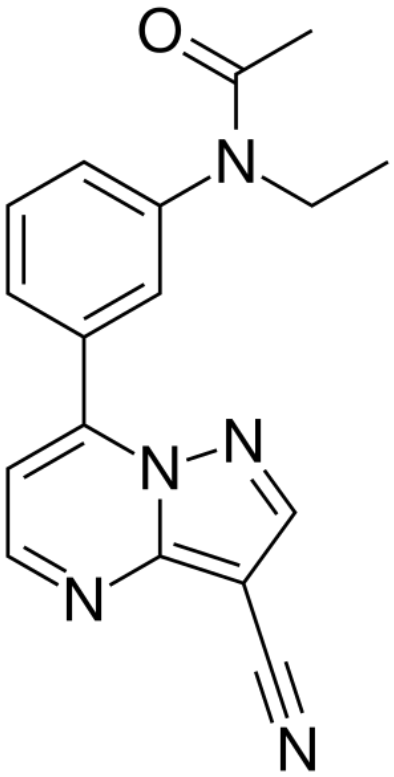
Mechanism of action: Facilitates the GABA action via α_1-$GABA_A$ binding.

Pharmcokinetics: Zolpidem is rapidly absorbed from GIT with rapid onset of action half-life 1-2 hours and metabolized by the CYP450 system,

Therapeutic uses : It provides a hypnotic effect for approximately 5 hours.

Adverse effects of zolpidem include:
Nightmares, agitation, anterograde amnesia, and daytime drowsiness

4- Zaleplon



It is an oral nonbenzodiazepine hypnotic,
Facilitates the GABA action via $GABA_A$ binding.

Q- zaleplon causes fewer residual effects on psychomotor and cognitive function compared to zolpidem or the benzodiazepines, **why?**

This may be due to its rapid elimination, with a half-life of approximately 1 hour.

The drug is metabolized by CYP3A4.

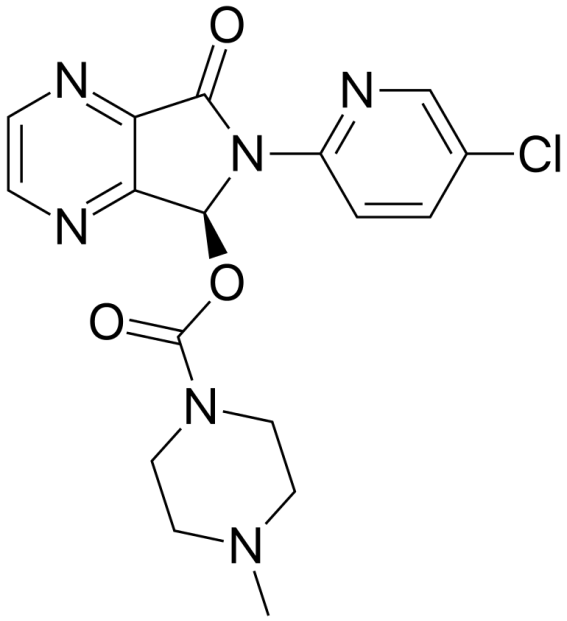
Q/ Non-BZD drugs zolpidem, zaleplon, and eszopiclone,are often the preferred hypnotics over BZD, WHY?
A/ This may be due to : Do not significantly alter the various sleep stages.

5- Eszopiclone

Eszopiclone is an oral nonbenzodiazepine hypnotic that has been shown to be effective for insomnia for up to 6 months.

Facilitates the GABA action via α_1-$GABA_A$ binding.

Eszopiclone is rapidly absorbed and reachs peak within 1 hour, metabolized by CYP450 system, and excreted in urine. Elimination half-life is approximately 6 hours.



Adverse events include:

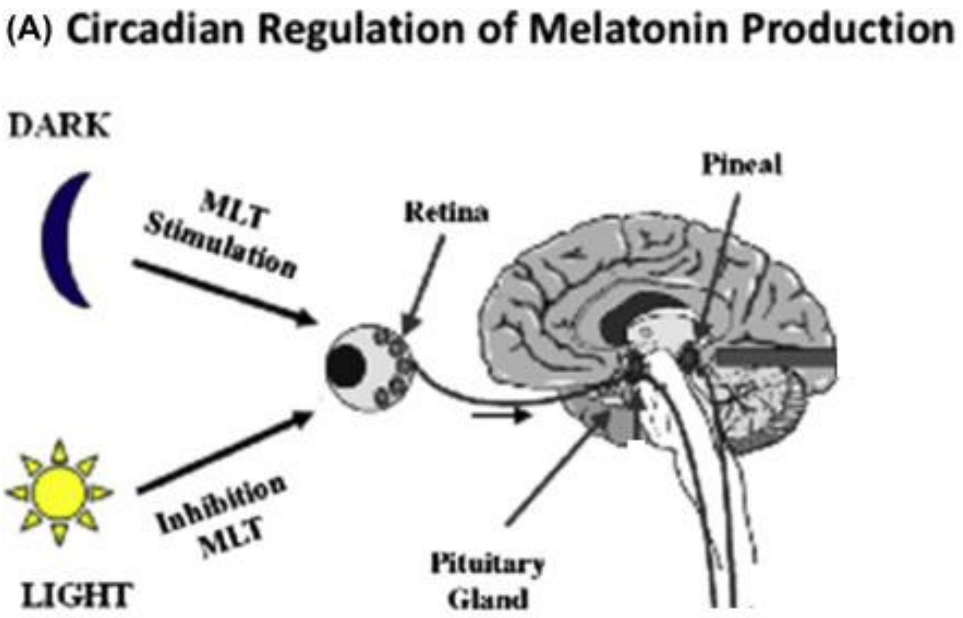
anxiety,
dry mouth,
headache,
peripheral edema,
somnolence,
and unpleasant taste.

6- Melatonin receptor agonists

Ramelteon and tasimelteon are selective agonists at the MT_1 and MT_2 subtypes of melatonin receptors.

Melatonin is a hormone secreted by the pineal gland that helps to maintain the circadian rhythm underlying the normal sleep-wake cycle.

Stimulation of MT_1 and MT_2 receptors by ramelteon and tasimelteon is thought to induce and promote sleep.



Q- ramelteon and tasimelteon can be administered for long-term. **Why?**

A- Because They have minimal potential for abuse, and no evidence of dependence or withdrawal has been observed.

Ramelteon is indicated for the treatment of insomnia characterized by difficulty falling asleep.

Common adverse effects of ramelteon include dizziness, fatigue, and somnolence. Ramelteon may also increase prolactin levels.

Tasimelteon is indicated for non-24-hour sleep-wake disorder.

The most common adverse effects of tasimelteon are headache, abnormal dreams, increase in liver function tests, and possible upper respiratory tract infections.

They are metabolized by CYP450 system.

7- Antihistamines

The undesirable adverse effects of sedating antihistamines (anticholinergic effects) make them less useful than the benzodiazepines and the nonbenzodiazepines.

8- Antidepressants

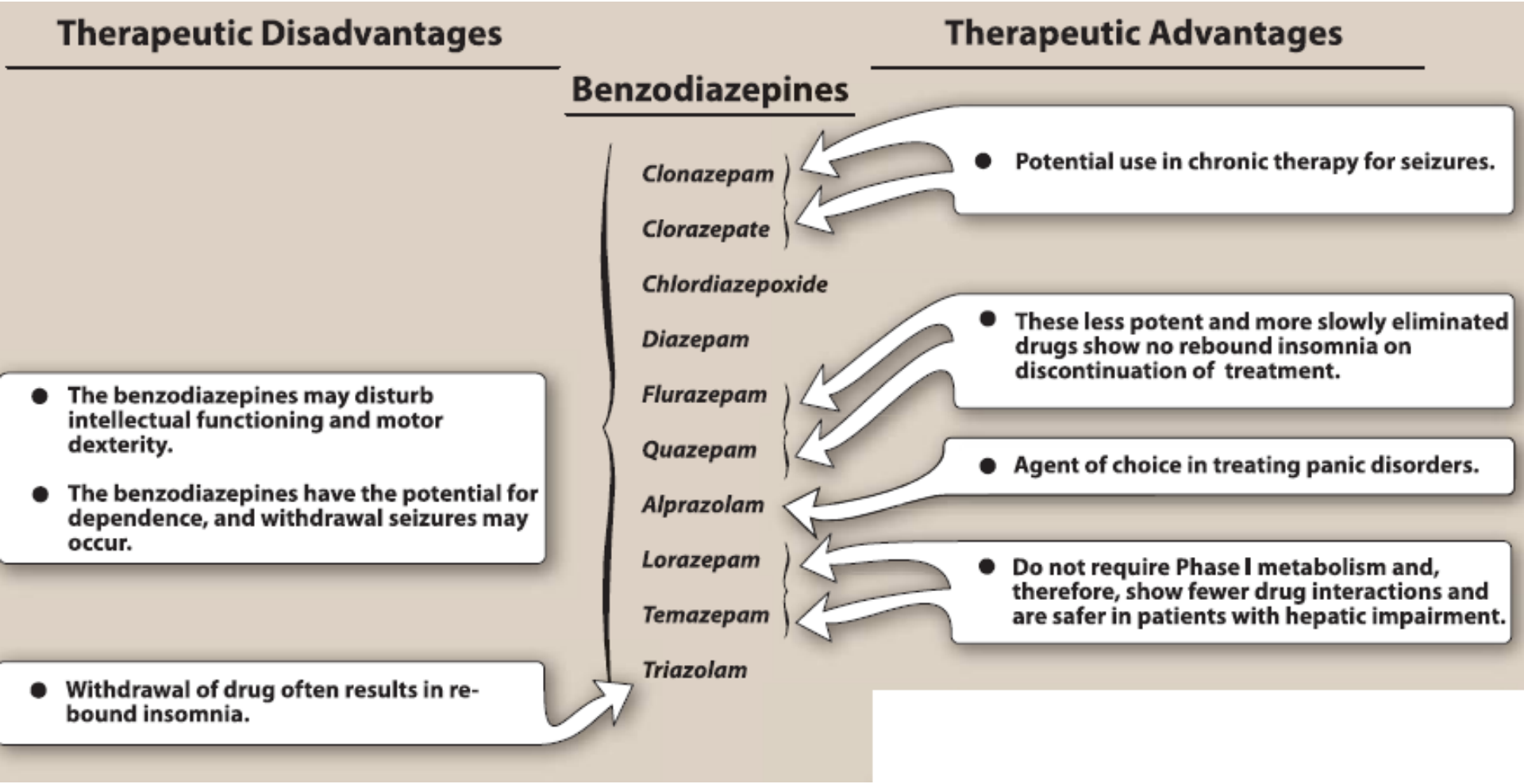
Doxepin, an older tricyclic agent with SNRI mechanisms of antidepressant and anxiolytic action, is approved at low doses for the management of insomnia.

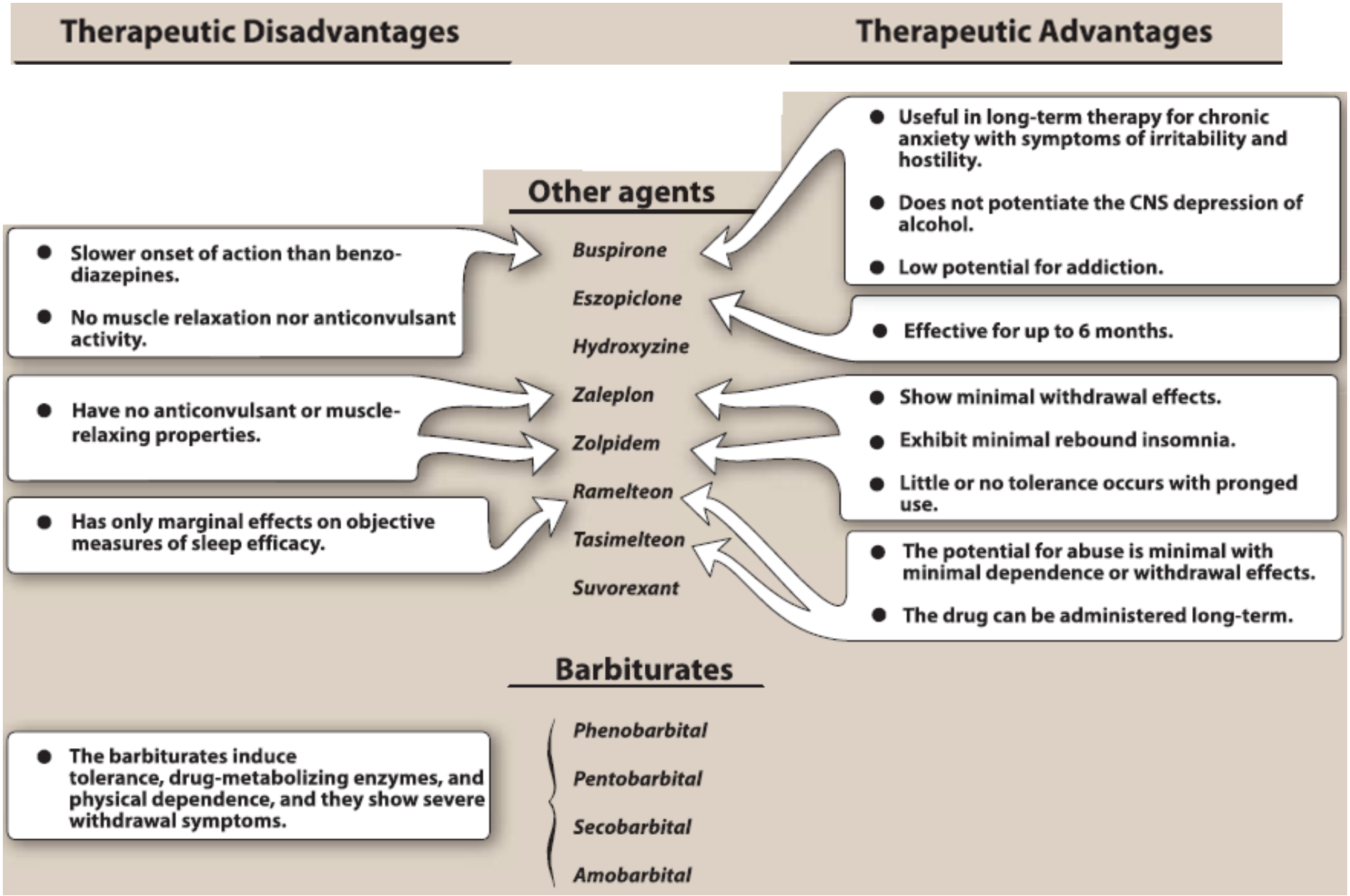
Other antidepressants, such as trazodone, mirtazapine, and other older tricyclic antidepressants with strong antihistamine properties are used off-label for the treatment of insomnia.

9- Suvorexant

Suvorexant [soo-voe-REX-ant] is an antagonist of the orexin receptor.
Orexin is a neuropeptide that promotes wakefulness.
Antagonism of the effects of orexin suppresses the wake drive from this neuropeptide.
This antagonism may also explain the adverse events that are similar to signs of narcolepsy and cataplexy.

The loss of orexin producing neurons is believed to be an underlying pathology for narcolepsy.
Daytime somnolence and increased suicidal ideation are other reported adverse effects.
The drug is metabolized by CYP3A4.


Therapeutic Disadvantages
Therapeutic Advantages
Benzodiazepines
Clonazepam
Clorazepate
Chlordiazepoxide
Diazepam
Flurazepam
Quazepam
Alprazolam
Lorazepam
Temazepam
Triazolam
Potential use in chronic therapy for seizures.
These less potent and more slowly eliminated drugs show no rebound insomnia on discontinuation of treatment.
Agent of choice in treating panic disorders.
Do not require Phase I metabolism and, therefore, show fewer drug interactions and are safer in patients with hepatic impairment.
The benzodiazepines may disturb intellectual functioning and motor dexterity.
The benzodiazepines have the potential for dependence, and withdrawal seizures may occur.
Withdrawal of drug often results in re-bound insomnia.


Therapeutic Disadvantages
Therapeutic Advantages
Other agents
Buspirone
Eszopiclone
Hydroxyzine
Zaleplon
Zolpidem
Ramelteon
Tasimelteon
Suvorexant
Slower onset of action than benzo-diazepines.
No muscle relaxation nor anticonvulsant activity.
Have no anticonvulsant or muscle-relaxing properties.
Has only marginal effects on objective measures of sleep efficacy.
Useful in long-term therapy for chronic anxiety with symptoms of irritability and hostility.
Does not potentiate the CNS depression of alcohol.
Low potential for addiction.
Effective for up to 6 months.
Show minimal withdrawal effects.
Exhibit minimal rebound insomnia.
Little or no tolerance occurs with pronged use.
The potential for abuse is minimal with minimal dependence or withdrawal effects.
The drug can be administered long-term.
Barbiturates
Phenobarbital
Pentobarbital
Secobarbital
Amobarbital
The barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence, and they show severe withdrawal symptoms.


Thank You