Anxiolytics and hypnotic drugs

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Introduction

- Anxiety: unpleasant state of tension, apprehension, or uneasiness (a fear that seems to arise from unknown source)
- Physical symptoms of anxiety are similar to fear:
  - Tachycardia
  - Sweating
  - Trembling
  - Palpitations
- Anxiety involves sympathetic activation

Introduction

- Mild anxiety episodes are common life experiences and do not require treatment
- Severe, chronic debilitating anxiety may be treated with anti-anxiety drugs and/or some kind of behavioural therapy or psychotherapy
- Anti-anxiety drugs cause sedation and can be used as hypnotic (sleep-inducing) agents
- Some anti-anxiety drugs have anticonvulsant effects

Graded dose dependent series of CNS depressant actions:

- Sedation
- Sleep
- Coma
- Death

Duration of action

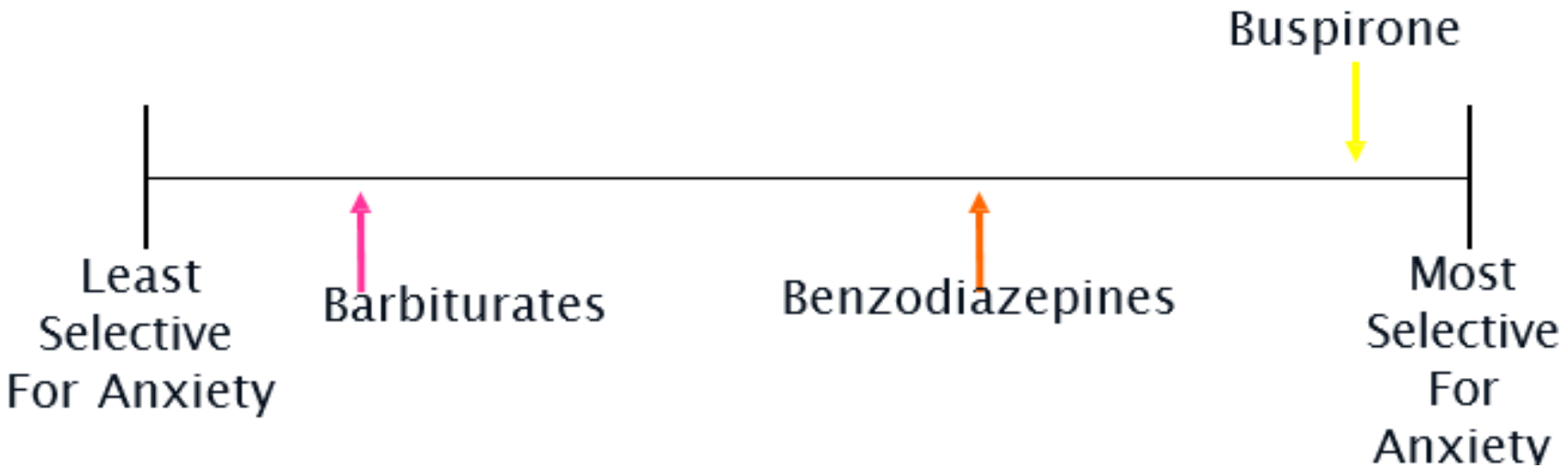
- Determines both uses and side effects
- Short-acting drugs are sleep inducers, have no risk of residual depression, but can cause increased early morning awakenings and next day anxiety
- Intermediate-acting drugs are sleep sustainers but cause residual depression
- Long-acting drugs cause so much residual depression they cannot be used in ambulatory patients: Useful in epilepsy

Categories of sedatives-hypnotics

- Chemical Families
  - Barbiturates
  - Benzodiazepines
  - Other (Nonbarbiturate, nonbenzodiazepine)

- Duration of action
  - Long-acting (used mainly in epilepsy)
  - Intermediate-acting (sleep sustainers)
  - Short-acting (sleep inducers)
  - Ultrashort-acting (IV anesthetics)

Progress in anxioselectivity



Anxiolytic and hypnotic drugs

- Anti-anxiety drug=Anxiolytics=Minor tranquilizers
- Benzodiazepines
- Other anxiolytic drugs
- Barbiturates
- Other hypnotic agents

Benzodiazepines

- Alprazolam
- Triazolam
- Midazolam
- Estazolam
- Clonazepam
- Diazepam
- Lorazepam
- Flurazepam
- Oxazepam
- Quazepam
- Temazepam
- Clorazepate
- Chlordiazepoxide

Benzodiazepines

- Most widely used anxiolytic drugs
- Safer and more effective than barbiturates
- Commonly used but often not the drug of choice for treating either anxiety or insomnia.
- Certain antidepressants with anxiolytic action, such as SSRIs are preferred in many cases for anxiety, and nonbenzodiazepine hypnotics and antihistamines may be preferable for insomnia

Benzodiazepines MOA

Mechanism of action:

- Bind to γ-aminobutyric acid (GABAA) receptors
- GABA is the main inhibitory neurotransmitter in the CNS
- Benzodiazepines increase the frequency of chloride channel opening produced by GABA
- The influx of chloride causes hyperpolarization, that moves the postsynaptic potential away from its firing threshold inhibiting formation of action potentials

Benzodiazepines MOA

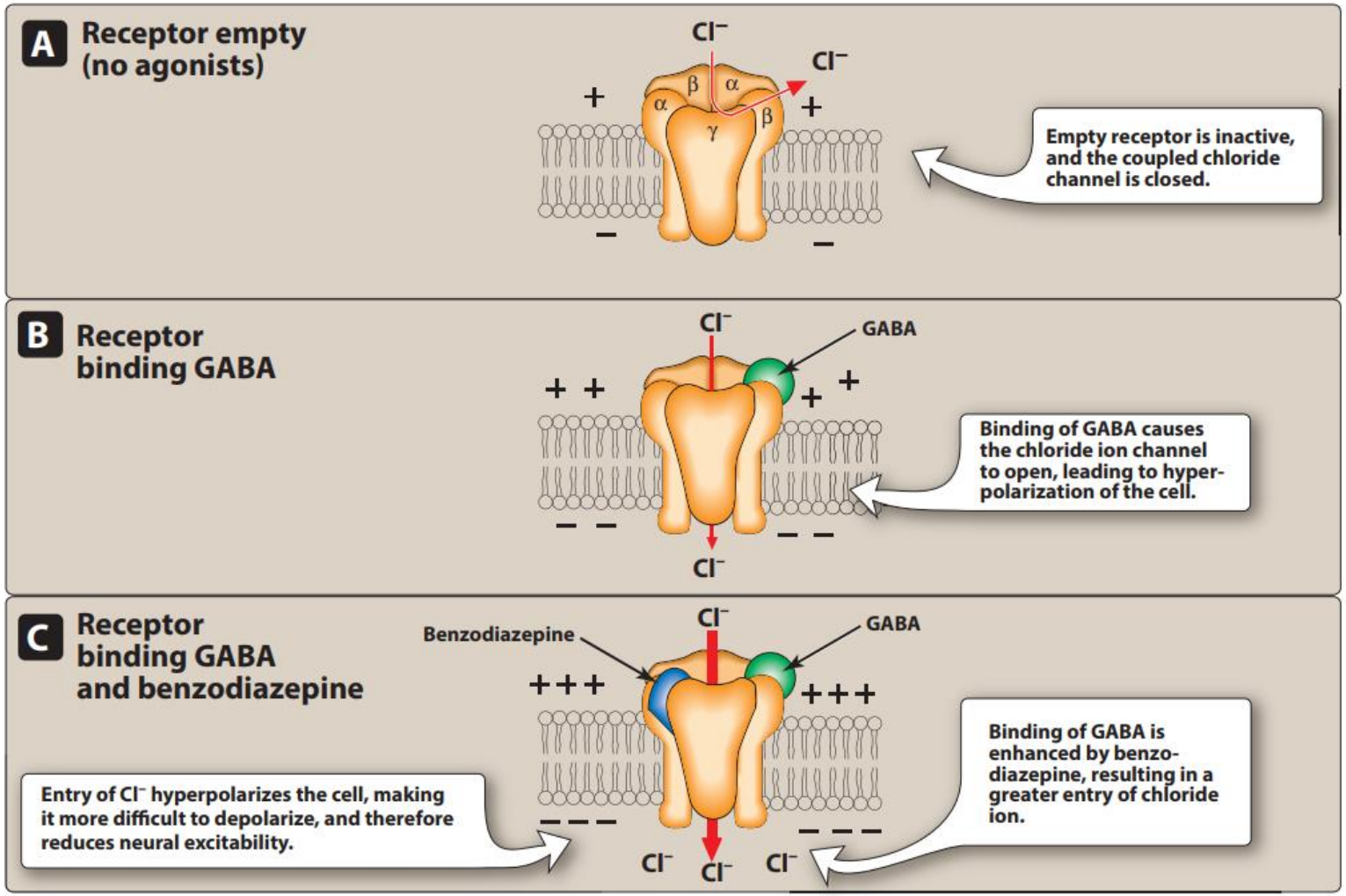


Figure 9.3

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

Benzodiazepines

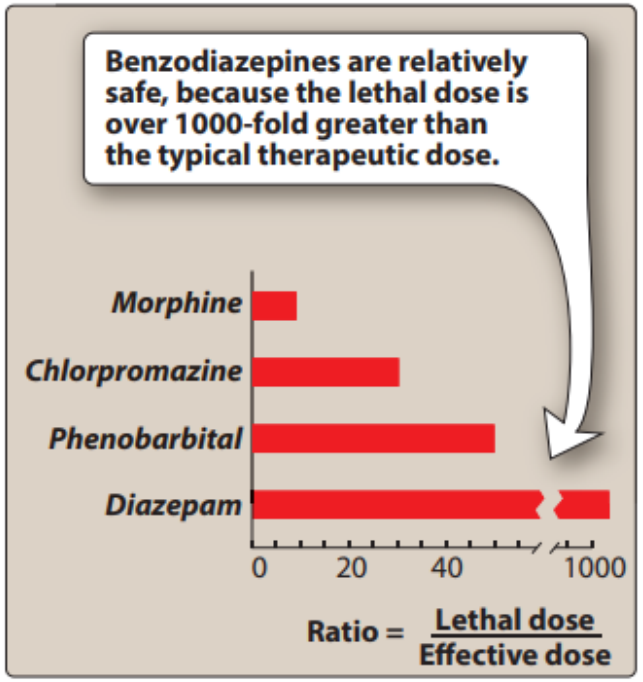


Figure 9.2

Ratio of lethal dose to effective dose for *morphine* (an opioid, see Chapter 14), *chlorpromazine* (an antipsychotic, see Chapter 11), and the anxiolytic, hypnotic drugs, *phenobarbital* and *diazepam*.

Benzodiazepines

Actions

- Reduce anxiety at low doses
- Sedative and hypnotic at higher doses
- Anterograde amnesia: temporary impairment of ability to learn and to form new memories
- Anticonvulsant
- Muscle relaxant by affecting the GABA receptors at the spinal cord level

Benzodiazepines: Therapeutic Uses

1. Treatment of anxiety associated with panic disorder, GAD, PTSD, OCD, etc.

- Should be reserved for severe anxiety and should not be used to manage the stress of everyday life
- Because of their addictive potential, should be used for short periods of time
- Longer acting agents (clonazepam, lorazepam, diazepam) are preferred in patients that require prolonged treatment
- The anxiolytic effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects.

Benzodiazepines: Therapeutic Uses

2. Sleep disorders

- Decrease sleep onset latency, increase stage II NREM sleep. Decrease REM sleep and slow-wave sleep.
- In treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation upon awakening.
- Short-acting agents with a rapid onset of action (triazolam) are effective with problems falling asleep
- Intermediate-acting (temazepam) or long-acting agents are useful for frequent awakenings or difficulty staying asleep
- The risk of withdrawal and rebound insomnia after discontinuation is higher with shorter-acting agents such as triazolam, while the possibility of daytime sedation is greater with longer-acting agents.
- Hypnotics should be used for only a limited time, (1 to 3 weeks)

Benzodiazepines: Therapeutic Uses

3. Amnesia:

- The shorter-acting agents are often employed as premedication for anxiety-provoking and unpleasant procedures, such as endoscopic, bronchoscopic, and certain dental procedures.
- They also cause a form of conscious sedation, allowing the person to be receptive to instructions during procedure.
- (Midazolam is commonly used)

4. Seizures:

- Clonazepam is used as an adjunctive therapy for certain types of seizures
- Lorazepam and diazepam are the drugs of choice in terminating status epilepticus

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

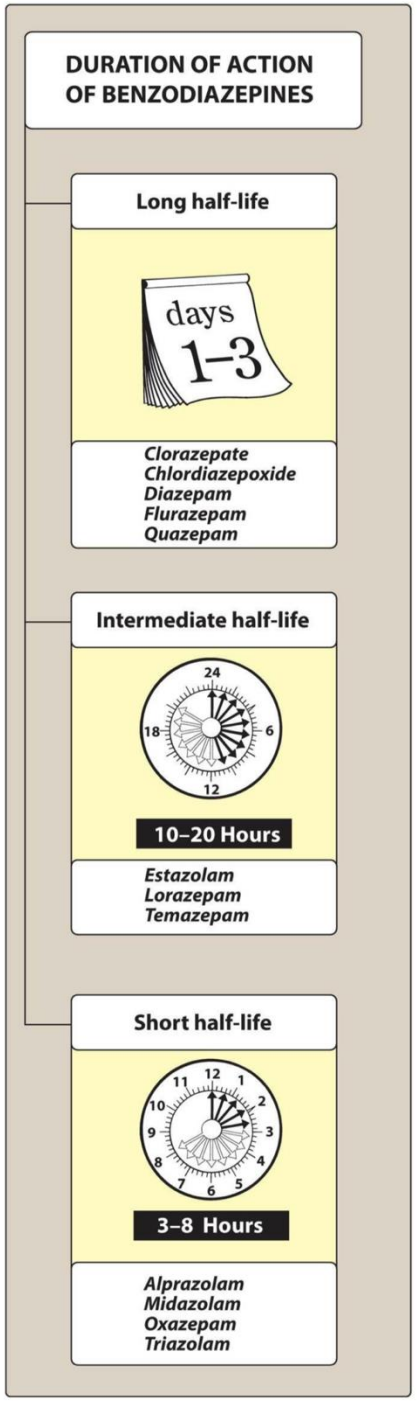
Benzodiazepines and sleep disorders

- In general, hypnotics should be given for only a limited time (< 2-4 weeks)
- In treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation upon awakening
- Not all benzodiazepines are useful as hypnotic agents, although all have sedative or calming effects

Benzodiazepines PK

- Absorption and distribution:
- Benzodiazepines are lipophilic. They are rapidly and completely absorbed after oral administration, distribute throughout the body (large volume of distribution), and penetrate the CNS.
- Metabolism and elimination:
- Most are metabolized by the hepatic microsomal system to compounds that are also active.
- Many are metabolized by CYP3A4 and are subject to numerous drug interactions
- Excreted in the urine as glucuronides or oxidized metabolites.
- Lorazepam, oxazepam, and temazepam are glucuronidated to inactive metabolites
- All cross the placenta and may depress the CNS of the newborn if given before birth.
- Not recommended for use during pregnancy. Nursing infants may also be exposed to the drugs in breast milk.

Benzodiazepines



Benzodiazepines dependence

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

Should be reserved for continued severe anxiety, and then should only be used for short periods of time because of their addiction potential

All benzodiazepines are controlled substances

- Abrupt discontinuation of these agents results in withdrawal symptoms:
- Confusion, anxiety, agitation, 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
- Withdrawal reactions and rebound anxiety or insomnia, and return of panic symptoms, are common with discontinuation of alprazolam, even when the drug is tapered.

Benzodiazepines

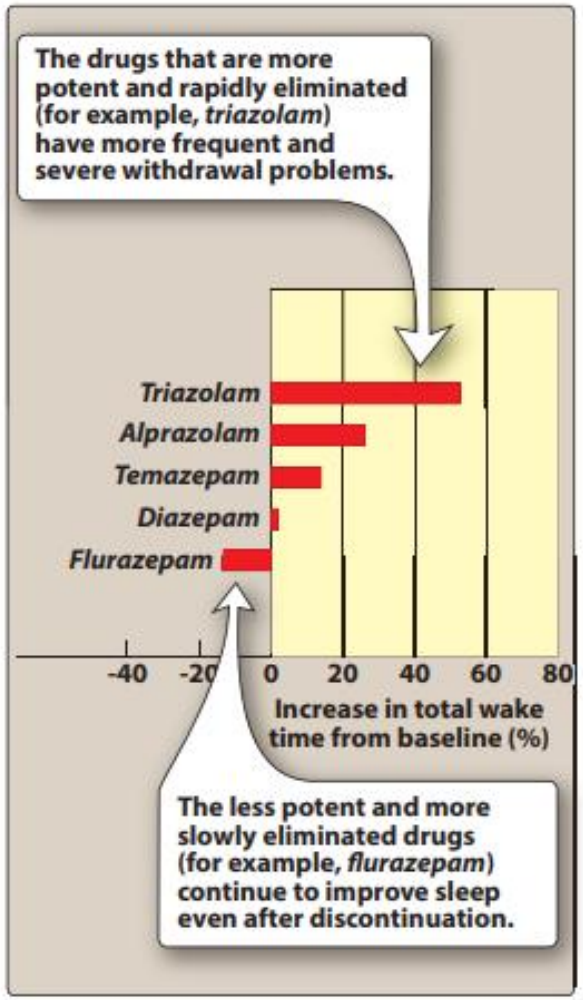


Figure 9.5
Frequency of rebound insomnia resulting from discontinuation of benzodiazepine therapy. Modified from A. Kales, Excertpa Medical Congress Series 899: 149 (1989).

Benzodiazepines

Adverse effects

- Drowsiness and confusion
- Ataxia
- Cognitive impairment
- Confusion
- Day time anxiety

Precautions

- Should be used in caution in patients with liver disease
- Should not be used with alcohol and other CNS depressants like opioids (risk of profound sedation, respiratory depression, coma, death)

In case of toxicity administer benzodiazepine: antagonist **flumazenil** (IV)

Flumazenil

- GABA-receptor antagonist that can rapidly reverse the effects of benzodiazepines
- The drug is administered IV
- Rapid onset
- Short duration, t1/2 = 1 hour, requires frequent administration to maintain reversal of a long-acting benzodiazepine
- Adverse effects: Dizziness, nausea, vomiting, and agitation

Other anxiolytic agents

- Antidepressants
- Buspirone

Antidepressants

- Many antidepressants have proven efficacy in managing symptoms of chronic anxiety disorders and should be considered as first-line agents, especially in patients with concerns for addiction or dependence
- SSRIs, such a escitalopram or paroxetine, or SNRIs, such as venlafaxine or duloxetine may be used alone, or prescribed in combination with a low dose of a benzodiazepine which can be tapered after 4-6 weeks, when the antidepressant begins to produce an anxiolytic effect
- SSRIs and SNRIs have a lower potential for physical dependence than the benzodiazepines, and have become first-line treatment for GAD

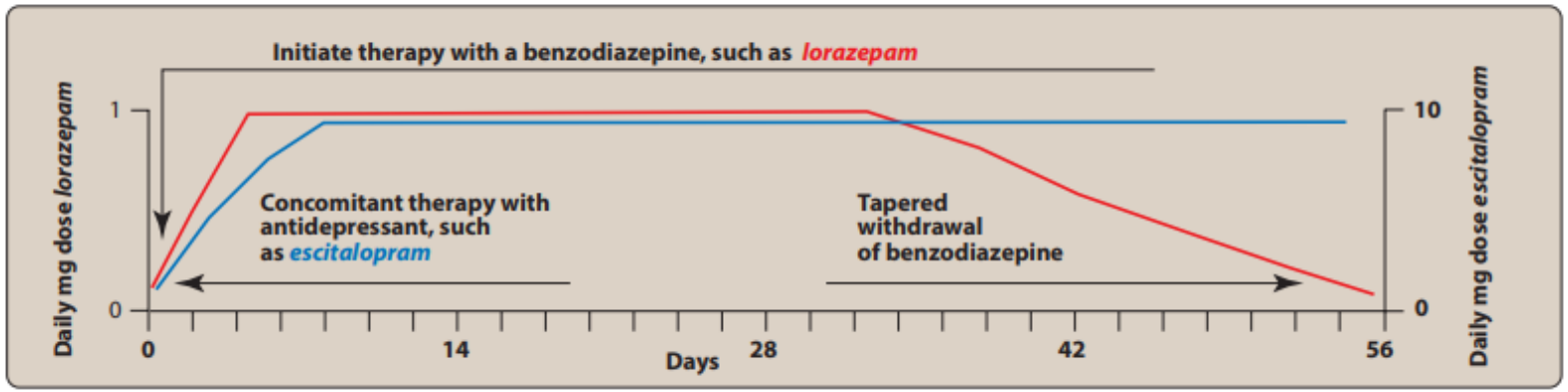


Figure 9.6

Treatment guideline for persistent anxiety. From data of E. C. Dimitrion, A. J. Parashos, and J. S. Giouzepas, Drug Invest. 4: 316 (1992).

Buspirone

- Useful for chronic treatment of GAD

Not effective for short-term or as needed treatment of acute anxiety

Acts through dopamine and serotonin (5-HT1A) receptors

- More selective for anxiety
- Less sedation than benzodiazepines
- No anticonvulsant or muscle relaxant activity
- No dependence
- Less side effects than benzodiazepines

Side effects: headache, dizziness, nervousness, nausea, and light-headedness

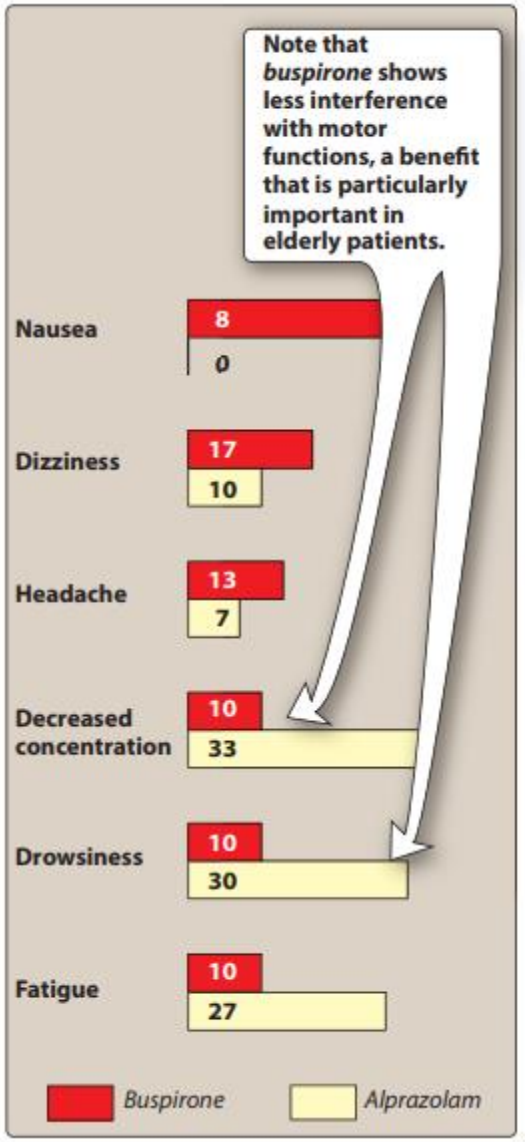


Figure 9.8

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

Barbiturates

- Sedative
- Being replaced by benzodiazepines because
  - Barbiturates cause more tolerance and physical dependence
  - Barbiturates induce drug metabolizing enzymes
  - Barbiturates are associated with severe withdrawal symptoms
  - Barbiturates are lethal in overdose
- All barbiturates are controlled substances and have the potential for abuse

Barbiturates

- Pentobarbital
- Phenobarbital
- Amobarbital
- Secobarbital
- Methohexital

Barbiturates

Mechanism of action

- Bind to GABAA receptors enhancing GABA transmission by prolonging the duration of chloride channel opening
- Block excitatory glutamate receptors
- Anesthetic concentrations of pentobarbital also block high-frequency sodium channels
- All of these molecular actions lead to decreased neuronal activity

Barbiturates

Actions

- CNS depression (dose dependent)
  - At low doses, produce sedation (calming effect and reduce excitement)
  - At higher doses, cause hypnosis, followed by anesthesia, and finally coma and death
- Respiratory depression: barbiturates suppress the hypoxic chemoreceptor response to CO2 (overdose causes respiratory depression and death)
- Enzyme induction: Barbiturates induce CYP450 microsomal enzymes in the liver and diminishes the action of many drugs that are dependent on CYP450 metabolism to reduce their concentration

Barbiturates

Uses

- Anesthesia (Methohexital is an ultra short acting barbiturate that is used IV to induce anesthesia)
- Anticonvulsant: Phenobarbital (Long acting barbiturate), used for refractory status epilepticus.
- Anxiety (Being replaced by benzodiazepines)

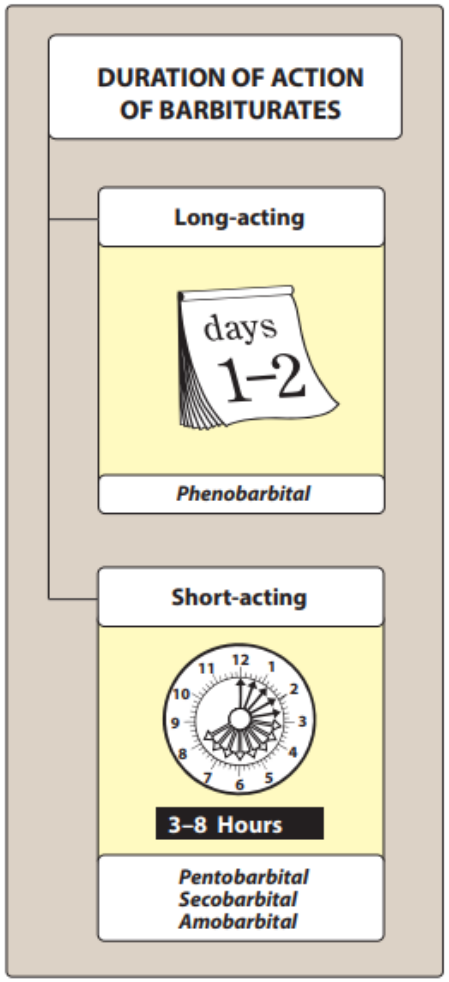


Figure 9.9
Barbiturates classified according to their durations of action.

Barbiturates

Adverse effects

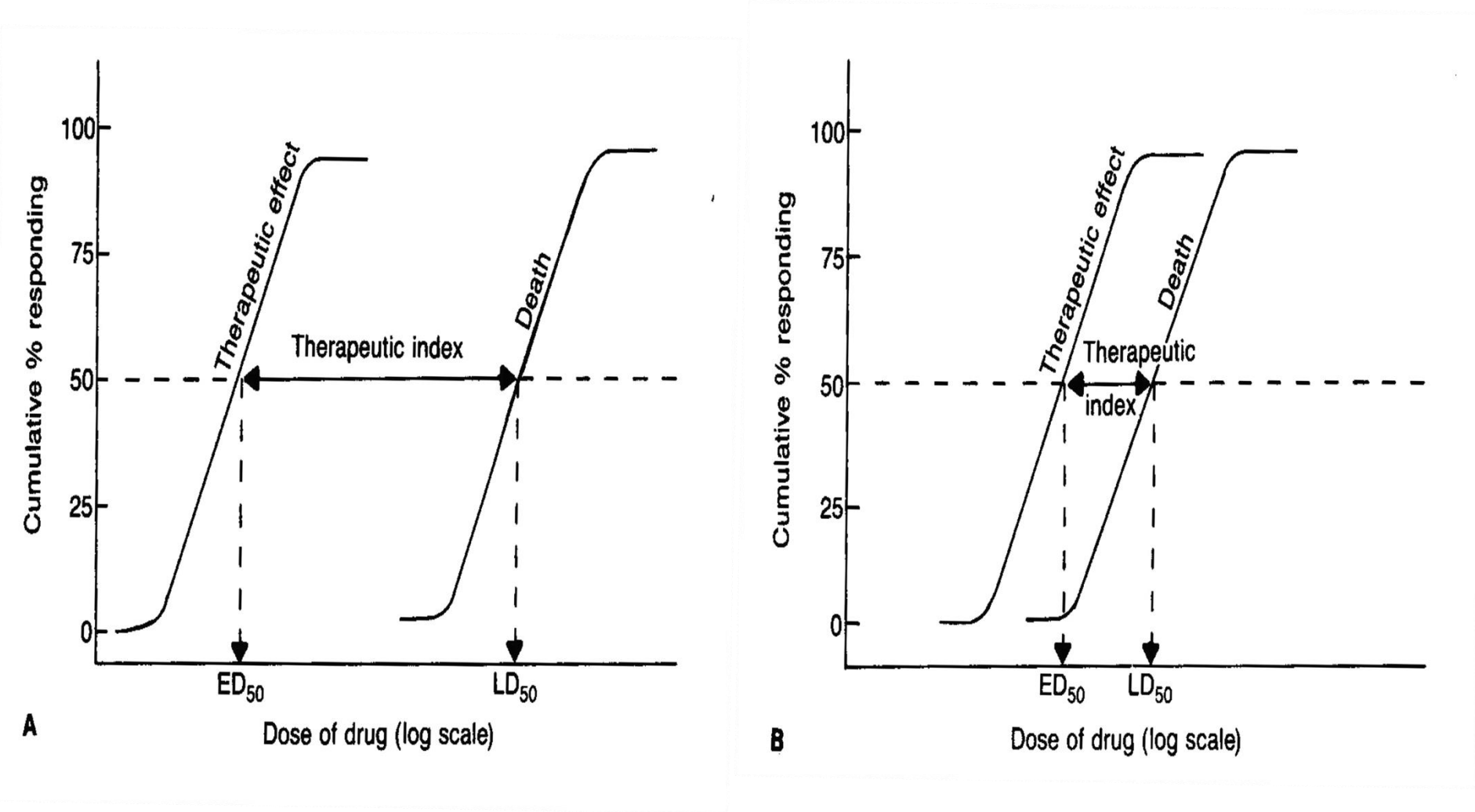
- Drowsiness and impaired concentration
- Addiction potential
- Nausea
- Vertigo
- Tremors
- Physical dependence
- Poisoning

Figure 9.10
Adverse effects of barbiturates.

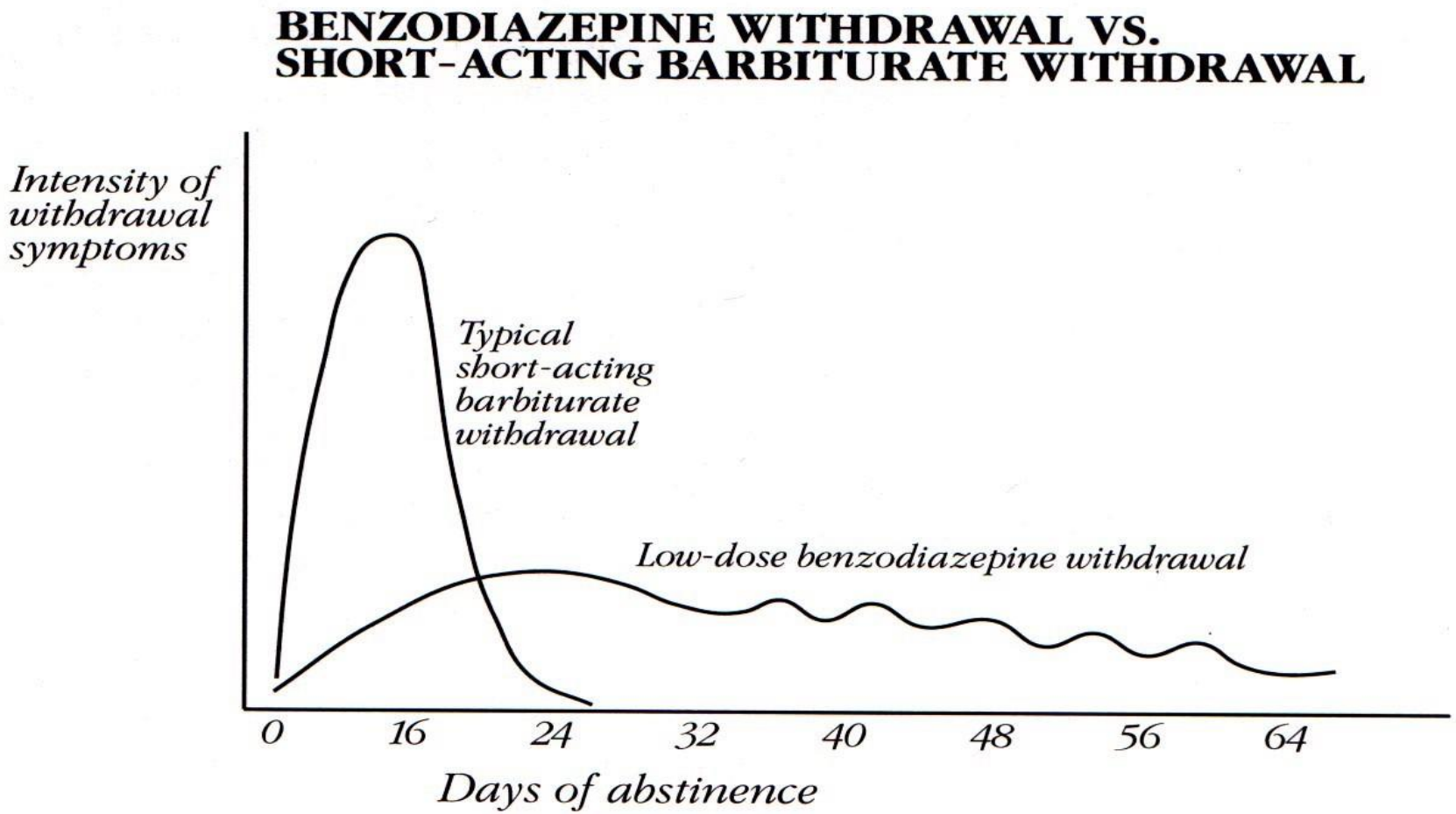
Barbiturates

- Precautions: can cause enzyme induction, drug interactions
- Cross the placenta and can cause respiratory depression in newborns if administered around the time of delivery.
- Abrupt withdrawal causes tremors, anxiety, weakness, restlessness, nausea, seizures, delirium and cardiac arrest
- Toxicity: (Can cause respiratory and cardiovascular depression)
    - There is no specific antidote available
    - Artificial respiration, purging the stomach of its contents, hemodialysis may be necessary
    - Alkalinization of the urine often aids in the elimination of phenobarbital

TIS for Benzodiazepines vs. Barbiturates



Relative Abuse Liability



Other hypnotic agents

Zolpidem

- Binds to benzodiazepine receptor (not a benzodiazepine)
- No anticonvulsant or muscle relaxing effects
- Few withdrawal effects and minimal rebound insomnia
- Little or no tolerance with prolonged use
- Adverse effects: headache, dizziness, anterograde amnesia, day time drowsiness, nightmares

Zaleplon

- Similar to zolpidem
- Fewer residual effects on psychomotor and cognitive functions compared to zolpidem or other benzodiazepines, due to its rapid elimination

Eszopiclone

- Acts on the BZ receptor
- Effective for insomnia for up to 6 months
- Adverse events include anxiety, dry mouth, headache, peripheral edema, somnolence, and unpleasant taste

- All three agents are controlled substances with warnings for dependency

Other hypnotic agents

Ramelteon

- 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.
- Useful as a sleep-inducer
- No dependence, abuse liability or withdrawal symptoms
- Can be administered long-term
- Metabolized by CYP1A2 and 3A4
- Adverse effects: dizziness, fatigue, somnolence, increase in prolactin levels.

Other hypnotic agents

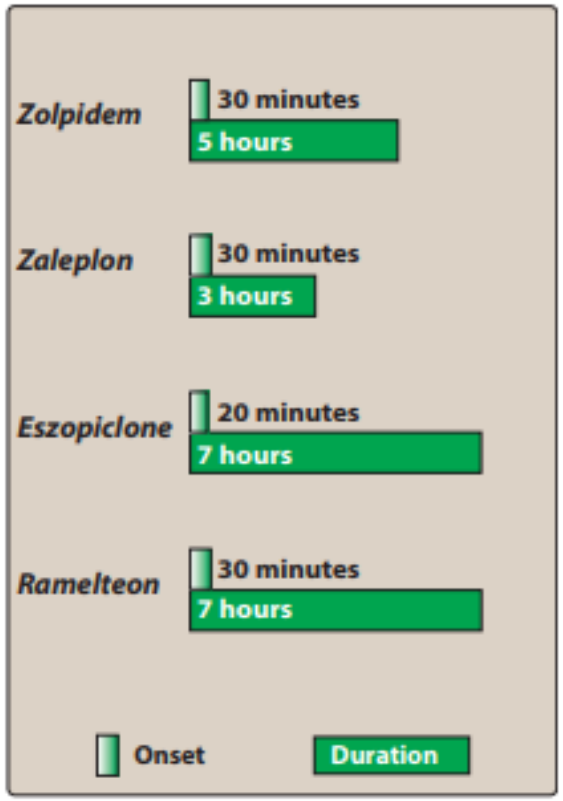


Figure 9.11
Onset and duration of action of the commonly used nonbenzodiazepine hypnotic agents.

Other hypnotic agents

Antihistamines

- Diphenhydramine
- Hydroxyzine
- Doxylamine
- Effective for mild insomnia
- Low risk
- Found in OTC products
- Anticholinergic side effects

Other hypnotic agents

Antidepressants

- The use of sedating antidepressants with strong antihistamine profiles has been ongoing for decades.
- Doxepin is approved at low doses for insomnia
- Trazodone, mirtazapine and older tricyclic antidepressants with strong antihistamine properties are used off-label for the treatment of insomnia

Other hypnotic agents

Suvorexant

- Antagonist of the orexin receptor, a neuropeptide that promotes wakefulness

- Adverse effects:
- Daytime somnolence and increased suicidal ideation

- Drug interactions with CYP3A4 inducers or inhibitors

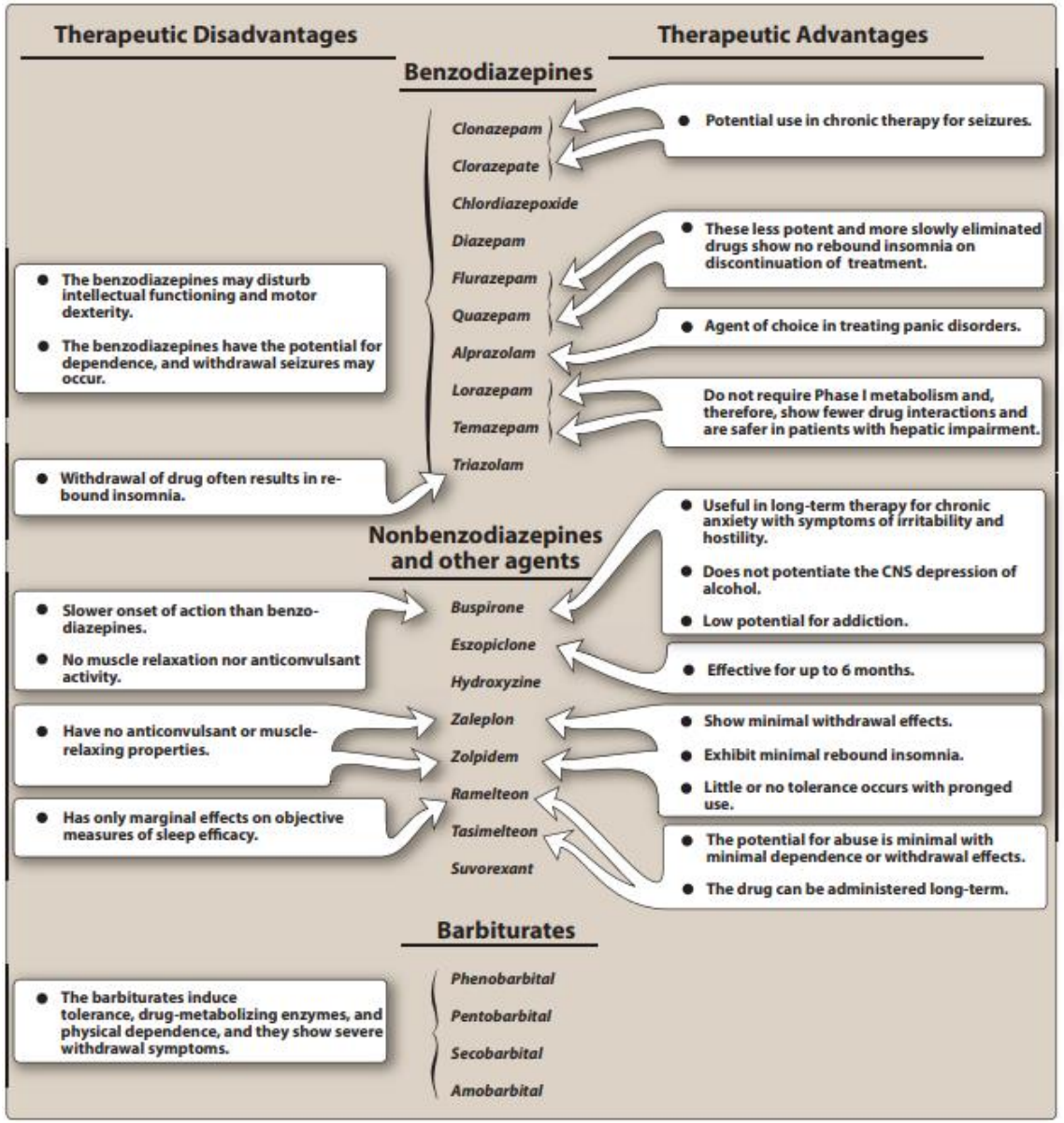


Figure 9.12

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