DRUGS THAT ACT IN THE CNS

Anxiolytic and Hypnotic Drugs

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OTHER ANXIOLYTIC AGENTS/

A. Antidepressants

Many antidepressants are effective in the treatment of chronic anxiety disorders and should be considered as first-line agents, especially in patients with **concerns for addiction or dependence.**

Selective serotonin reuptake inhibitors (**SSRIs**) or serotonin/norepinephrine reuptake inhibitors (**SNRIs**) may be used alone or prescribed in combination with a benzodiazepine.

SSRIs and SNRIs have a **lower potential for physical dependence** than the benzodiazepines and have become first-line treatment for GAD.

OTHER ANXIOLYTIC AGENTS/

B. Buspirone

Buspirone is useful for the chronic treatment of **GAD** and has an efficacy comparable to that of the benzodiazepines.

It has a **slow onset of action** and is not effective for short-term or “as-needed” treatment of acute anxiety states.

The actions of buspirone appear to be mediated by serotonin (**5-HT1A**) receptors, although it also displays some affinity for **D2 dopamine** receptors and **5-HT2A** serotonin receptors.

Buspirone lacks the **anticonvulsant** and **muscle-relaxant** properties of the benzodiazepines.

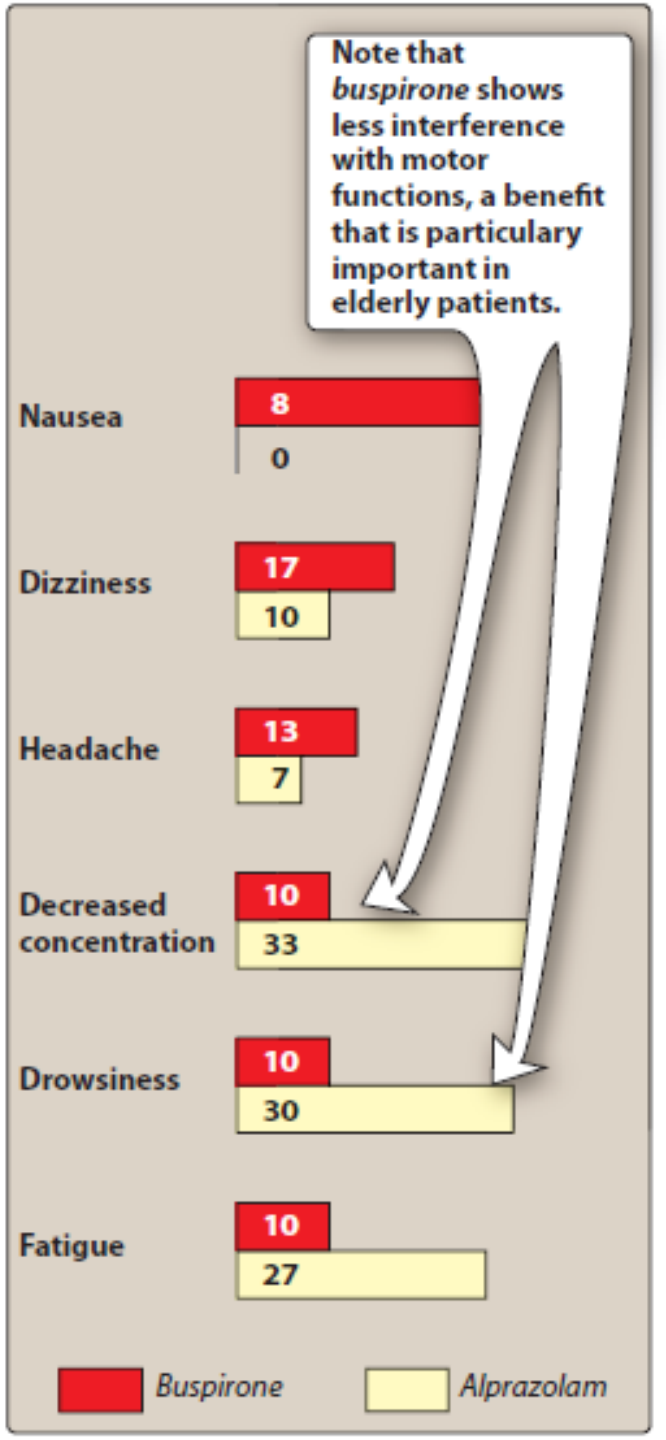
OTHER ANXIOLYTIC AGENTS

B. Buspirone

The frequency of **adverse effects is low**, with the most common effects being headaches, dizziness, nervousness, nausea, and light-headedness.

Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely.

Buspirone does not potentiate the CNS depression of **alcohol**.



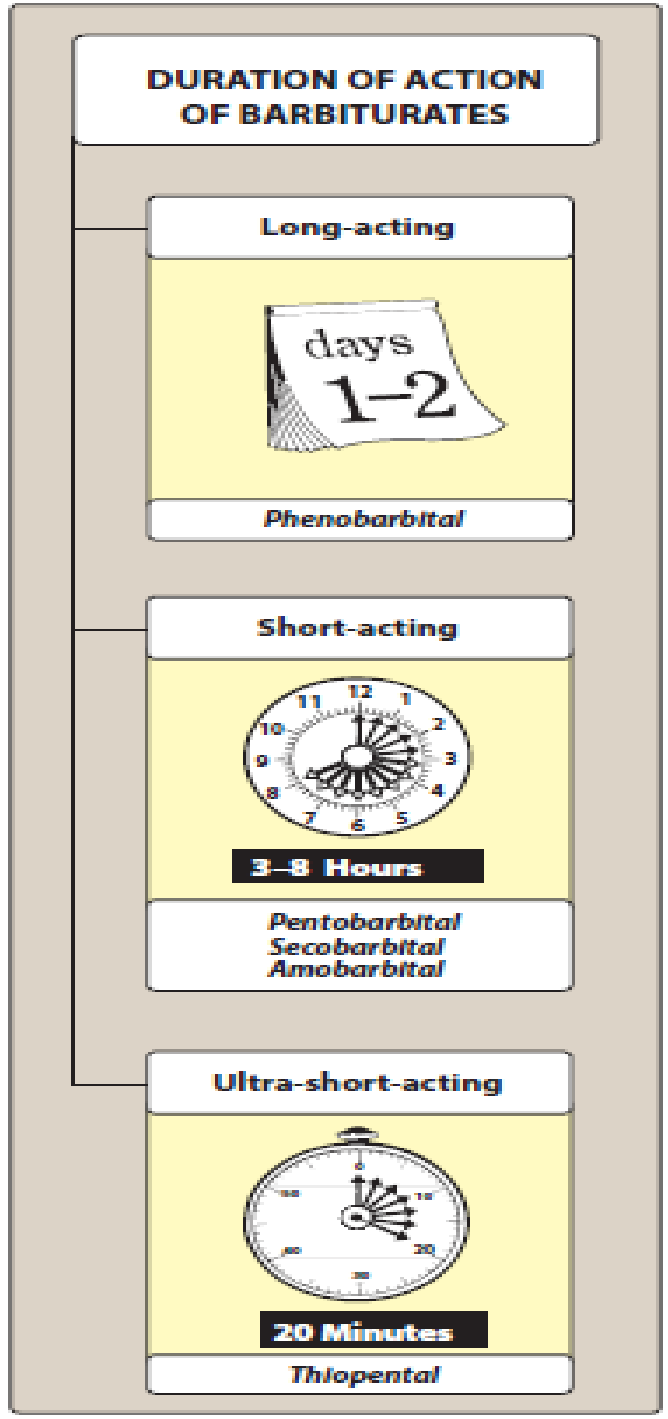
V. BARBITURATES

The barbiturates were formerly the mainstay of treatment to sedat patients or to induce and maintain sleep.

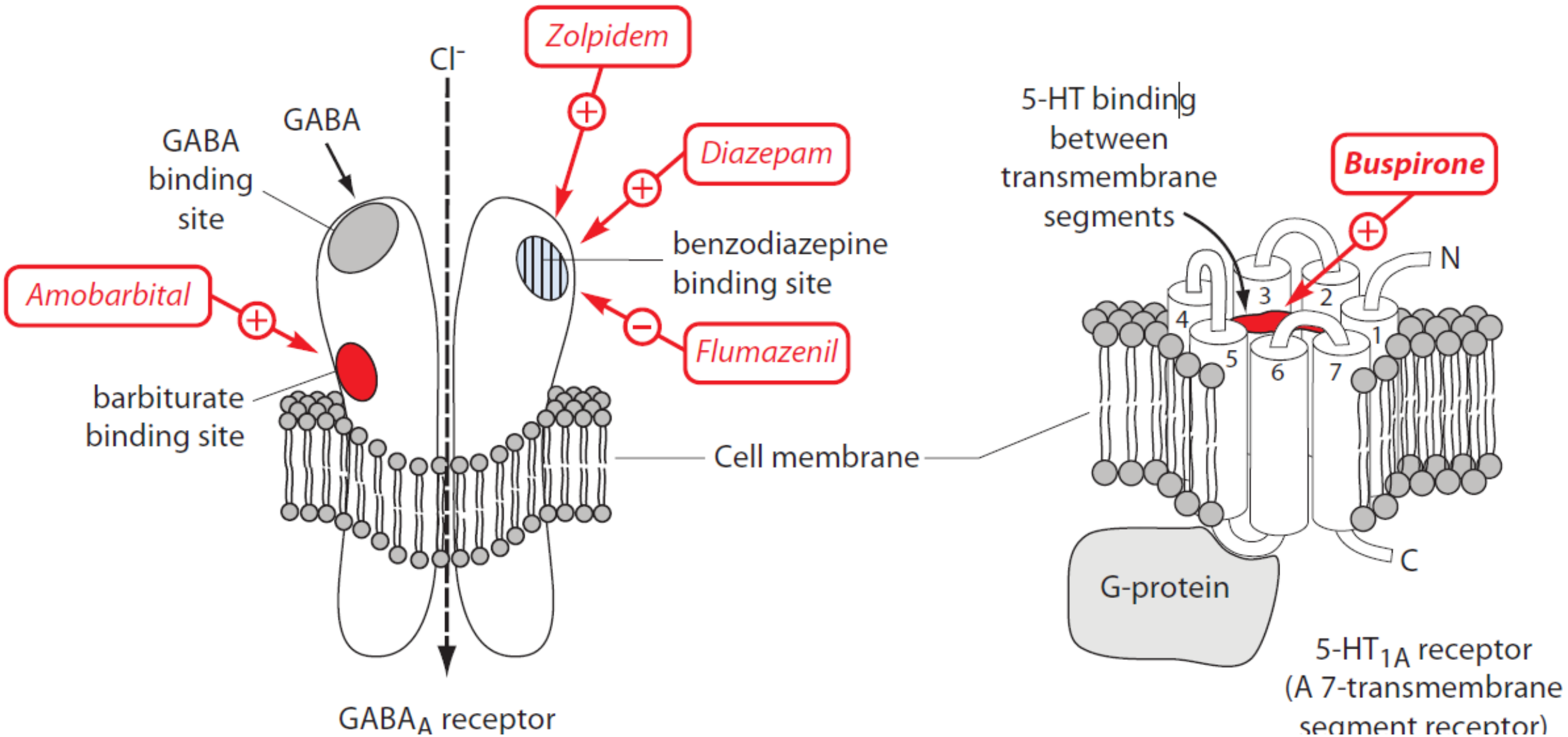
Today, they have been largely **replaced by the benzodiazepines**, primarily because barbiturates induce **tolerance** and physical **dependence** and are associated with very severe **withdrawal** symptoms.

All barbiturates are **controlled substances**.

Certain barbiturates, such as the **very short-acting thiopental**, have been used to induce **anesthesia** but are infrequently used today due to the advent of newer agents with fewer adverse effects.



V. BARBITURATES/ Mechanism of action



V. BARBITURATES/ Mechanism of action

The sedative–hypnotic action of the barbiturates is due to their interaction with **$GABA_A$** receptors, which enhances GABAergic transmission.

The binding site of barbiturates **on the GABA receptor** **is distinct** from that of the benzodiazepines.

Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the **chloride channel openings**.

In addition, barbiturates can **block excitatory glutamate receptors**.

Anesthetic concentrations of pentobarbital also block high-frequency **sodium channels**.

V. BARBITURATES/ Action

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.

Barbiturates do not raise the pain threshold and have **no analgesic properties**. They may even exacerbate pain. Chronic use leads to tolerance.

2. Respiratory depression:

Barbiturates suppress the hypoxic and **chemoreceptor response to CO2**, and overdosage is followed by respiratory depression and death.

V. BARBITURATES/ Therapeutic Uses

1. Anesthesia:

The ultra–short-acting barbiturates, such as thiopental, have been used intravenously to induce anesthesia but have largely been replaced by other agents.

2. Anticonvulsant:

Phenobarbital has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.

It is used in long-term management of **tonic–clonic seizures**.

However, phenobarbital can **depress cognitive development** in children and decrease cognitive performance in adults, and it should be used only if other therapies have failed.

Similarly, phenobarbital may be used for the treatment of **refractory status epilepticus**.

V. BARBITURATES/ Therapeutic Uses

3. Sedative/hypnotic:

Barbiturates have been used as **mild sedatives** to relieve anxiety, nervous tension, and insomnia.

When used as hypnotics, they suppress REM sleep more than other stages.

However, the use of barbiturates for insomnia is **no longer accepted**, given their adverse effects and potential for tolerance.

V. BARBITURATES/ 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.

This movement is important in causing the **short duration** of action of thiopental and similar short-acting derivatives.

Barbiturates readily **cross the placenta** and can depress the fetus.

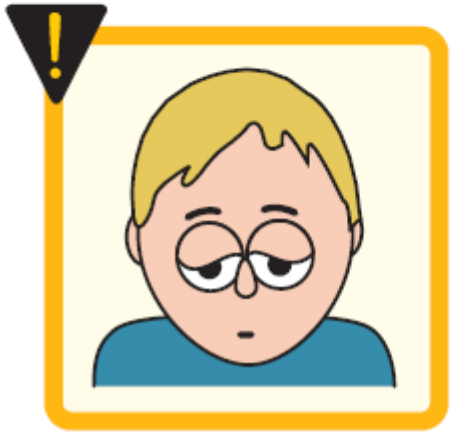
These agents are metabolized in the liver, and inactive metabolites are excreted in urine.

V. BARBITURATES/ Adverse effects

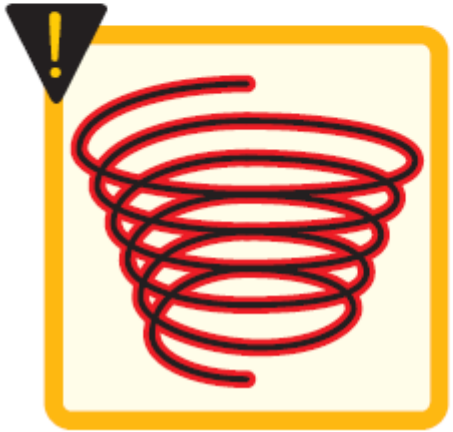
Potential for addiction

Nausea

Tremors



Drowsiness



Vertigo

Enzyme induction

V. BARBITURATES/ Adverse effects

Barbiturates cause **drowsiness, impaired concentration, and mental and physical** sluggishness.

Hypnotic doses of barbiturates produce a drug "**hangover**" that may lead to impaired ability to function normally for many hours after waking.

Barbiturates **induce cytochrome P450** (CYP450) microsomal enzymes in the liver.

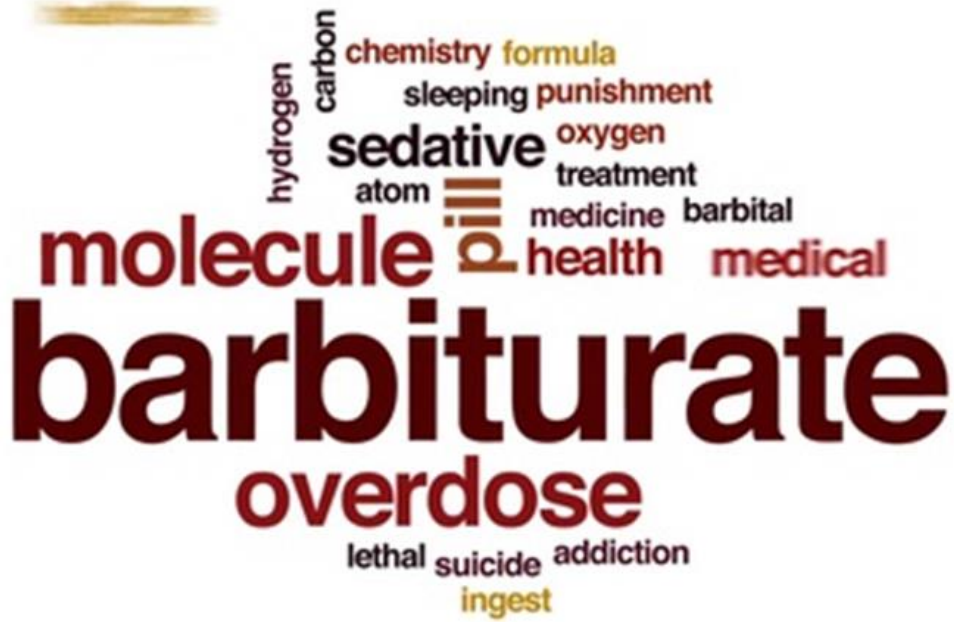
Barbiturates are contraindicated in patients with acute **porphyria**.

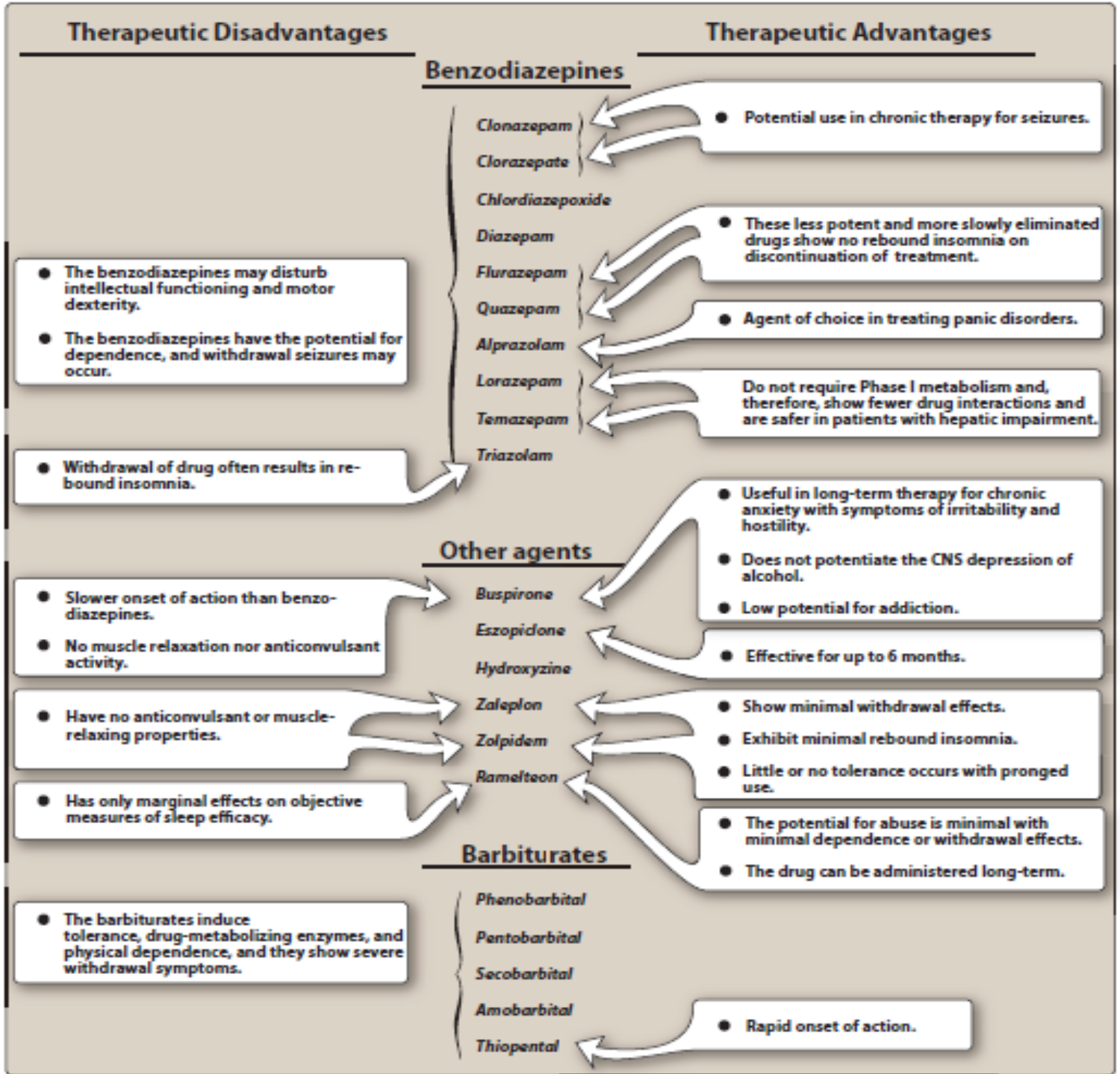
V. BARBITURATES/ Adverse effects

Abrupt **withdrawal** from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest.

Death may also result from **overdose**.

Severe **depression of respiration** is coupled with central cardiovascular depression and results in a shock-like condition with shallow, infrequent breathing.




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.
Other agents
Buspirone
Eszopiclone
Hydroxyzine
Zaleplon
Zolpidem
Ramelteon
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.
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.
Barbiturates
Phenobarbital
Pentobarbital
Secobarbital
Amobarbital
Thiopental
Rapid onset of action.
The barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence, and they show severe withdrawal symptoms.

OTHER HYPNOTIC AGENTS

A. Zolpidem

The hypnotic zolpidem is **not structurally** related to benzodiazepines, but it selectively binds to the benzodiazepine receptor subtype **BZ_1**.

Zolpidem has **no anticonvulsant or muscle-relaxing** properties.

It shows **few withdrawal** effects, exhibits **minimal rebound** insomnia, and **little tolerance** occurs with prolonged use.

Zolpidem is rapidly absorbed from the GI tract, and it has a rapid onset of action and short elimination half-life (2 to 3hr).

It provides a hypnotic effect for approximately 5 hours .

OTHER HYPNOTIC AGENTS

A. Zolpidem …. Cont

Zolpidem undergoes **hepatic oxidation** by the CYP450 system to inactive products.

Adverse effects of zolpidem include nightmares, agitation, anterograde amnesia, headache, GI upset, dizziness, and daytime drowsiness.

Unlike the benzodiazepines, at usual hypnotic doses, the **non**benzodiazepine drugs, zolpidem, zaleplon, and eszopiclone, do not significantly alter the various **sleep stages** and, hence, are often the **preferred hypnotics**.

This may be due to their relative selectivity for the BZ1 receptor.

All three agents are **controlled substances**.

OTHER HYPNOTIC AGENTS

B. Zaleplon

Zaleplon is an oral **nonbenzodiazepine** hypnotic similar to zolpidem; however, zaleplon causes **fewer residual effects** on psychomotor and cognitive function compared to zolpidem or the benzodiazepines.

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

The drug is metabolized by CYP3A4.

OTHER HYPNOTIC AGENTS

C. Eszopiclone

Eszopiclone is an oral **nonbenzodiazepine** hypnotic that also acts on the **BZ1 receptor**.

It has been shown to be effective for insomnia for up to 6 months.

Eszopiclone is rapidly absorbed (time to peak, 1 hour), extensively metabolized by oxidation and demethylation via **the CYP450 system**, and mainly excreted in urine.

Elimination half-life is approximately 6 hours.

Adverse events with eszopiclone include anxiety, dry mouth, headache, peripheral edema, somnolence, and unpleasant taste.

OTHER HYPNOTIC AGENTS

D. Ramelteon

Ramelteon is a selective **agonist** at **the MT1 and MT2** 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 MT1 and MT2 receptors by ramelteon is thought to induce and promote **sleep**.

Ramelteon is indicated for the treatment of insomnia characterized by difficulty falling asleep (increased sleep latency).

OTHER HYPNOTIC AGENTS

D. Ramelteon …. Cont

It has **minimal potential for abuse**, and no evidence of dependence or withdrawal effects has been observed.

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

OTHER HYPNOTIC AGENTS

E. Antihistamines

Some antihistamines with **sedating properties**, such as diphenhydramine, hydroxyzine, and doxylamine, are effective in treating mild types of situational insomnia.

However, they have **undesirable side effects** (such as anticholinergic effects) that make them less useful than the benzodiazepines and the nonbenzodiazepines.

OTHER HYPNOTIC AGENTS

F. Antidepressants

The use of sedating antidepressants with strong **antihistamine** profiles has been ongoing for decades.

Doxepin, an older **tricyclic agent** with **SNRI** mechanisms of antidepressant and anxiolytic action, was recently 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.