- Hallucinogens
- Anxiolytic and Hypnotic drugs

Lecture 2

College of Pharmacy

By:

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2- Hallucinogens

A few drugs have, as their primary action, the ability to induce altered perceptual states reminiscent of dreams. Many of these altered states are accompanied by visions of bright, colorful changes in the environment and by a plasticity of constantly changing shapes and color. The individual under the influence of these drugs is incapable of normal decision-making because the drug interferes with rational thought. These compounds are known as **hallucinogens**, and **lysergic acid diethylamide (LSD)** and **tetrahydrocannabinol** (from marijuana) are examples of agents in this class.

A- lysergic acid diethylamide (LSD):

- LSD produces its psychedelic effects through serving as a **potent partial agonist at 5-hydroxytryptamine $_{2A}$ (5-HT$_{2A}$) receptors.**
- A side from the very colorful hallucinations, the drug is also responsible for mood alterations, sleep disturbances, and anxiety.
- Repeated use rapidly produces tolerance through downregulation of serotonin receptors.
- Although physical adverse effects are typically minimal, LSD may cause tachycardia, increased blood pressure and body temperature, dizziness, decreased appetite, and sweating.
- Perhaps, the most troubling side effects are the loss of judgment and impaired reasoning associated with use of LSD. This can sometimes be an exaggerated effect with extreme panic, which is known by individuals as a **“bad trip,”** and may lead to trauma.
- Recently, a group of **synthetic serotonin agonists collectively known as “N-Bomb”** have been substituted for LSD.

B. Marijuana

- Marijuana is the most frequently used illicit drug, and the illicit drug that new users are most likely to try.
- The species **Cannabis sativa** is the plant most often used for its psychoactive properties.
- The main psychoactive alkaloid contained in marijuana is **Δ^9-tetrahydrocannabinol (Δ^9-THC).**
- **Specific receptors in the brain, cannabinoid or CB1 receptors**, were found to be reactive to THC.
- When CB1 receptors are activated by marijuana, effects include physical relaxation, hyperphagia, increased heart rate, decreased muscle coordination, conjunctivitis, and minor pain control. THC can produce euphoria, followed by drowsiness and relaxation.
- Marijuana stimulates the amygdala, causing the user to have a sense of novelty to anything the user encounters through an enhancement of sensory activity. Thus, heavy users have a down-regulation in their CB1 receptors, leaving them with a feeling of boredom when not taking the drug.
- The effects of marijuana on γ-aminobutyric acid (GABA) in the hippocampus diminish the capacity for short term memory in users, and this effect seems to be more pronounced in adolescents.
- THC decreases muscle strength and impairs highly skilled motor activity, such as that required to drive a car.
- The effects of THC appear immediately after smoking marijuana, but maximum effects take about 20 minutes. By 3 hours, the effects largely disappear.
- In chronic marijuana users, tolerance develops rapidly, 9% of all users and 17% of adolescent users will develop dependence, and withdrawal has been observed.

- Marijuana may be found in the body up to 3 months after last usage in heavy chronic users.
- Withdrawal may include cravings, insomnia, depression, pain, and irritability.
- Marijuana has been used as an adjuvant in the treatment of chemotherapy-induced nausea and vomiting (CINV), cachexia secondary to cancer and AIDS, epilepsy, chronic pain, multiple sclerosis, glaucoma, and anxiety.
- Synthetic THC medications are available as prescription products and include **dronabinol** and **nabilone**. These medications are used for the prevention of CINV.
- **Nabiximols,** a medication created from the extract of the Cannabis sativa plant, is an oromucosal spray available for the treatment of spasticity in multiple sclerosis.

C. Synthetic cannabinoids

- Synthetic cannabinoids are sprayed onto plant material in a process known as dusting.
- These first-generation products such as “Spice” and “K2” are then smoked to produce intoxication. Sympathomimetic effects may also be seen in users, including tachycardia and hypertension.
- The greatest danger with use of these agents includes extreme hallucinations and psychotic reactions.
- More recent formulations of synthetic cannabinoids and their contaminants have caused convulsions, acute kidney injury, and deaths.

Anxiolytic and Hypnotic drugs

- Disorders involving anxiety are among the most common mental disorders.
- **Anxiety** is an unpleasant state of tension, 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.
- Episodes of mild anxiety are common life experiences and do not warrant treatment. **However,** 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. (Figure 1)

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

Figure 1: Summary of anxiolytic and hypnotic drugs

❖ Benzodiazepines

- Benzodiazepines are widely used anxiolytic drugs.

- They have largely replaced barbiturates and meprobamate in the treatment of anxiety and insomnia, because benzodiazepines are generally considered to be safer and more effective (Figure 2). Though benzodiazepines are commonly used, they are not necessarily the best choice for anxiety or insomnia.

- Certain antidepressants with anxiolytic action, such as **the selective serotonin reuptake inhibitors (SSRIs)**, are preferred in many cases, and **nonbenzodiazepine hypnotics** and **antihistamines** may be preferable for insomnia.

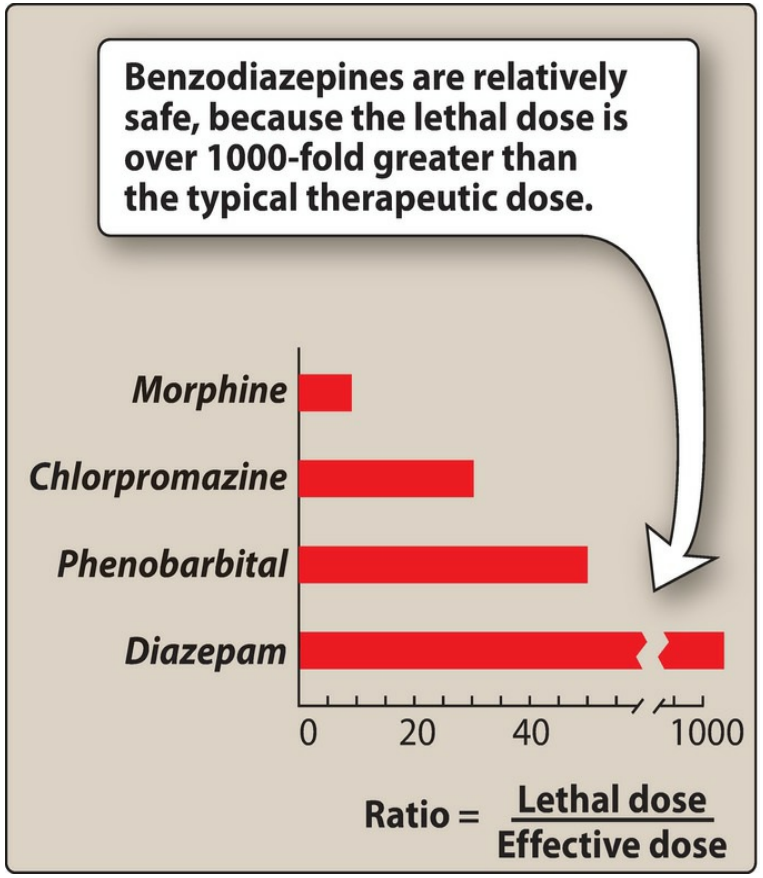

Figure 2: Ratio of lethal dose to effective dose for morphine (an opioid), chlorpromazine (an antipsychotic), and the anxiolytic, hypnotic drugs, phenobarbital and diazepam.

A. Mechanism of action

- The targets for benzodiazepine actions are **the γ-aminobutyric acid ($GABA_A$) receptors**. [*GABA is the **major inhibitory neurotransmitter** in the central nervous system (CNS).*]
- The $GABA_A$ receptors are composed of a combination of five α, β, and γ subunits that span the postsynaptic membrane.
- For each subunit, many subtypes exist (for example, there are six subtypes of the α subunit).
- Binding of GABA to its receptor triggers an opening of the central ion channel, allowing chloride through the pore.
- The influx of chloride ions causes hyperpolarization of the neuron and decreases neurotransmission by inhibiting the formation of action potentials.
- Benzodiazepines modulate GABA 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 (Figure 3).
- Benzodiazepines increase the frequency of channel openings produced by GABA.
- The clinical effects of individual benzodiazepines correlate well with the binding affinity of each drug for the GABA receptor–chloride ion channel complex.

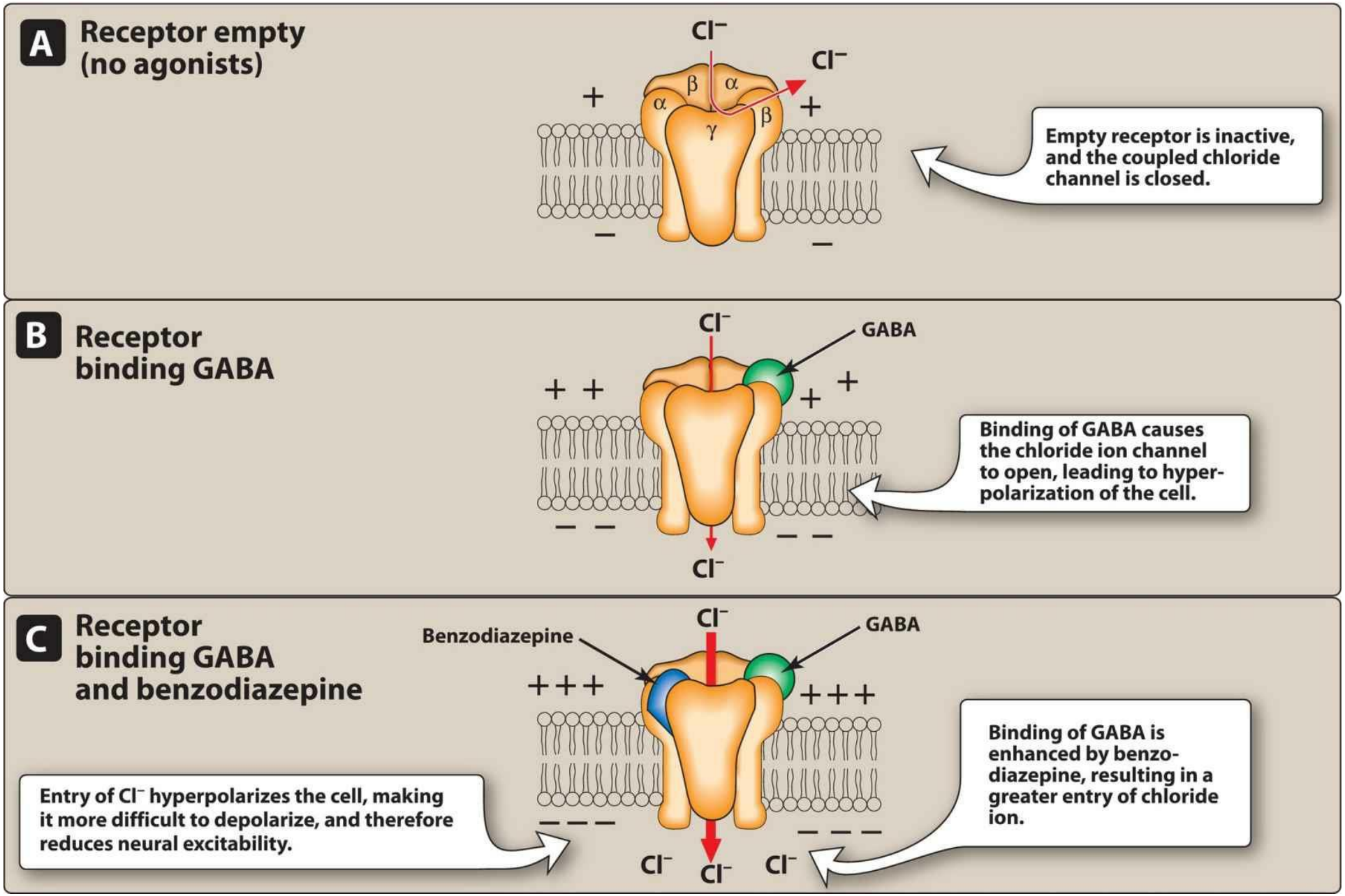

Figure 3: Schematic diagram of benzodiazepine–GABA–chloride ion channel complex. GABA = γ-aminobutyric acid.

B. Actions

All benzodiazepines exhibit the following actions to some extent:

1. Reduction of anxiety

At **low doses**, the benzodiazepines are **anxiolytic**. They are thought to reduce anxiety by selectively enhancing GABAergic transmission in neurons having **the α2 subunit in their $GABA_A$ receptors**, thereby **inhibiting neuronal circuits in the limbic system of the brain**.

2. Sedative/hypnotic

All benzodiazepines have **sedative and calming properties**, and some can produce **hypnosis** at **higher doses**. The hypnotic effects are mediated by the **α1-$GABA_A$ receptors**.

3. Anterograde amnesia

Temporary impairment of memory with the use of the benzodiazepines is also mediated by the **α1-$GABA_A$ receptors**. The ability to learn and form new memories is also impaired.

4. Anticonvulsant

This effect is partially, although not completely, mediated by **α1-$GABA_A$ receptors**.

5. Muscle relaxant

At **high doses**, the benzodiazepines relax the spasticity of skeletal muscle, **probably by increasing presynaptic inhibition in the spinal cord**, where the **α2-GABA $_A$** receptors are largely located.

C. Therapeutic uses

1. Anxiety disorders

- Benzodiazepines are effective for the treatment of anxiety associated with **panic disorder**, **generalized anxiety disorder (GAD),** social anxiety disorder, performance anxiety, and extreme phobias, such as fear of flying.
- The benzodiazepines are also useful in **treating anxiety related to depression and schizophrenia**.
- These drugs **should be reserved for severe anxiety** and should not be used to manage the stress of everyday life.
- Because of their addictive potential, they should only be used for short periods of time.
- The **longer-acting agents**, such as clonazepam, lorazepam, and diazepam, 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.

2. Sleep disorders

- Benzodiazepine hypnotics decrease the latency to sleep onset and increase stage II of non–rapid eye movement sleep.
- **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 have difficulty staying asleep. Temazepam should be administered 1 to 2 hours before the desired bedtime.
- **Long-acting flurazepam** is rarely used, due to its extended half-life, which may result in excessive daytime sedation and accumulation of the drug, especially in the elderly.
- **Estazolam** and **quazepam** are considered **intermediate- and long-acting agents**, respectively.
- In general, hypnotics should be used for only a limited time, usually 1 to 3 weeks.

3. Amnesia

- The shorter-acting agents are often employed as premedication for anxiety-provoking and unpleasant procedures, such as endoscopy, dental procedures, and angioplasty.
- They cause a form of conscious sedation, allowing the patient to be receptive to instructions during these procedures.
- **Midazolam** is a benzodiazepine used to facilitate anterograde amnesia while providing sedation prior to anesthesia.

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. Due to cross-tolerance, chlordiazepoxide, clorazepate, diazepam, lorazepam, and oxazepam are useful in the acute treatment of alcohol withdrawal and reduce the risk of withdrawal-related seizures.

5. Muscular disorders

Diazepam is useful in the treatment of skeletal muscle spasms and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

D. 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

The half-lives of the benzodiazepines are important clinically, because the duration of action may determine the therapeutic usefulness. The benzodiazepines can be roughly divided into **short-, intermediate-, and long-acting groups** (Figure 4). The longer-acting agents form active metabolites with long half-lives. However, with some benzodiazepines, the clinical duration of action does not correlate with the actual half-life (otherwise, a dose of diazepam could conceivably be given only every other day, given its long half-life and active metabolites). This may be due to receptor dissociation rates in the CNS and subsequent redistribution to fatty tissues and other areas.

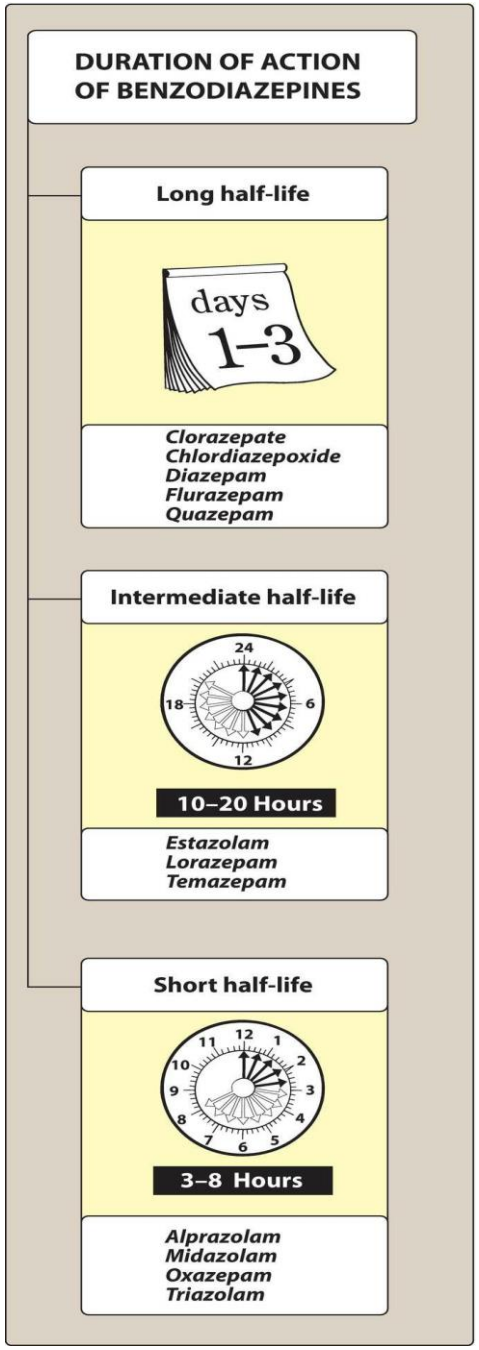

Figure 4: Comparison of the durations of action of the benzodiazepines

3. Fate

- Most benzodiazepines, including chlordiazepoxide and diazepam, are metabolized by the hepatic microsomal system to compounds that are also active.
- They are excreted in the urine as glucuronides or oxidized metabolites.
- All benzodiazepines cross the placenta and may depress the CNS of the newborn if given before birth; and they are not recommended for use during pregnancy.
- Nursing infants may also be exposed to the drugs in breast milk.

E. Dependence

- Psychological and physical dependence can develop if high doses of benzodiazepines are given for a prolonged period. All benzodiazepines are controlled substances; abrupt discontinuation of these agents results in withdrawal symptoms, including confusion, anxiety, restlessness, insomnia, tension, and (rarely) seizures.
- Benzodiazepines with a short elimination half-life, such as triazolam, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated such as flurazepam (Figure 5).

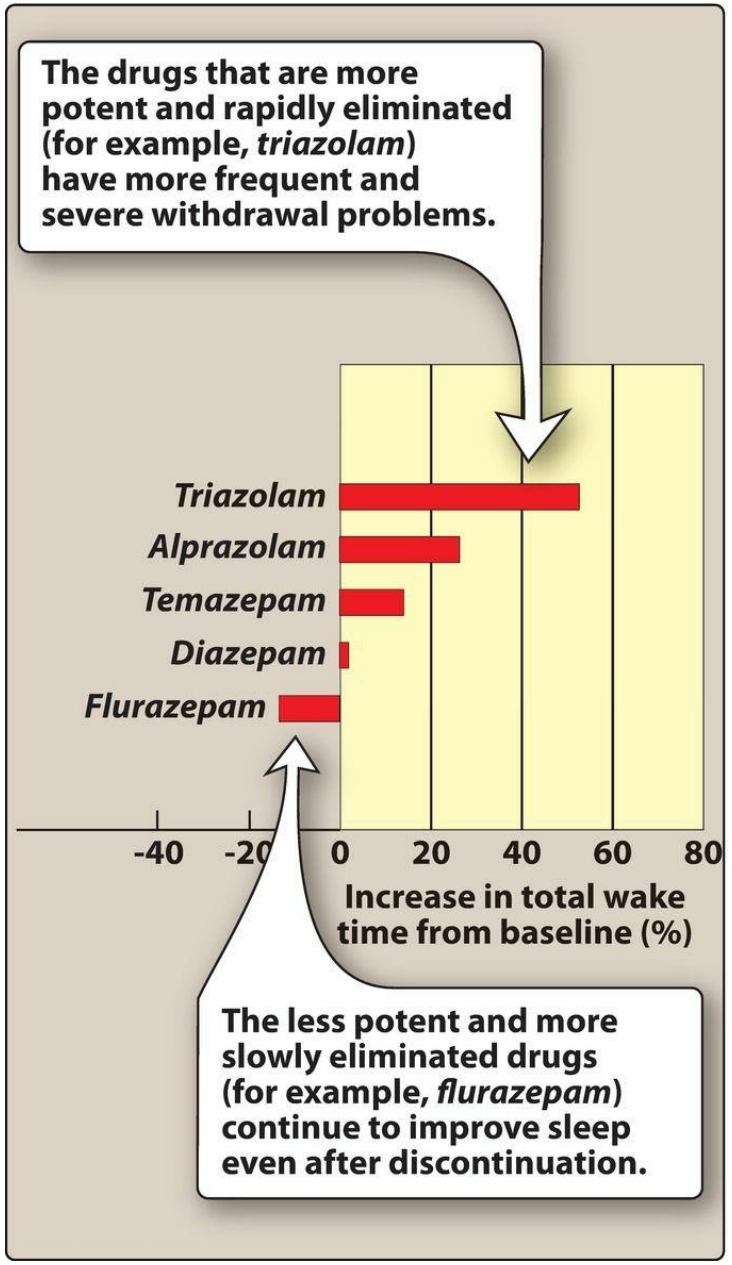

Figure 5: Frequency of rebound insomnia resulting from discontinuation of benzodiazepine therapy.

F. Adverse effects

- Drowsiness and confusion are the most common adverse effects of the benzodiazepines.
- Ataxia occurs at high doses and prevents activities that require fine motor coordination, such as driving an automobile.
- Cognitive impairment (decreased recall and retention of new knowledge) can occur with use of benzodiazepines.
- Benzodiazepines should be used cautiously in patients with liver disease.
- Alcohol and other CNS depressants enhance the sedative–hypnotic effects of the benzodiazepines.
- Benzodiazepines are, however, considerably less dangerous than the older anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal unless other central depressants, such as alcohol or opioids, are taken concurrently.

❖ Benzodiazepine Antagonist

- **Flumazenil** is a **GABA receptor antagonist** that rapidly reverses the effects of benzodiazepines.

- The drug is available for intravenous (IV) administration only. Onset is rapid, but the duration is short, with a half life of about 1 hour. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine.

- Administration of flumazenil may precipitate withdrawal in dependent patients or cause seizures if a benzodiazepine is used to control seizure activity. Seizures may also result if the patient has a mixed ingestion with tricyclic antidepressants or antipsychotics.

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

❖ 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)** (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.
- While only certain SSRIs or SNRIs have been approved for the treatment of anxiety disorders such as GAD, the efficacy of these drugs is most likely a class effect.
- Long-term use of antidepressants and benzodiazepines for anxiety disorders is often required to maintain ongoing benefit and prevent relapse.

B. Buspirone

- Buspirone is useful for the **chronic treatment of GAD** and has an efficacy comparable to that of benzodiazepines.
- It has a slow onset of action and is not effective for short-term or “as-needed” treatment of acute anxiety.
- The actions of buspirone appear to be mediated by **serotonin ($5\text{-}HT_{1A}$) receptors**, although it also displays some affinity for **D_2 dopamine receptors** and **$5\text{-}HT_{2A}$ serotonin receptors**. Thus, its mode of action differs from that of the benzodiazepines.
- In addition, buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines.
- The frequency of adverse effects is low, with the most common effects being headache, 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; (See, Figure 6).

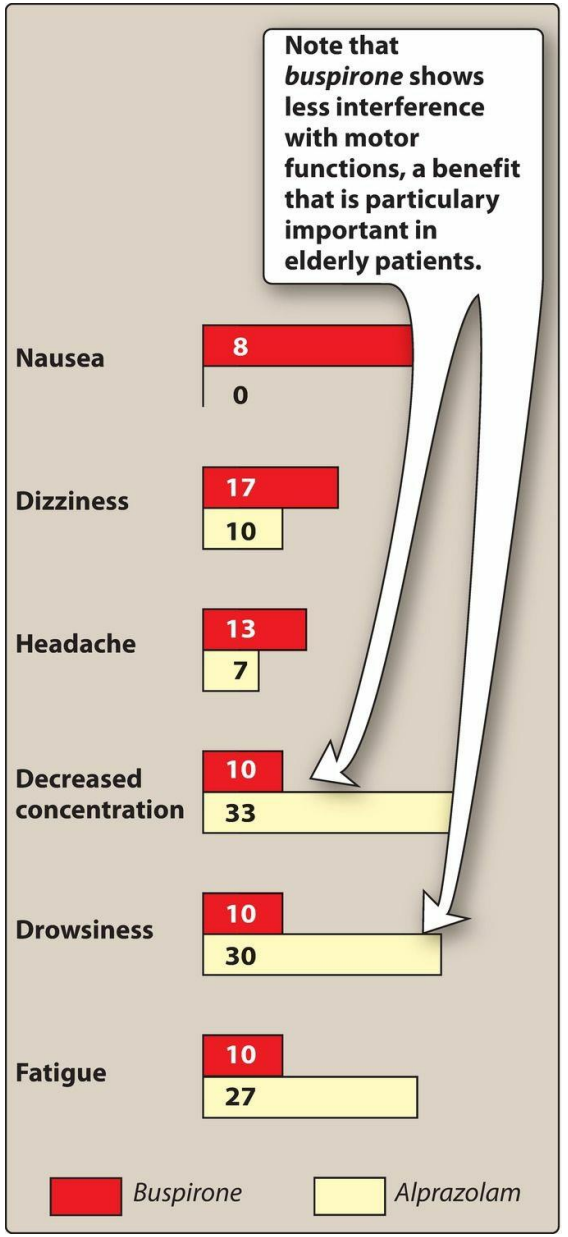

Figure 6: Comparison of common adverse effects of buspirone and alprazolam. Results are expressed as the percentage of patients showing each symptom.

❖ Barbiturates

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. 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. All barbiturates are controlled substances.

A- 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**. These molecular actions lead to decreased neuronal activity.

B. Actions

Barbiturates are classified according to their duration of action (Figure 7). **Long-acting phenobarbital** has a duration of action greater than a day. **Pentobarbital, secobarbital, amobarbital, and butalbital** are **short-acting barbiturates.** **Thiopental** is **an ultra–short-acting** barbiturate with **high lipid solubility**.

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**. Thus, any degree of depression of the CNS is possible, depending on the dose.
- 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 overdose is followed by respiratory depression and death.

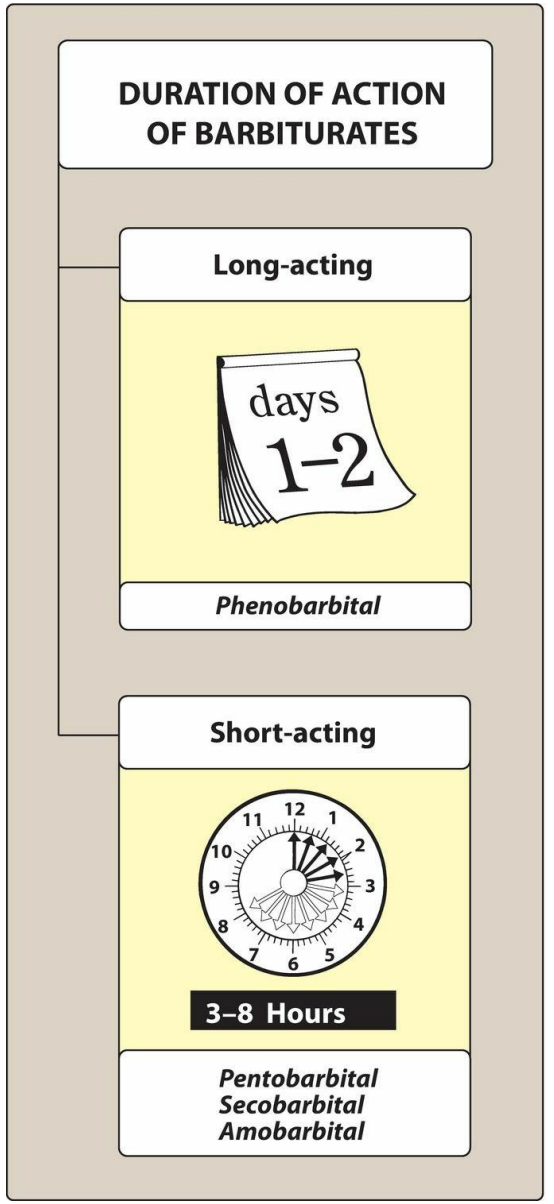

Figure 7: Barbiturates classified according to their durations of action

C. Therapeutic uses

1. Anesthesia

The **ultra–short-acting barbiturates** have been historically used intravenously to induce anesthesia but have been replaced by other agents.

2. Anticonvulsant

- Phenobarbital has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression. However, phenobarbital can depress cognitive development in children and decrease cognitive performance in adults, and it should be used for seizures only if other therapies have failed.
- Similarly, phenobarbital may be used for the treatment of refractory status epilepticus.

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 generally accepted, given their adverse effects and potential for tolerance.
- **Butalbital** is commonly used in combination products (with acetaminophen and caffeine or aspirin and caffeine) as a sedative to assist in the management of tension or migraine headaches.

D. 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.

E. Adverse effects

- Barbiturates cause drowsiness, impaired concentration, and mental and psychomotor impairment. The CNS depressant effects of barbiturates synergize with those of ethanol.
- Hypnotic doses of barbiturates produce a drug “hangover” that may lead to impaired ability to function normally for many hours after waking.
- Occasionally, nausea and dizziness occur.
- Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are metabolized by the CYP450 system.
- Barbiturates are contraindicated in patients with acute intermittent porphyria.
- Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opioids and can result in death. Death may also result from overdose.
- Severe depression of respiration and central cardiovascular depression results in a shock-like condition with shallow, infrequent breathing.
- Treatment includes supportive care and gastric decontamination for recent ingestions.

❖ Other Hypnotic Agents

A. Zolpidem

- The hypnotic zolpidem is not structurally related to benzodiazepines, but **it binds to $GABA_A$ receptors with relative selectivity for those with the α1 subunit**.
- It has no anticonvulsant or muscle-relaxing properties at hypnotic doses.
- It shows few withdrawal effects, exhibits minimal rebound insomnia, and little tolerance occurs with prolonged use.
- Zolpidem is rapidly absorbed after oral administration. It has a rapid onset of action and short elimination half-life (about 2 to 3 hours). The drug provides a hypnotic effect for approximately (5 hours).
- Zolpidem undergoes hepatic oxidation by the CYP450 system to inactive products. Thus, drugs such as rifampin, which induce this enzyme system, shorten the half-life of zolpidem, and drugs that inhibit the CYP3A4 isoenzyme may increase the half-life.
- Adverse effects of zolpidem include headache, dizziness, anterograde amnesia, and next-morning impairment (especially with extended-release formulations). Sleep-walking, sleep-driving, and performing other activities while not fully awake have been reported.

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.

C. Eszopiclone

- Eszopiclone is an **oral nonbenzodiazepine hypnotic** that 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, and unpleasant taste.

D. 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.
- They have minimal potential for abuse, and no evidence of dependence or withdrawal has been observed. Therefore, ramelteon and tasimelteon can be administered long-term.
- Ramelteon is indicated for the treatment of insomnia characterized by difficulty falling asleep (increased sleep latency).
- 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, often experienced by patients who are blind.
- The most common adverse effects of tasimelteon are headache, abnormal dreams, increase in liver function tests, and possible upper respiratory tract infections.
- CYP450 1A2 and 3A4 are the principle isoenzymes required for metabolism of ramelteon and tasimelteon, and, thus, drug–drug interactions are possible with inducers or inhibitors of these enzymes.

E. Antihistamines

Antihistamines with sedating properties, such as diphenhydramine, hydroxyzine, and doxylamine, are effective in treating mild situational insomnia. However, they have undesirable adverse effects (such as anticholinergic effects) that make them less useful than the benzodiazepines and the nonbenzodiazepines.

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, 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.

G. Suvorexant

- Suvorexant 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.
- Suvorexant is mainly metabolized by CYP450 3A4, and, thus, it may have drug interactions with CYP3A4 inducers or inhibitors.

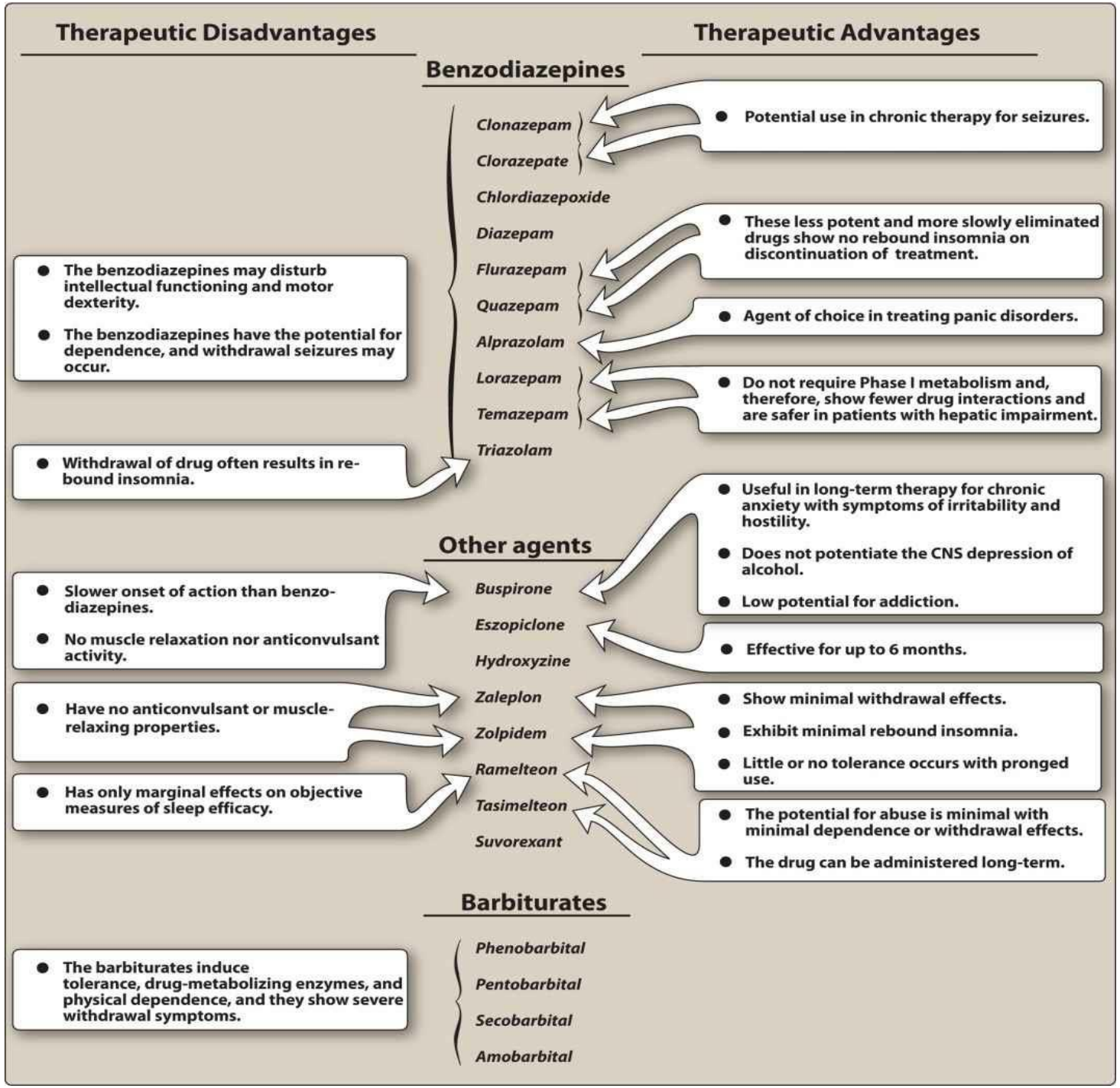

Figure 8:Therapeutic disadvantages and advantages of some anxiolytic and hypnotic agents. CNS = central nervous system.


Thank You!