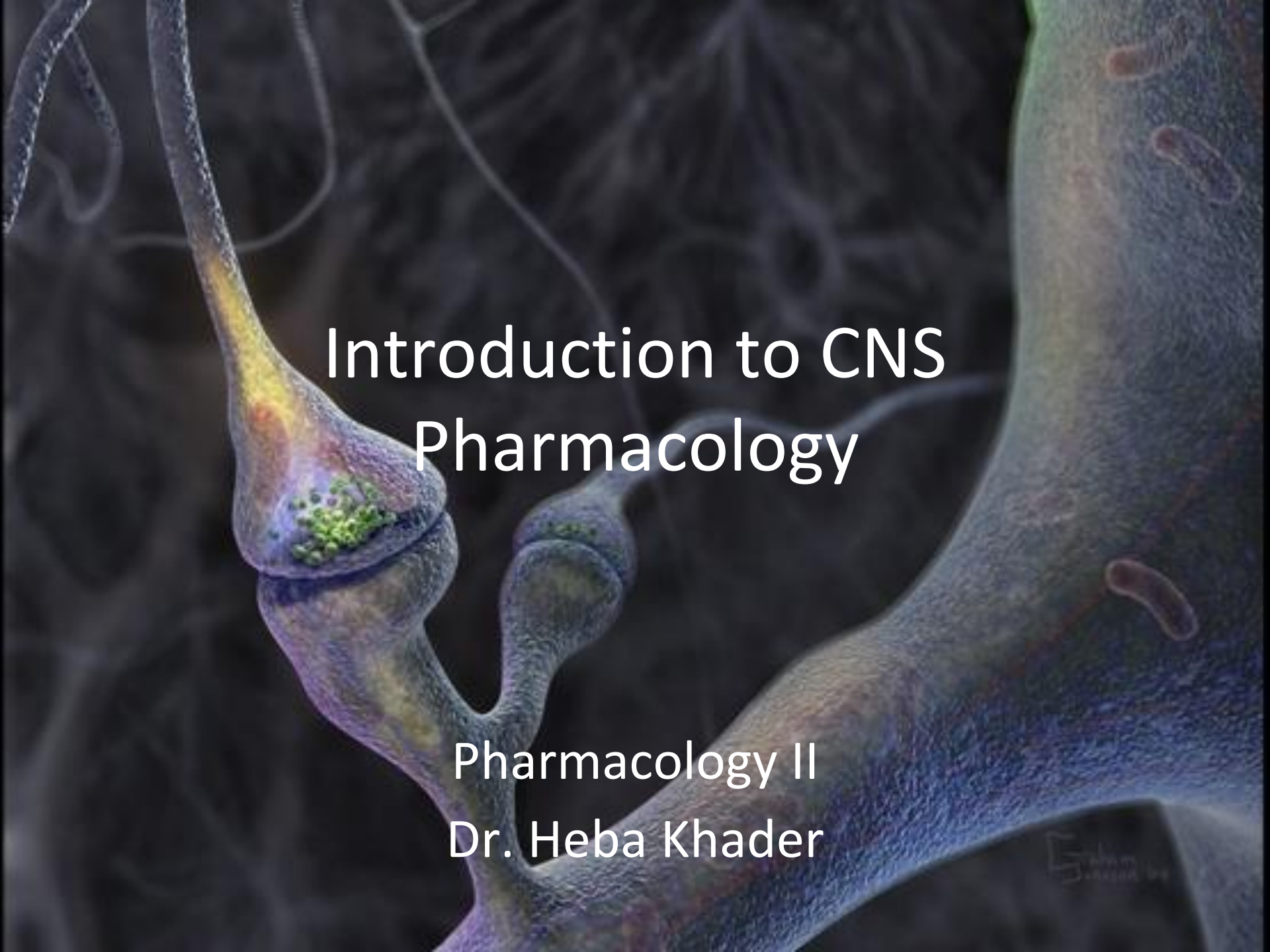


Introduction to CNS Pharmacology

Pharmacology II

Dr. Heba Khader

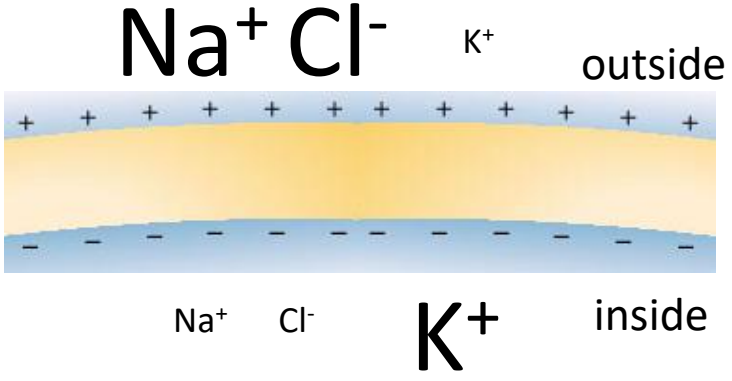
Introduction

- Drugs acting in the central nervous system (CNS) include medications used to treat a wide range of neurologic and psychiatric conditions as well as drugs that relieve pain, suppress nausea, and reduce fever.

- Drugs with CNS effects act on specific receptors that modulate synaptic transmission.

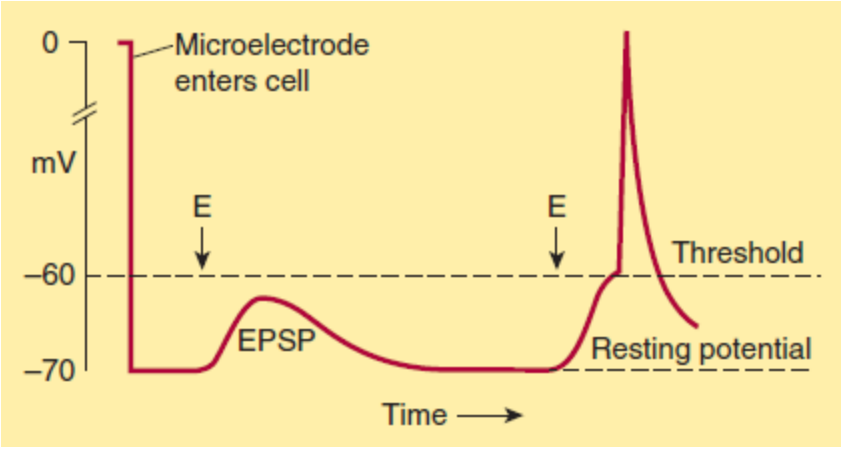
Neurotransmission in the CNS

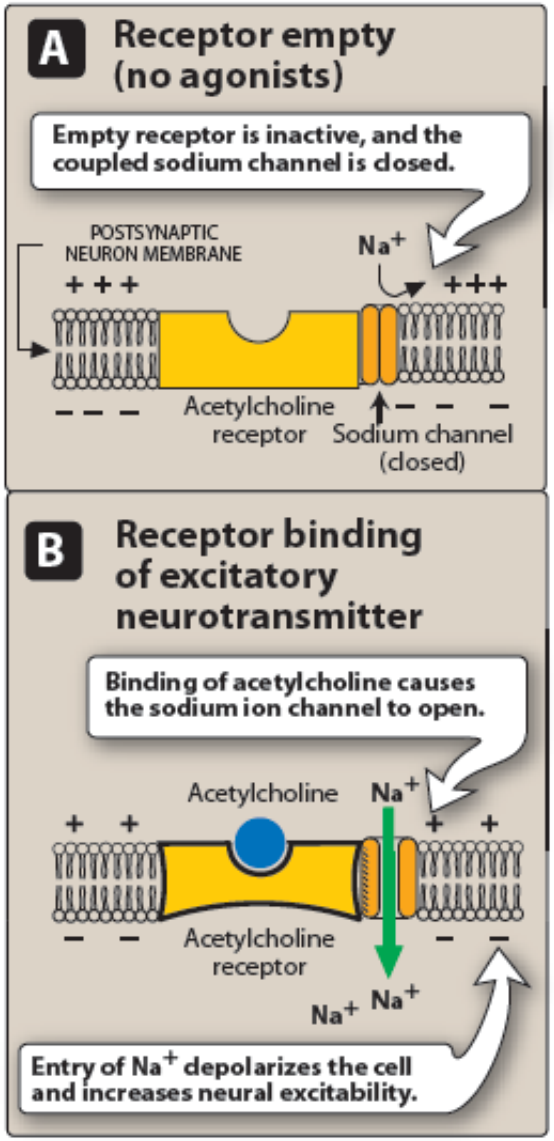
- Most drugs that act on the central nervous system (CNS) appear to do so by changing ion flow through transmembrane channels of nerve cells.
- Ion flow across the membrane of the neuron alters the postsynaptic potential, producing either depolarization (EPSP) or hyperpolarization (IPSP) of the postsynaptic membrane, depending on the specific ions that move and the direction of their movement.



Excitatory postsynaptic potential (EPSP)

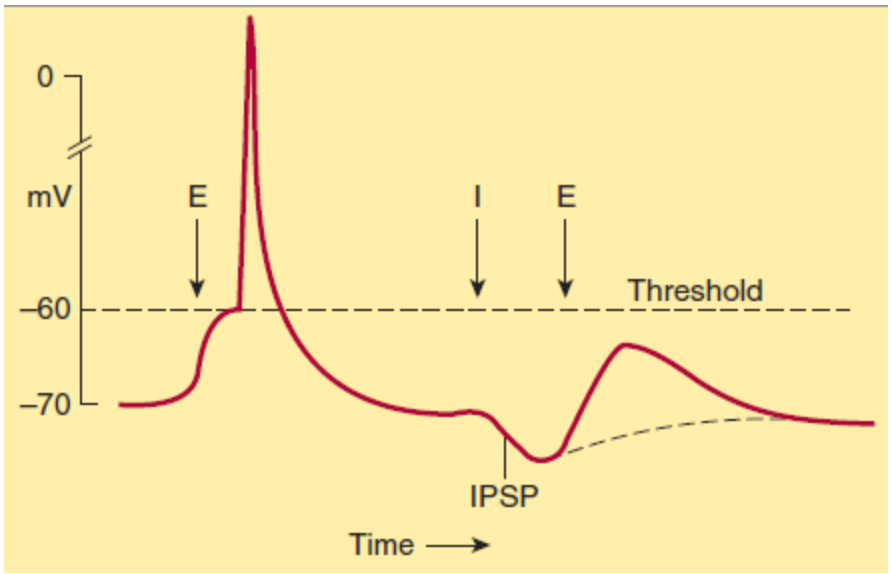
- Excitatory postsynaptic potentials (EPSPs) are usually generated by the opening of sodium or calcium channels.
- In some synapses, similar depolarizing potentials result from the closing of potassium channels.

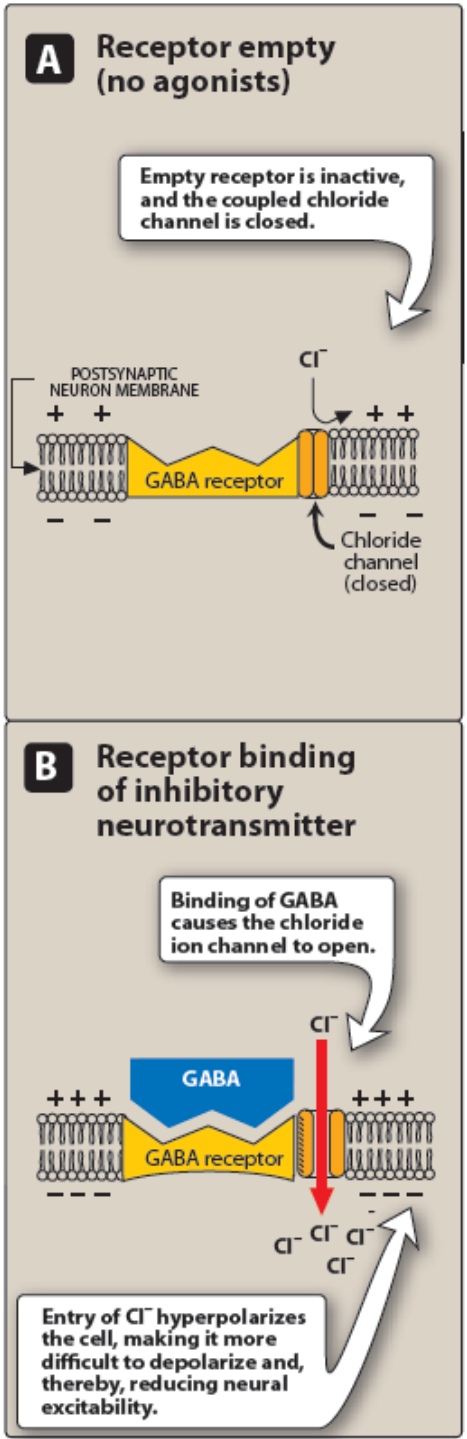




Inhibitory postsynaptic potential (IPSP)

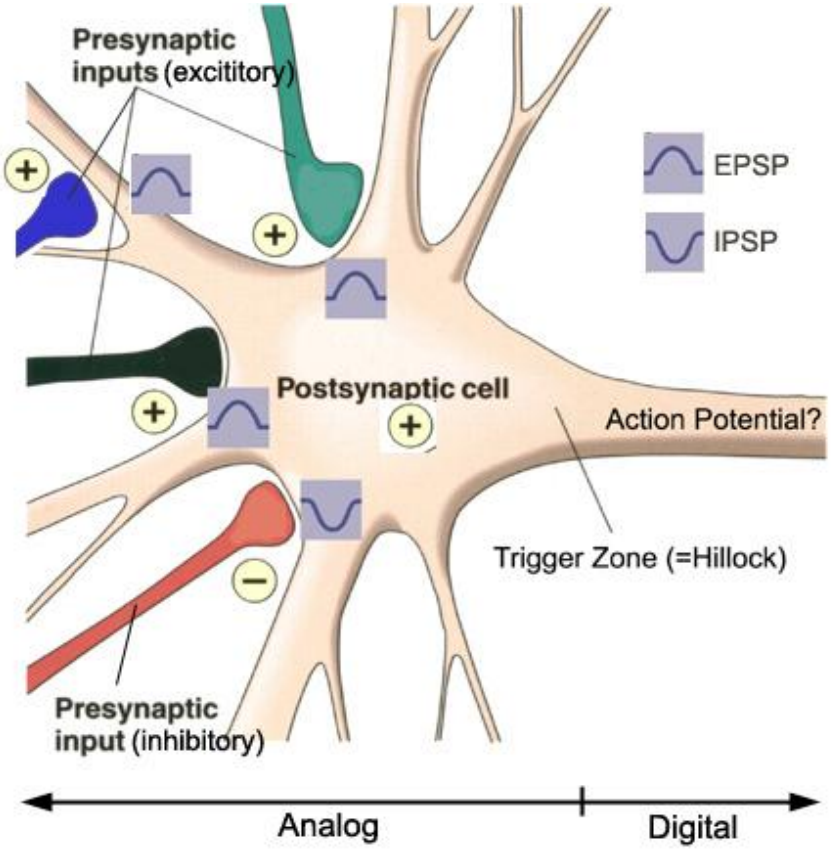
- Inhibitory postsynaptic potentials (IPSPs) are usually generated by the opening of potassium or chloride channels (efflux of K+ or influx of Cl-, respectively).





Combined effects of the EPSP and IPSP

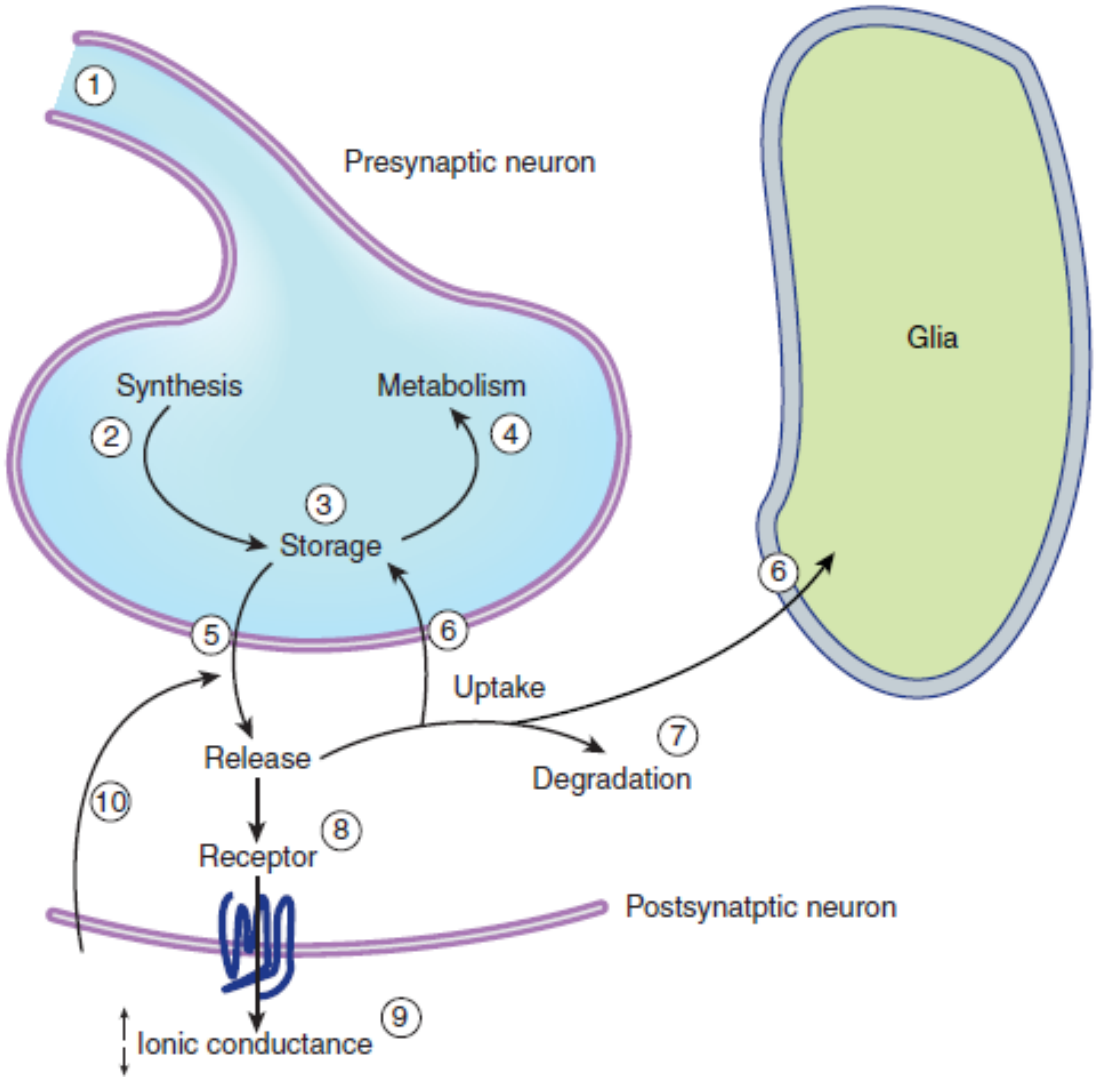
- The overall resultant postsynaptic potential is due to the summation of the individual actions of the various neurotransmitters on the neuron.



Transmitters at central synapses

1. Acetylcholine (+/-)
2. Dopamine (-)
3. γ-Aminobutyric acid (GABA) (-)
4. Glutamate (+/-)
5. Glycine (-)
6. 5-hydroxytryptamine (Serotonine) (-/+)
7. Opioid peptides (-)

Sites of drug action in CNS



Sedative-Hypnotic Drugs

Pharmacology II

Dr. Heba Khader

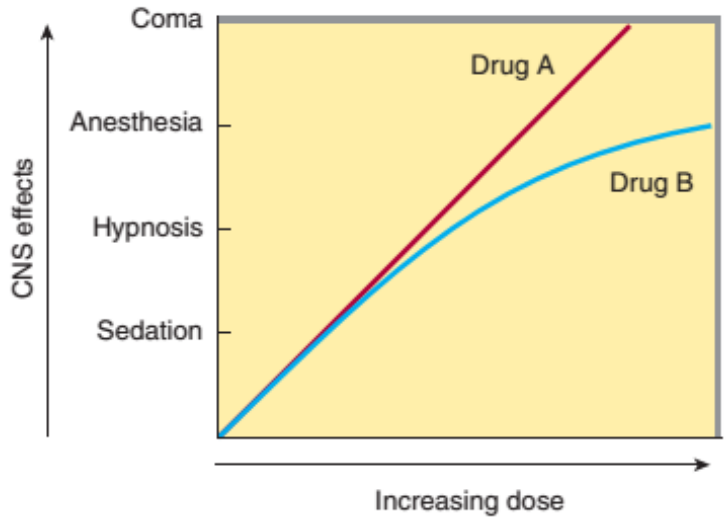
Terms to know…

High-Yield Terms to Learn	
Sedation	Reduction of anxiety
Addiction	The state of response to a drug whereby the drug taker feels compelled to use the drug and suffers anxiety when separated from it
Anesthesia	Loss of consciousness associated with absence of response to pain
Anxiolytic	A drug that reduces anxiety, a sedative
Dependence	The state of response to a drug whereby removal of the drug evokes unpleasant, possibly life-threatening symptoms, often the opposite of the drug's effects
Hypnosis	Induction of sleep

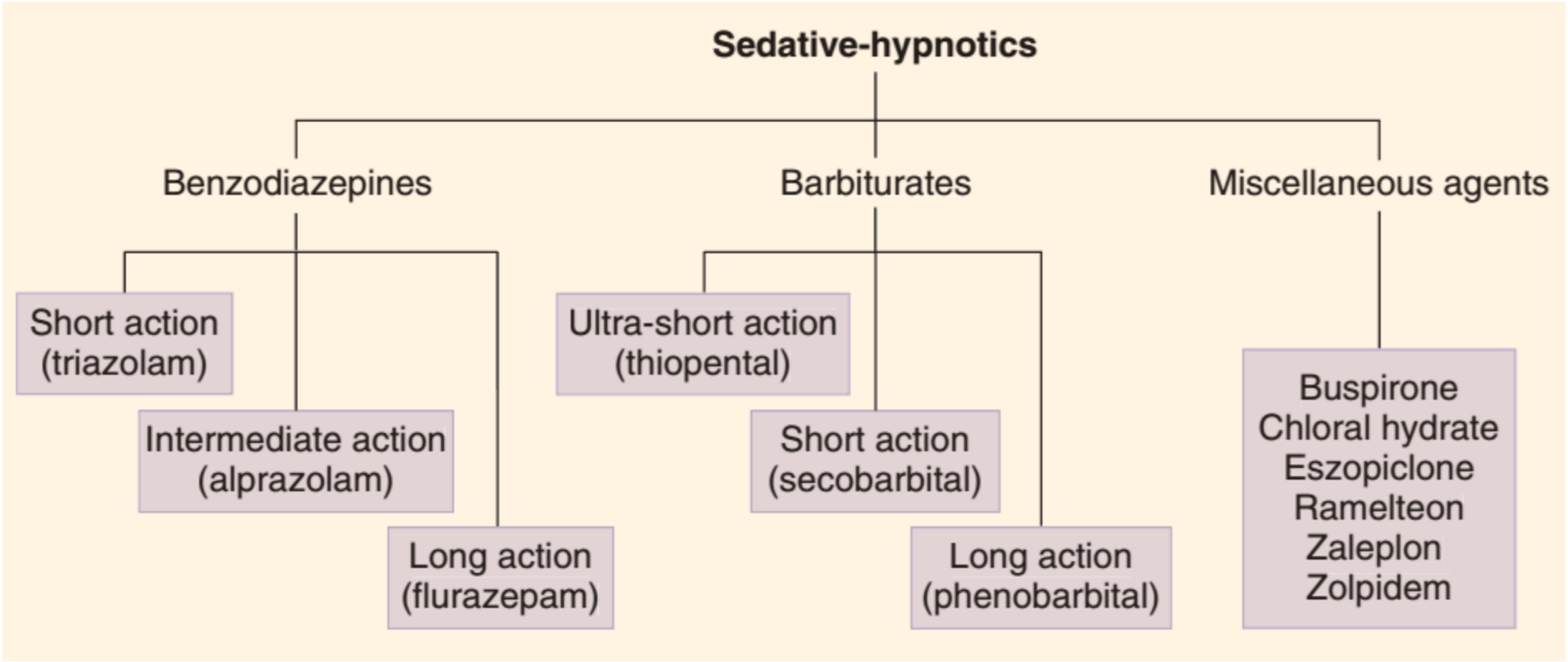
- What is anxiety?
- Anxiety is a state characterized by psychological symptoms, and often accompanied by physical symptoms such as fatigue, dizziness, vague pains, palpitations, headache, irritability and indigestion.

Basic Pharmacology of Sedative-Hypnotic Drugs

- An effective **sedative** (anxiolytic) agent should reduce anxiety and exert a calming effect.
- A **hypnotic** drug should produce drowsiness and encourage the onset and maintenance of a state of sleep.
- Hypnotic effects involve more pronounced depression of the central nervous system than sedation, and this can be achieved with many drugs in this class simply by increasing the dose.



Classification of Sedative-Hypnotic Drugs



Classification of Sedative-Hypnotic Drugs

1. Benzodiazepines (BZ)
   - Long-acting: diazepam, flurazepam, nitroazepam
   - Intermediate-acting: lorazepam, oxazepam, alprazolam
   - Short-acting: triazolam
2. Barbiturates (largely replaced by BZ)

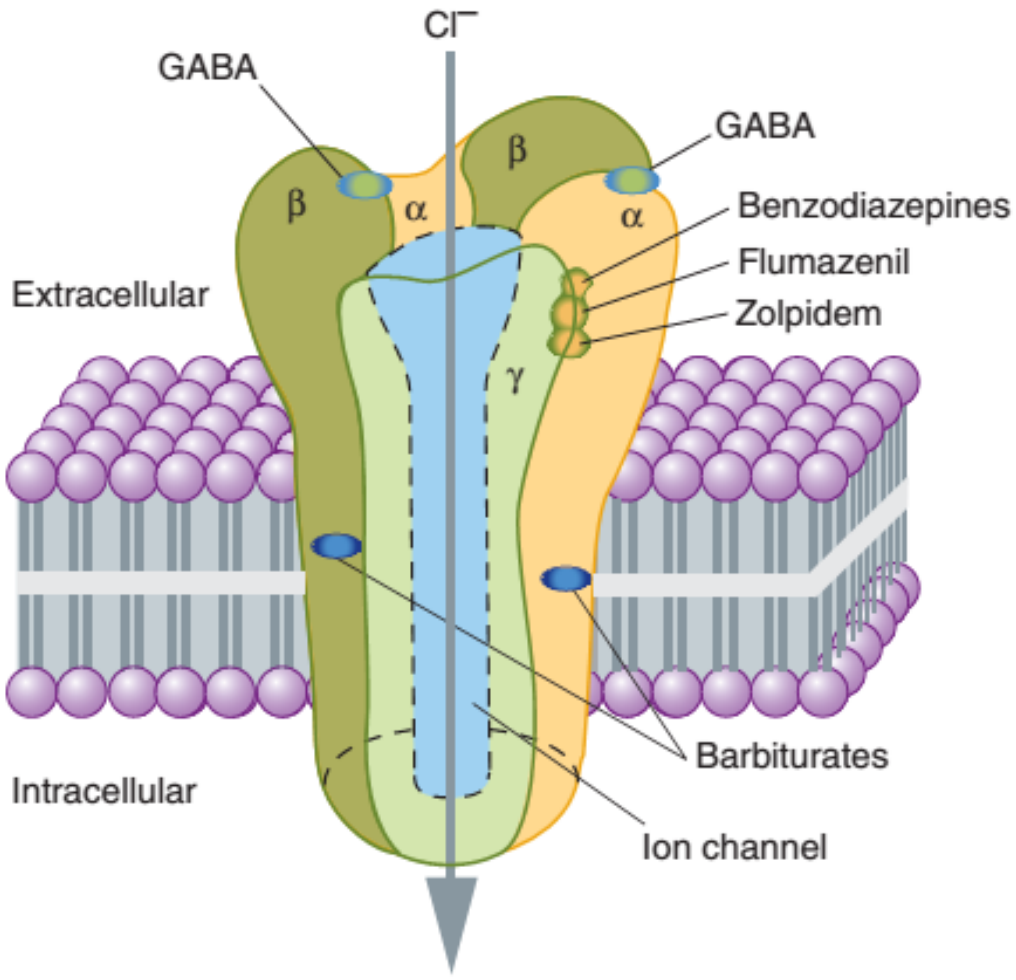
The barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence, and they show severe withdrawal symptoms.

1. Zolpidem, zaleplon and eszopiclone "the Z-drugs" (more recent drugs with MOA similar to BZ)
2. Ramelteon
3. Buspirone
4. Ethanol and chloral hydrate
5. Antipsychotics, antidepressants and antihistamines

Mechanism of action

A. Benzodiazepines

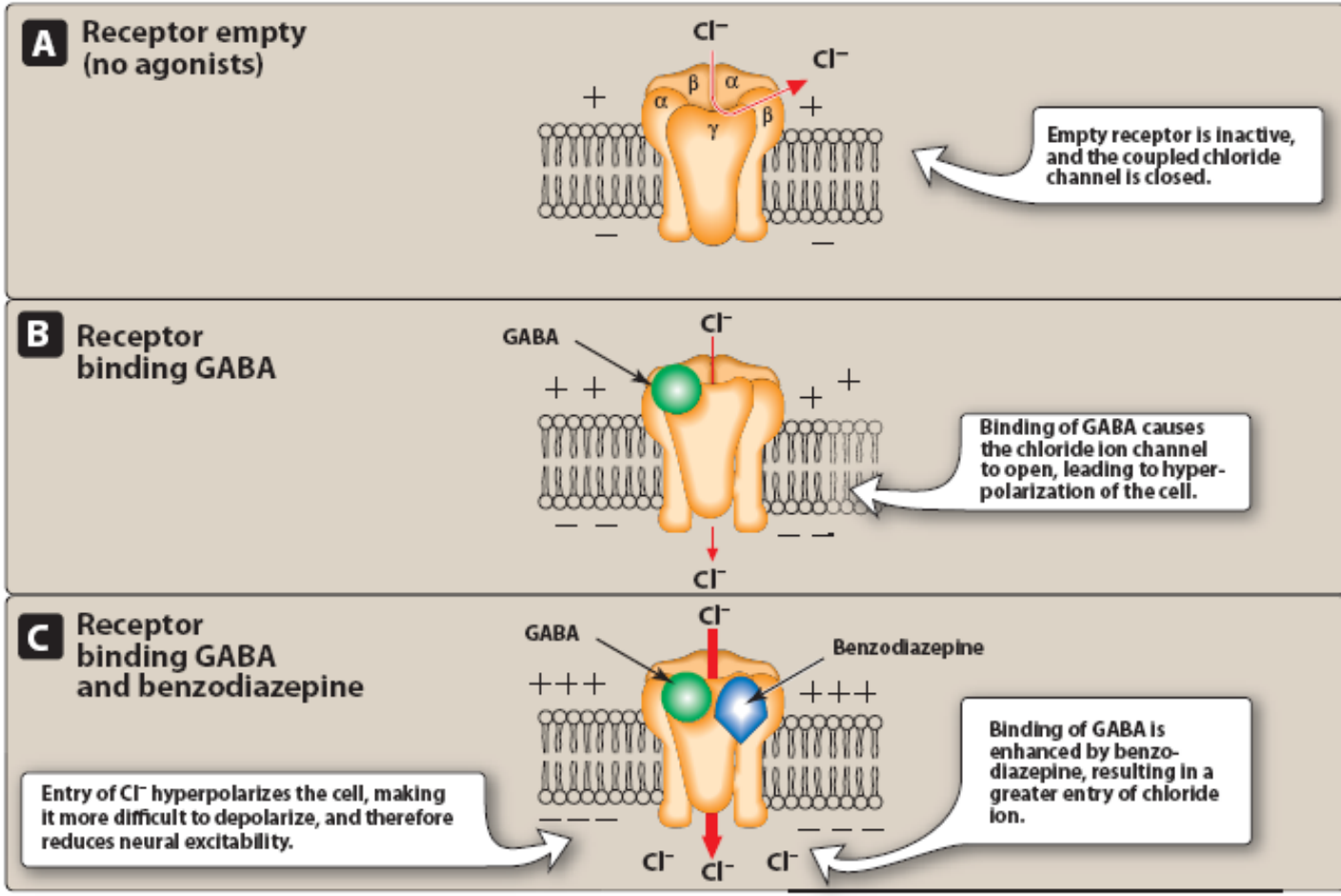
- The BZ receptors form part of a $GABA_A$ receptor chloride-ion channel macromolecular complex.
- GABA (γ-aminobutyric acid) is a major inhibitory in the CNS.
- Benzodiazepines increase the *frequency* of GABA-mediated chloride ion channel opening.



Mechanism of action

A. Benzodiazepines

- Benzodiazepines enhance the binding of of GABA to its receptor, which increases the permeability of chloride.



Benzodiazepine Antagonist

- **Flumazenil** reverses the CNS effects of benzodiazepines and is classified as an **antagonist at BZ** receptors.
- **Flumazenil** is available for intravenous (IV) administration only.
- Onset is rapid, but 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.

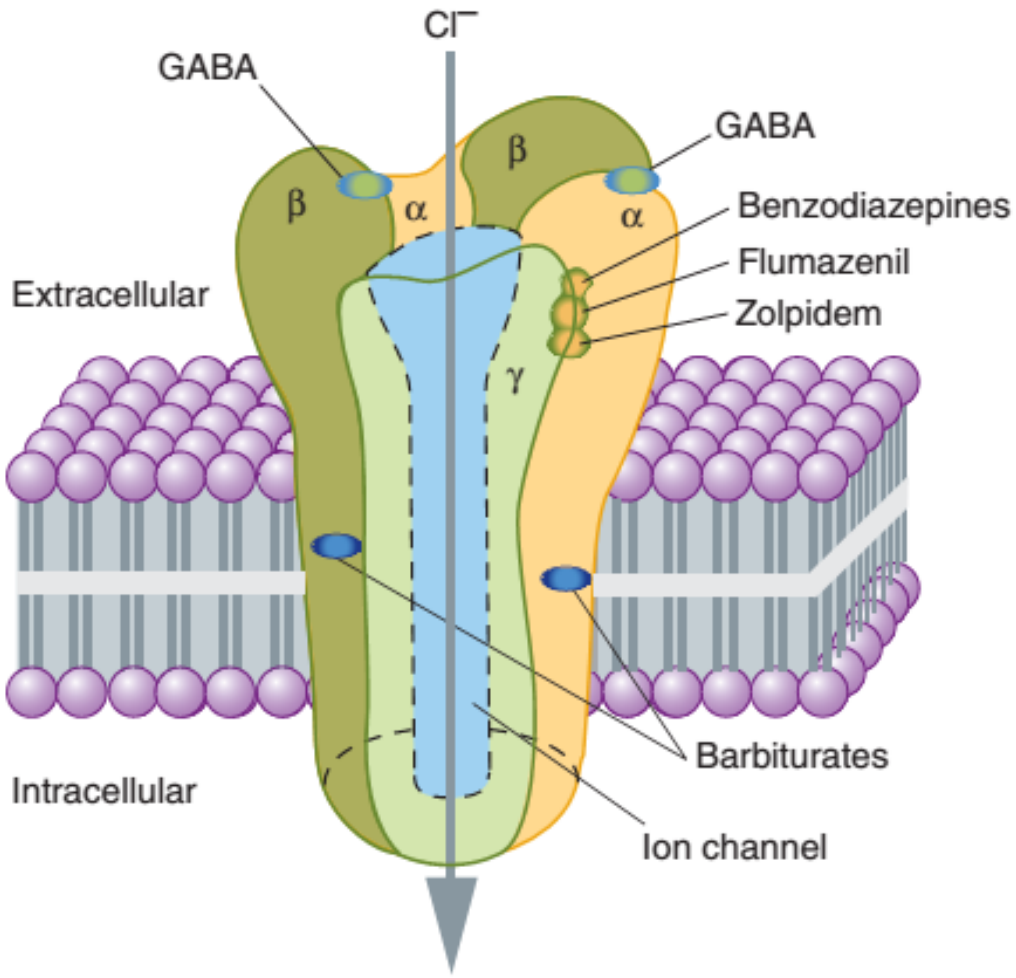
Mechanism of action

B. Barbiturates

- Barbiturates also bind to multiple isoforms of the $GABA_A$ receptor but at different sites from those with which benzodiazepines interact.

- Their actions are <u>not</u> antagonized by flumazenil.

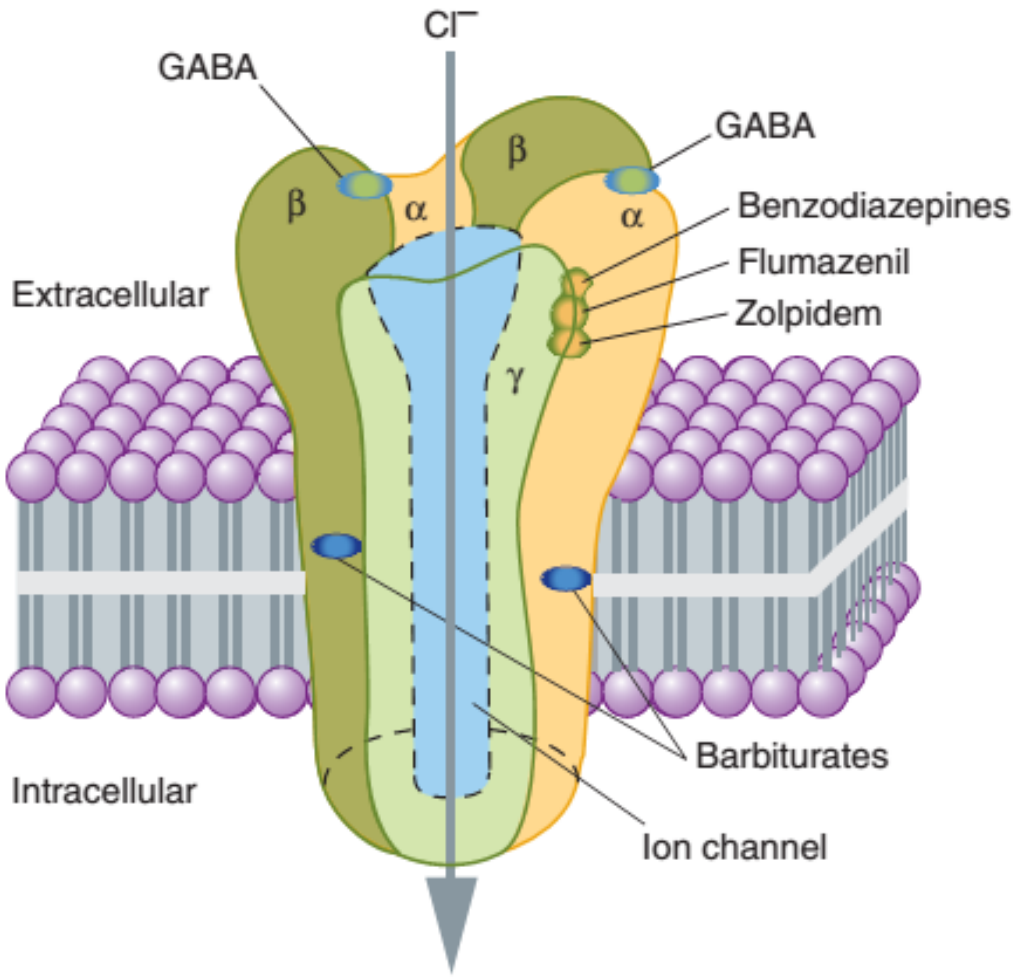
- Barbiturates increase the *duration* of GABA-mediated chloride ion channel opening.



Mechanism of action

C. Other Drugs

- The hypnotics **zolpidem, zaleplon,** and **eszopiclone** are not benzodiazepines but appear to exert their CNS effects via interaction with certain benzodiazepine receptors.
- Their CNS depressant effects can be antagonized by flumazenil.



Pharmacokinetics

A. Absorption and Distribution

- Most sedative-hypnotic drugs are lipid-soluble and are absorbed well from the gastrointestinal tract, with good distribution to the brain.

- Lipid solubility plays a major role in determining the rate at which a particular sedative-hypnotic enters the CNS. This property is responsible for the rapid onset of CNS effects of triazolam, thiopental , and the newer hypnotics eszopiclone, zaleplon, and zolpidem.

- The CNS effects of thiopental are terminated by rapid redistribution of the drug from brain to other highly perfused tissues, including skeletal muscle.

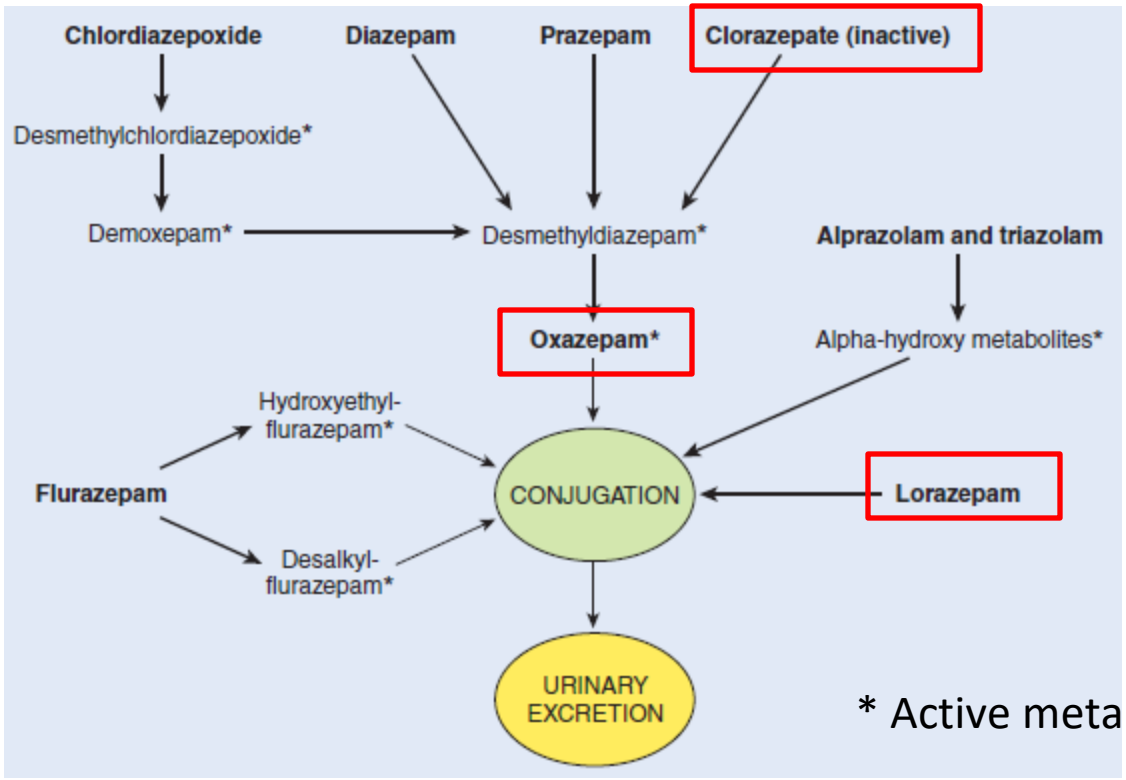
B. Biotransformation

- **CYP450 enzymes** are most important in the metabolism of sedative-hypnotics, so elimination half-life of these drugs depends mainly on the rate of their metabolic transformation.

- In very old patients and in patients with severe liver disease, the elimination half-lives of these drugs are often increased significantly. In such cases, multiple normal doses of these sedative hypnotics can result in excessive central nervous system effects.

B. Biotransformation

- Many **benzodiazepines** are converted initially to active metabolites with long half-lives. After several days of therapy with some drugs (eg, **diazepam, flurazepam**), accumulation of active metabolites can lead to excessive sedation and drowsiness.
- Cumulative effect such as excessive drowsiness appear to be less of a problem with such drugs as **lorazepam and oxazepam** which do not form active metabolites.



* Active metabolite

Pharmacokinetic properties of some benzodiazepines and newer hypnotics in humans

Drug	Peak Blood Level (hours)	Elimination Half-Life[1] (hours)	Comments
Alprazolam	1–2	12–15	Rapid oral absorption
Chlordiazepoxide	2–4	15–40	Active metabolites; erratic bioavailability from IM injection
Clorazepate	1–2 (nordiazepam)	50–100	Prodrug; hydrolyzed to active form in stomach
Diazepam	1–2	20–80	Active metabolites; erratic bioavailability from IM injection
Eszopiclone	1	6	Minor active metabolites
Flurazepam	1–2	40–100	Active metabolites with long half-lives
Lorazepam	1–6	10–20	No active metabolites
Oxazepam	2–4	10–20	No active metabolites
Temazepam	2–3	10–40	Slow oral absorption
Triazolam	1	2–3	Rapid onset; short duration of action
Zaleplon	< 1	1–2	Metabolized via aldehyde dehydrogenase
Zolpidem	1–3	1.5–3.5	No active metabolites

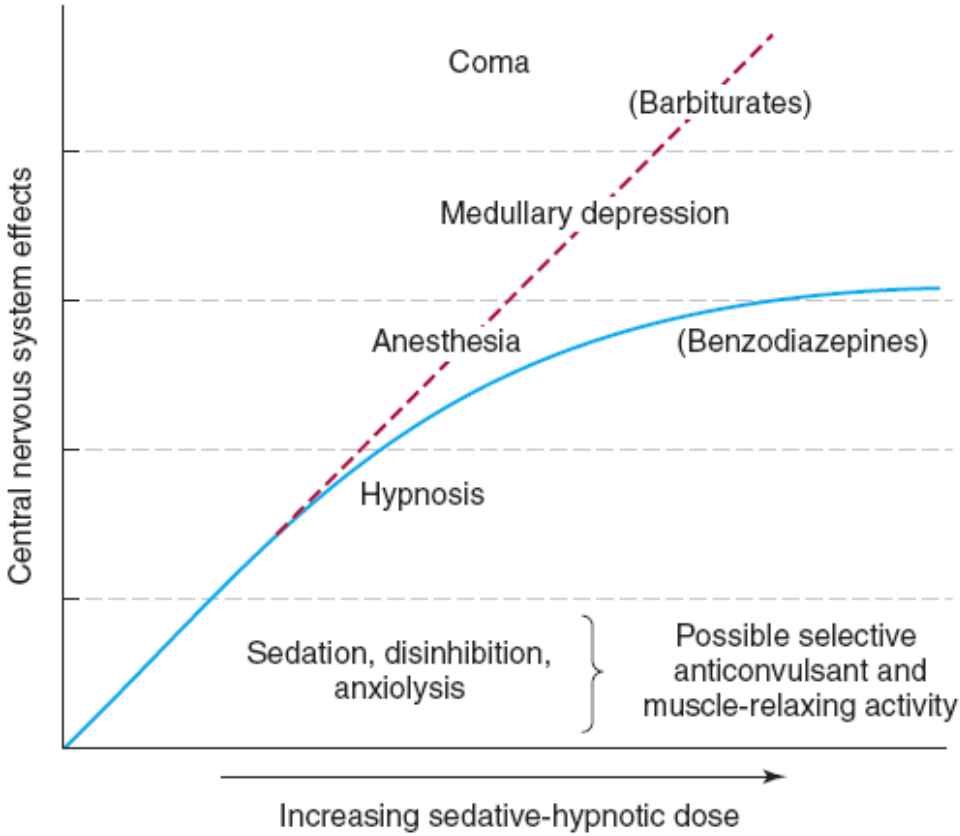
- The duration of CNS actions of sedative-hypnotic drugs ranges from just a few hours (eg, zaleplon < zolpidem = triazolam < eszopiclone) to more than 30 h (eg, chlordiazepoxide, clorazepate, diazepam, phenobarbital).

Pharmacodynamics

- The CNS effects of most sedative-hypnotics depend on dose. These effects range from sedation and relief of anxiety (anxiolysis), through hypnosis (facilitation of sleep), to anesthesia and coma.

- Depressant effects are additive when 2 or more drugs are given together.

- The steepness of the dose-response curve varies among drug groups; those with flatter curves, such as benzodiazepines and the newer hypnotics (eg, zolpidem), are safer for clinical use.



Pharmacodynamics

A. Sedation

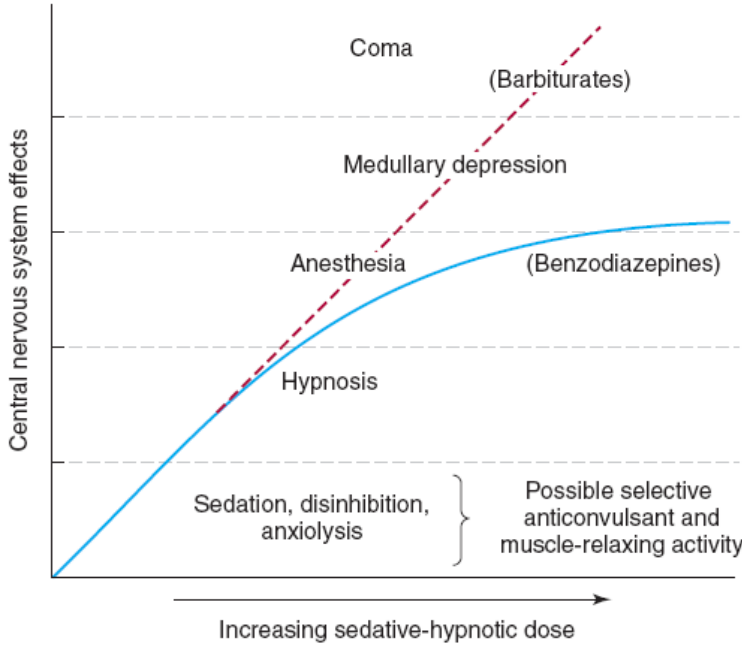
- Sedative actions, with relief of anxiety, occur with all drugs in this class.

B. Hypnosis

- Sedative-hypnotics can promote sleep onset and increase the duration of the sleep state.

C. Anesthesia

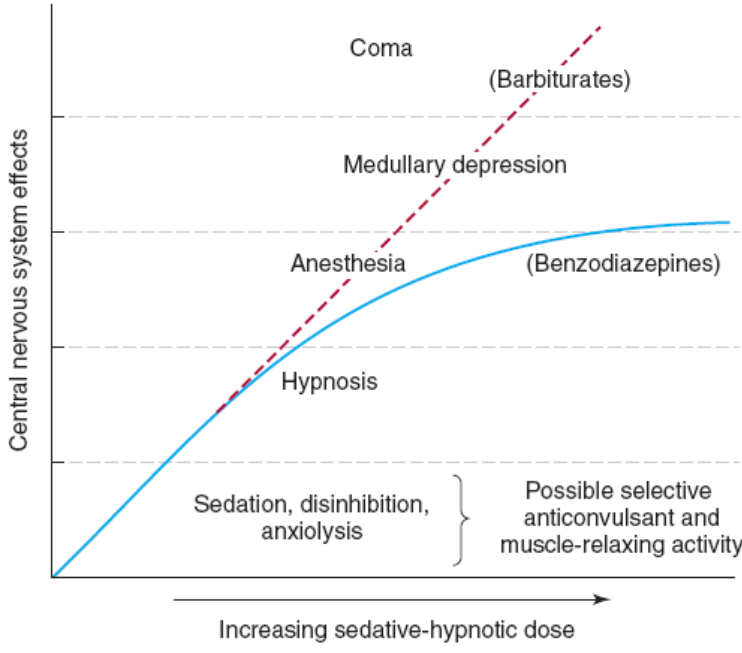
- At high doses of most older sedative-hypnotics (barbiturates), loss of consciousness may occur, with amnesia (loss of memory) and suppression of reflexes.



Pharmacodynamics

D. Anticonvulsant Actions

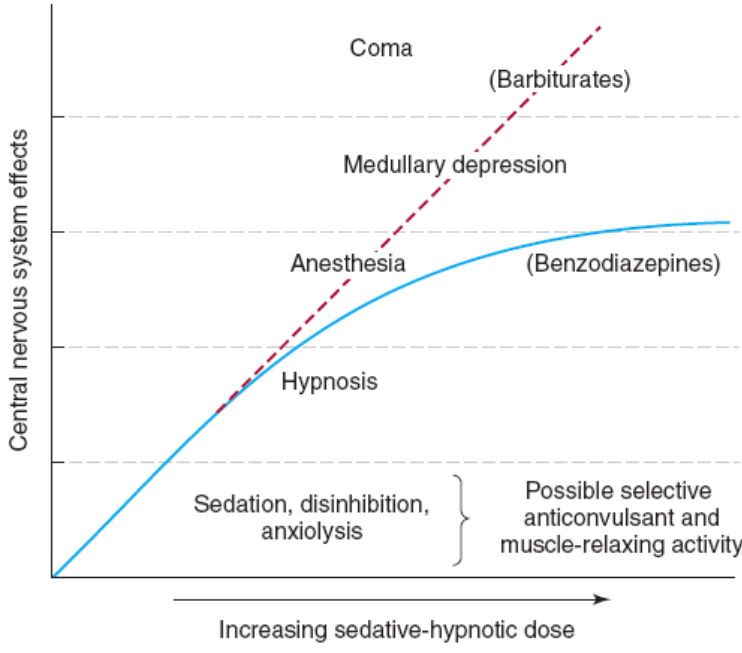
- Suppression of seizure activity occurs with high doses of most of the barbiturates and some of the benzodiazepines, but this is usually at the cost of marked sedation.
- High doses of intravenous **diazepam**, **lorazepam**, or **phenobarbital** are used in status epilepticus. In this condition, heavy sedation is desirable.



Pharmacodynamics

E. Muscle Relaxation

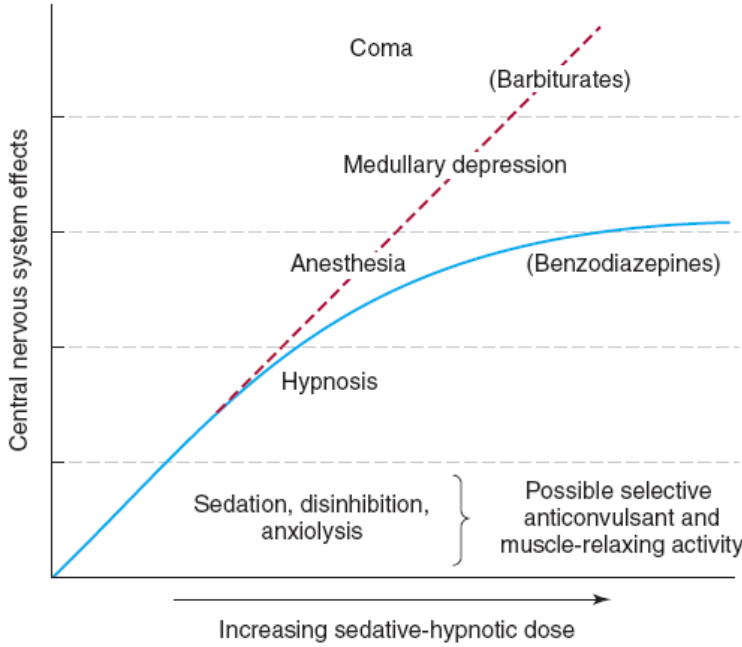
- Relaxation of skeletal muscle occurs only with high doses of most sedative-hypnotics.
- However, **diazepam** is effective at sedative dose levels for specific spasticity states, including cerebral palsy.
- **Meprobamate** also has some selectivity as a muscle relaxant.



Pharmacodynamics

F. Medullary Depression

- High doses of conventional sedative-hypnotics, especially alcohols and barbiturates, can cause depression of medullary neurons, leading to respiratory arrest, hypotension, and cardiovascular collapse.
- These effects are the cause of death in suicidal overdose.



Pharmacodynamics

Tolerance and Dependence

- **Tolerance**—a decrease in responsiveness to a drug following repeated exposure—is a common feature of sedative-hypnotic use.
- Cross-tolerance may occur among different chemical subgroups.
- **Psychological dependence** occurs frequently with most sedative-hypnotics and is manifested by the compulsive use of these drugs to reduce anxiety.
- **Physiologic dependence** constitutes an altered state that leads to an abstinence syndrome (withdrawal state) when the drug is discontinued.
- Withdrawal signs are characterized by states of increased anxiety, insomnia, and CNS excitability that may progress to convulsions.
- The dependence liability of zolpidem, zaleplon, and eszopiclone may be less than that of the benzodiazepines since withdrawal symptoms are minimal after their abrupt discontinuance.

Clinical uses

TABLE 22–2 Clinical uses of sedative-hypnotics.

For relief of anxiety
For insomnia
For sedation and amnesia before and during medical and surgical procedures
For treatment of epilepsy and seizure states
As a component of balanced anesthesia (intravenous administration)
For control of ethanol or other sedative-hypnotic withdrawal states
For muscle relaxation in specific neuromuscular disorders
As diagnostic aids or for treatment in psychiatry

Clinical uses

A. Anxiety States

- Benzodiazepines are favored in the drug treatment of acute anxiety states and for rapid control of panic attacks.

- **Alprazolam** has been used in the treatment of panic disorders and appears to be more selective in these conditions than other benzodiazepines.

- Newer antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are now considered by many authorities to be drugs of first choice in the treatment of generalized anxiety disorders.

Clinical uses

B. Sleep Disorders

- Sleep disorders are common and often result from inadequate treatment of underlying medical conditions or psychiatric illness. True primary insomnia is rare.
- Nonpharmacologic therapies that are useful for sleep problems include:

1. Proper diet and exercise,
2. Avoiding stimulants before retiring,
3. Ensuring a comfortable sleeping environment,
4. Retiring at a regular time each night.

- In some cases, however, the patient will need and should be given a sedative-hypnotic for a limited period. It should be noted that the abrupt discontinuance of many drugs in this class can lead to rebound insomnia.

Clinical uses

B. Sleep Disorders

- The drug selected should be one that provides sleep of fairly rapid onset (decreased sleep latency) and sufficient duration, with minimal “hangover” effects such as drowsiness, and mental or motor depression the following day.

- Older drugs such as chloral hydrate, secobarbital, and pentobarbital continue to be used, but **benzodiazepines, zolpidem, zaleplon, or eszopiclone** are generally preferred.

- **Zolpidem**, one of the most frequently prescribed hypnotic drugs in the United States, is available in a biphasic release formulation that provides sustained drug levels for sleep maintenance.

Clinical uses

C. Other Uses

1. **Thiopental** is commonly used for the induction of **anesthesia**, and certain benzodiazepines (eg, diazepam, midazolam) are used as components of anesthesia protocols including those used in day surgery.
2. Management of **seizure** disorders (eg, clonazepam, phenobarbital)
3. Management of **bipolar disorder** (eg, clonazepam)
4. Treatment of **muscle spasticity** (eg, diazepam).
5. Longer acting benzodiazepines (eg, chlordiazepoxide, diazepam) are used in the management of withdrawal states in persons physiologically dependent other shorter-acting sedative-hypnotics, including ethanol.

Toxicity

A. Psychomotor Dysfunction

- This includes:
  1. Cognitive impairment
  2. Decreased psychomotor skills
  3. Unwanted daytime sedation.
- These adverse effects are more common with benzodiazepines that have active metabolites with long half-lives (eg, diazepam, flurazepam).

Toxicity

A. Psychomotor Dysfunction

- The dosage of a sedative-hypnotic should be reduced in elderly patients, who are more susceptible to drugs that cause psychomotor dysfunction.
- All prescription drugs used as sleep aids may cause functional impairment, including "sleep driving," defined as "driving while not fully awake after ingestion of a sedative-hypnotic product, with no memory of the event."

Toxicity

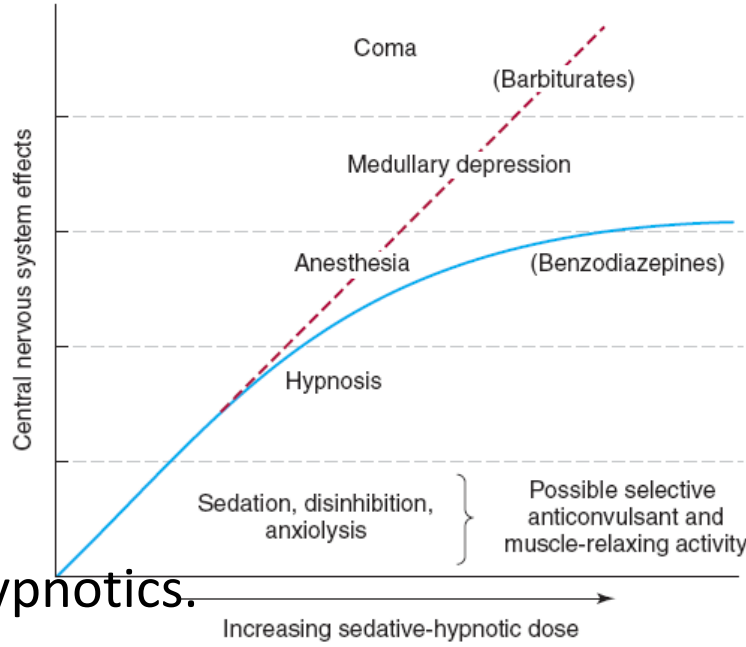
B. Additive CNS Depression

- This occurs when sedative-hypnotics are used with other drugs in the class as well as with alcoholic beverages, antihistamines, antipsychotic drugs, opioid analgesics, and tricyclic antidepressants.

Toxicity

C. Overdosage

- Overdosage of sedative-hypnotic drugs causes severe respiratory and cardiovascular depression; these potentially lethal effects are more likely to occur with alcohols, barbiturates, and carbamates than with benzodiazepines or the newer hypnotics such as zolpidem.
- Management of intoxication requires maintenance of a patent airway and ventilatory support.
- Flumazenil may reverse CNS depressant effects of benzodiazepines, eszopiclone, zolpidem, and zaleplon but has no beneficial actions in overdosage with other sedative-hypnotics.

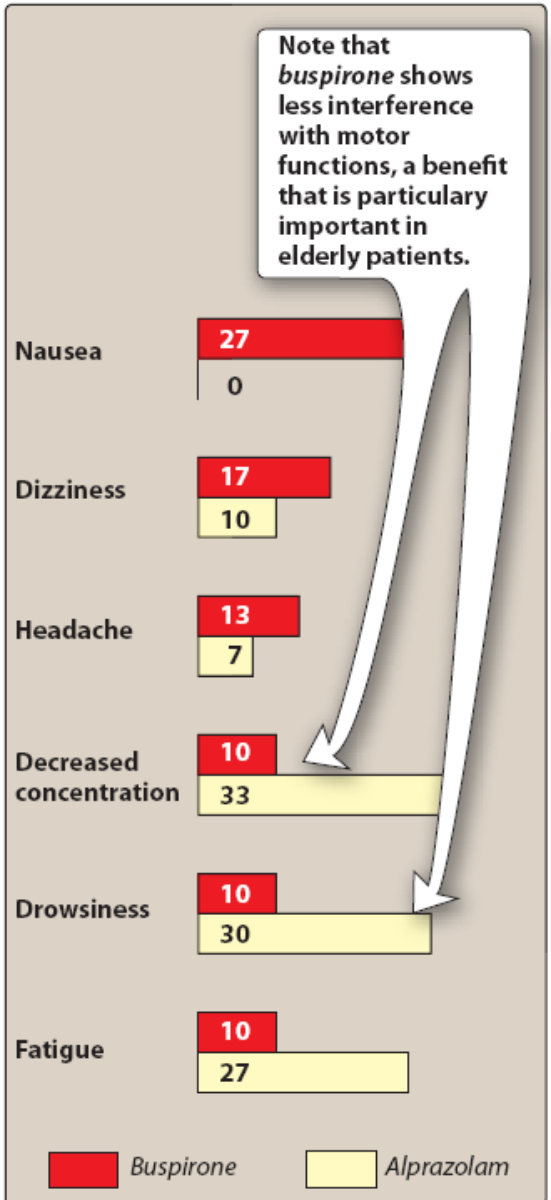


Atypical Sedative-Hypnotics

A. Buspirone

Self reading…P.399

- Buspirone is a selective anxiolytic, with minimal CNS depressant effects (relieves anxiety without causing marked sedative or hypnotic effects, it does not affect driving skills, and has no anticonvulsant or muscle relaxant properties.
- Buspirone has a slow onset of action (>1 week) and it is used in generalized anxiety disorder(s), but it is unsuitable for management of acute anxiety states.
- Tolerance development is minimal with chronic use, and there is little rebound anxiety or withdrawal symptoms on discontinuance.
- Buspirone has minimal abuse liability.



Atypical Sedative-Hypnotics

B. Ramelteon and tasimelteon

- This novel hypnotic drug that activates melatonin receptors in the CNS.
- It decreases the latency of sleep onset with minimal rebound insomnia or withdrawal symptoms.
- Rapidly absorbed after oral administration.
- Metabolized by CYP1A2 and CYP2C9 enzymes.
  - Concurrent use with the antidepressant fluvoxamine (CYP1A2 inhibitor) increases the peak plasma concentration of ramelteon over 50-fold.
- Unlike conventional hypnotics, ramelteon appears to have minimal abuse liability.

Atypical Sedative-Hypnotics

Orexin Receptor Antagonists: Sleep-Enabling Drugs

Orexin A and B are peptides found in specific hypothalamic neurons that are involved in the control of wakefulness and that are silent during sleep. Orexin levels increase in the day and decrease at night. Loss of orexin neurons is associated with narcolepsy, a disorder characterized by daytime sleepiness and cataplexy. Animal studies show that orexin receptor antagonists have sleep-enabling effects. This has prompted the development of a new class of hypnotic drugs, orexin antagonists, which include the drugs **almorexant** and **suvorexant**, the latter agent approved by the FDA.

TABLE 22–3 Dosages of drugs used commonly for sedation and hypnosis.

Sedation		Hypnosis	
Drug	**Dosage**	**Drug**	**Dosage (at Bedtime)**
Alprazolam	0.25–0.5 mg 2–3 times daily	Chloral hydrate	500–1000 mg
Buspirone	5–10 mg 2–3 times daily	Estazolam	0.5–2 mg
Chlordiazepoxide	10–20 mg 2–3 times daily	Eszopiclone	1–3 mg
Clorazepate	5–7.5 mg twice daily	Lorazepam	2–4 mg
Diazepam	5 mg twice daily	Quazepam	7.5–15 mg
Halazepam	20–40 mg 3–4 times daily	Secobarbital	100–200 mg
Lorazepam	1–2 mg once or twice daily	Temazepam	7.5–30 mg
Oxazepam	15–30 mg 3–4 times daily	Triazolam	0.125–0.5 mg
Phenobarbital	15–30 mg 2–3 times daily	Zaleplon	5–20 mg
		Zolpidem	5–10 mg

CASE STUDY

At her annual physical examination, a 53-year-old middle school teacher complains that she has been having difficulty falling asleep, and after falling asleep, she awakens several times during the night. These episodes now occur almost nightly and are interfering with her ability to teach. She has tried various over-the-counter sleep remedies, but they were of little help and she experienced "hangover" effects on the day following their use. Her general health is good, she is not overweight, and she takes no prescription drugs. She drinks decaffeinated coffee but only one cup in the morning; however, she drinks as many as 6 cans per day of diet cola. She drinks a glass of wine with her evening meal but does not like stronger spirits. What other aspects of this patient's history would you like to know? What therapeutic measures are appropriate for this patient? What drug, or drugs, (if any) would you prescribe?

CASE STUDY ANSWER

As described in this chapter, nonpharmacologic factors are very important in the management of sleep problems: proper diet (and avoidance of snacks before bedtime), exercise, and a regular time and place for sleep. Avoidance of stimulants is very important, and the large intake of diet colas reported by the patient should be reduced, especially in the latter half of the day. If problems persist after these measures are implemented, one of the newer hypnotics (eszopiclone, zaleplon, or zolpidem) may be tried on a short-term basis.

QUESTIONS??