Anxiolytic and hypnotic drugs

- 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

- 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 behavioral 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 Sedative-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)

Anxiolytic and hypnotic drugs

- Anti-anxiety drug=Anxiolytics=Minor tranquilizers

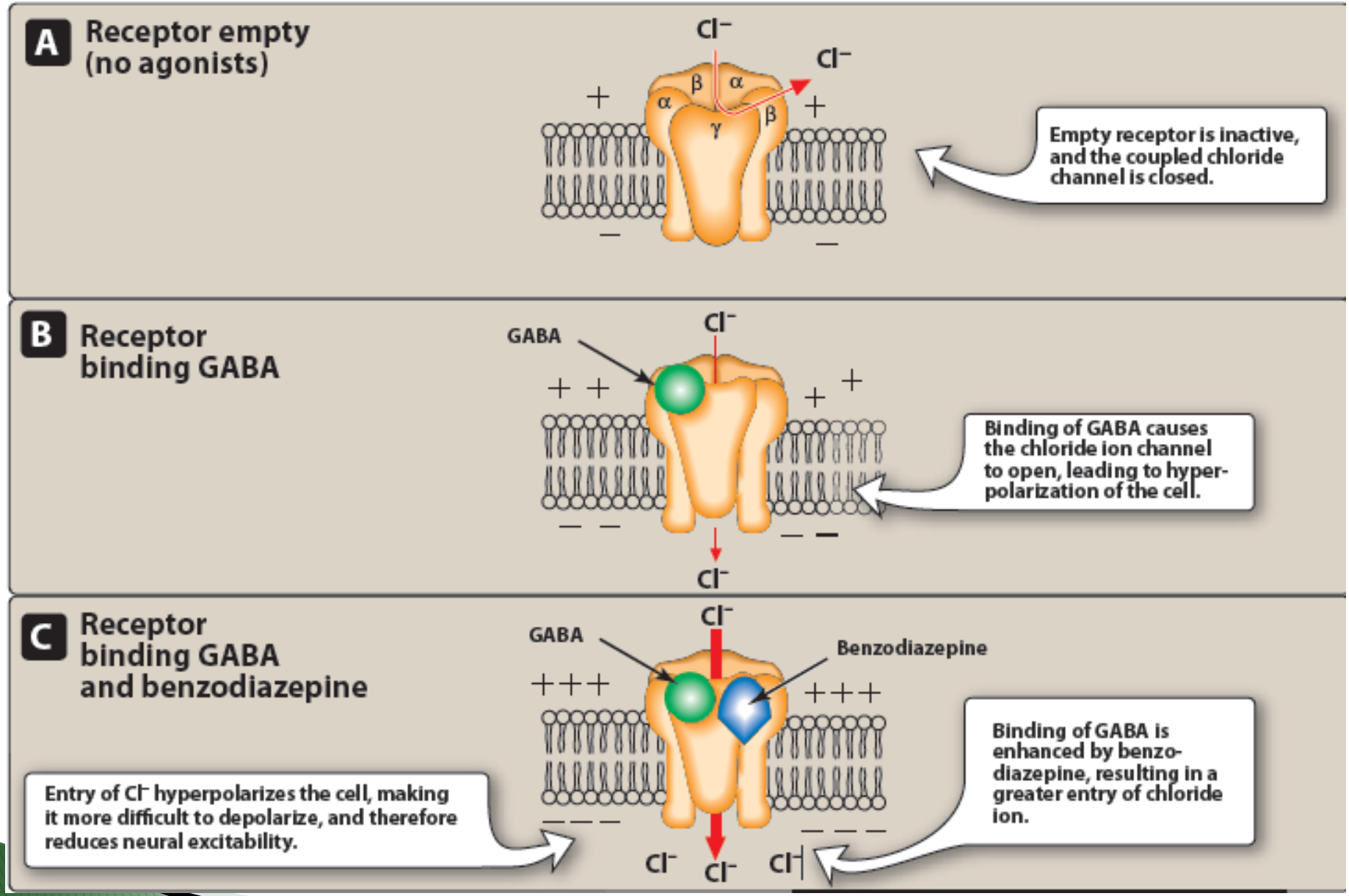
- Benzodiazepines
- Other anxiolytic drugs
- Barbiturates
- Other hypnotic agents

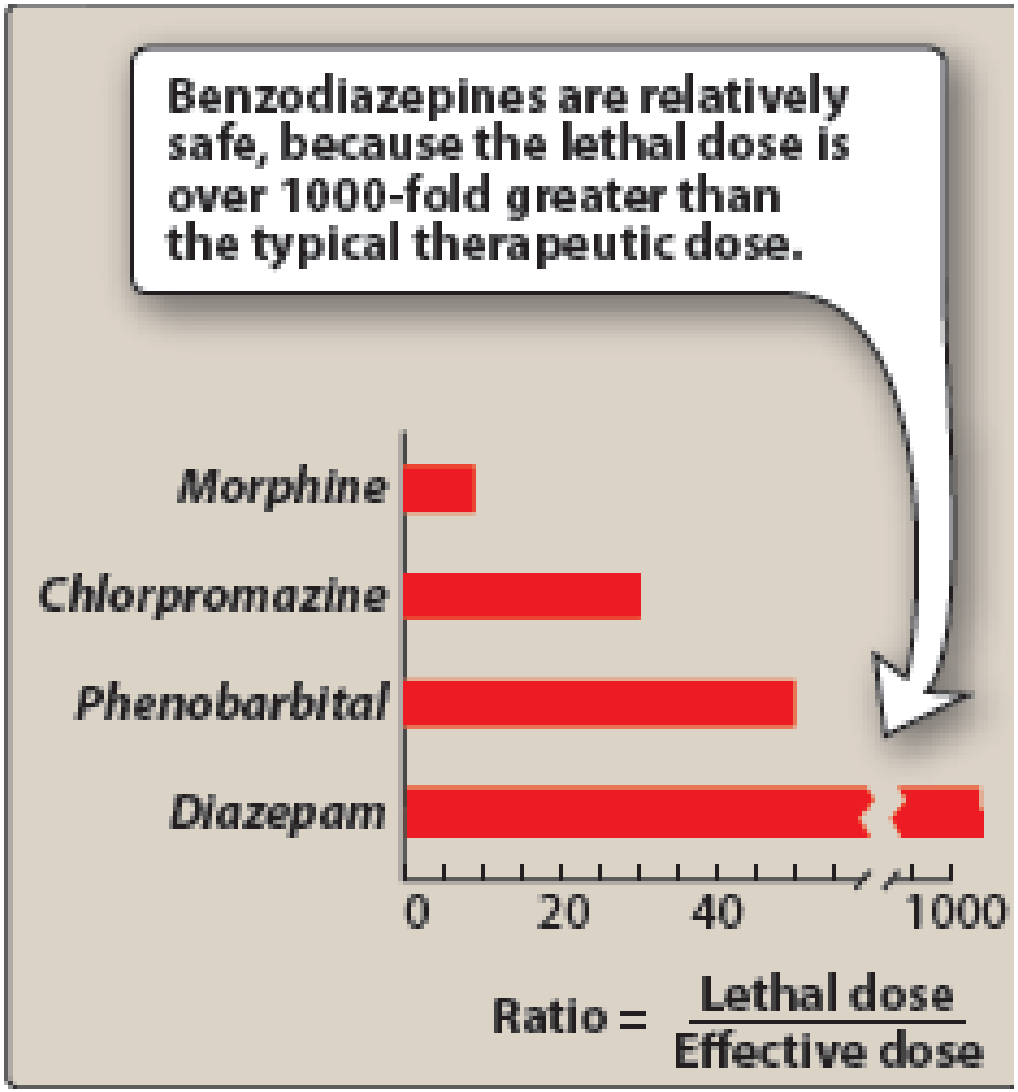
Benzodiazepines

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

Benzodiazepines

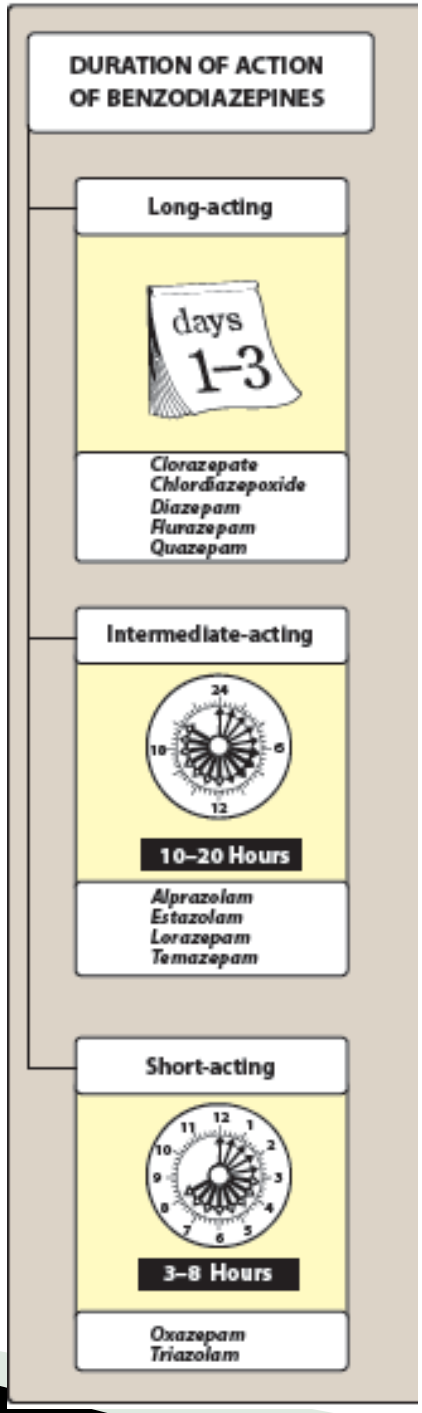
- Most widely used anxiolytic drugs
- Safer and more effective than barbituates
- Mechanism of action:
  - Bind to γ-aminobutyric acid ($GABA_A$) receptors
  - GABA is the main inhibitory neurotransmitter in the CNS
  - Benzodiazepines increase the frequency of chloride channel opening produced by GABA
  - The influx of chloride causes hyperpolarization, that moves the postsynaptic potential away from its firing threshold inhibiting formation of action potentials


A
Receptor empty (no agonists)
Cl⁻
Cl⁻
β
α
α
β
γ
+
+
−
−
Empty receptor is inactive, and the coupled chloride channel is closed.
B
Receptor binding GABA
GABA
Cl⁻
+ +
+
+
− −
− −
Binding of GABA causes the chloride ion channel to open, leading to hyper-polarization of the cell.
Cl⁻
C
Receptor binding GABA and benzodiazepine
Cl⁻
GABA
Benzodiazepine
+++
+++
− − −
− − −
Entry of Cl⁻ hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.
Cl⁻
Cl⁻
Cl⁻
Binding of GABA is enhanced by benzo-diazepine, resulting in a greater entry of chloride ion.


Benzodiazepines are relatively safe, because the lethal dose is over 1000-fold greater than the typical therapeutic dose.
Morphine
Chlorpromazine
Phenobarbital
Diazepam
0
20
40
1000
Ratio = Lethal dose / Effective dose

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


DURATION OF ACTION OF BENZODIAZEPINES
Long-acting
days 1–3
Clorazepate
Chlordiazepoxide
Diazepam
Flurazepam
Quazepam
Intermediate-acting
10–20 Hours
Alprazolam
Estazolam
Lorazepam
Temazepam
Short-acting
3–8 Hours
Oxazepam
Triazolam

Benzodiazepines

- Therapeutic uses
  - Treatment of anxiety symptoms secondary to panic disorder, GAD, PTSD, OCD, and others
  - Muscular disorders (Diazepam is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain, and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy)
  - 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 used for induction of anesthesia)
  - Seizures (Clonazepam, diazepam, lorazepam)
  - Sleep disorders (Triazolam is used for insomnia, it has a short duration of action)

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 and sleep disorders

- Commonly prescribed benzodiazepines for sleep disorders:
  - Flurazepam
    - Long-acting, reduces sleep-induction time and number of awakenings, increases the duration of sleep and causes little rebound insomnia
    - Effectiveness maintained for up to 4 weeks
    - Flurazepam and its active metabolites have a t1/2 of ~85 hours, which may result in daytime sedation and accumulation of the drug
  - Temazepam
    - Intermediate-acting, useful in patients with frequent wakening
    - Given 1-2 hours before bedtime; Peak sedative effect occurs 1-3 hours after an oral dose
  - Triazolam
    - Short acting, used to induce sleep in patients with recurring insomnia
    - Effective in individuals with difficulty in falling sleep
    - Best used intermittently rather than daily
    - Tolerance develops within a few days, and withdrawal of the drug often results in rebound insomnia, leading the patient to demand higher dose

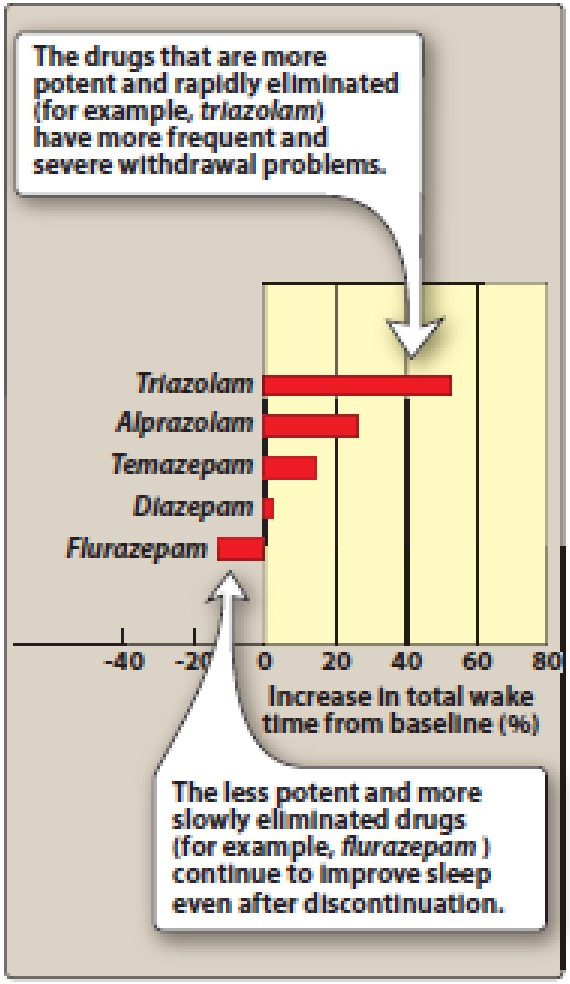


Figure 9.5
Frequency of rebound insomnia resulting from discontinuation of benzodiazepine therapy.

Benzodiazepines

- Can cause psychological and physical dependence if given over a prolonged period of time
- Should be reserved for continued severe anxiety, and then should only be used for short periods of time because of their addiction potential
- These drugs should not be used to alleviate the normal stress of everyday life
- For panic disorders, alprazolam is effective for short and long-term treatment, although it may cause withdrawal reactions
- Abrupt discontinuation of benzodiazepines causes withdrawal symptoms
  - Confusion
  - Anxiety
  - Agitation
  - Insomnia
  - Tension

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
- 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 seriously considered as first-line agents, especially in patients with concerns for addiction or dependence

- Selective serotonin reuptake inhibitors (SSRIs, such a escitalopram), or selective serotonin and norepinephrine reuptake inhibitors (SNRIs, such as venlafaxine) may be used alone, or prescribed in combination with a low dose of a benzodiazepine which can be tapered after four to six 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

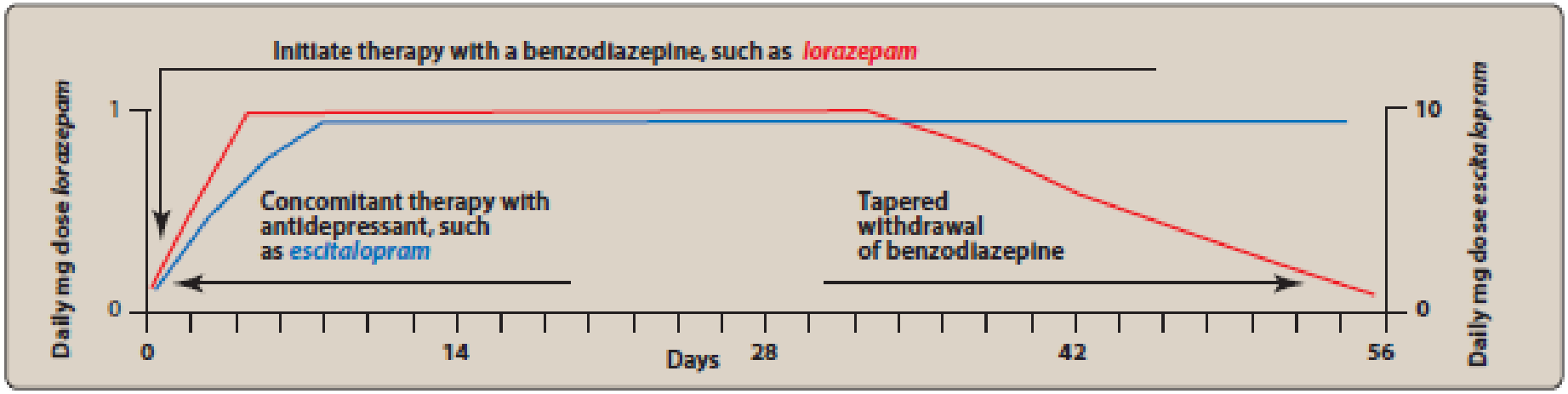
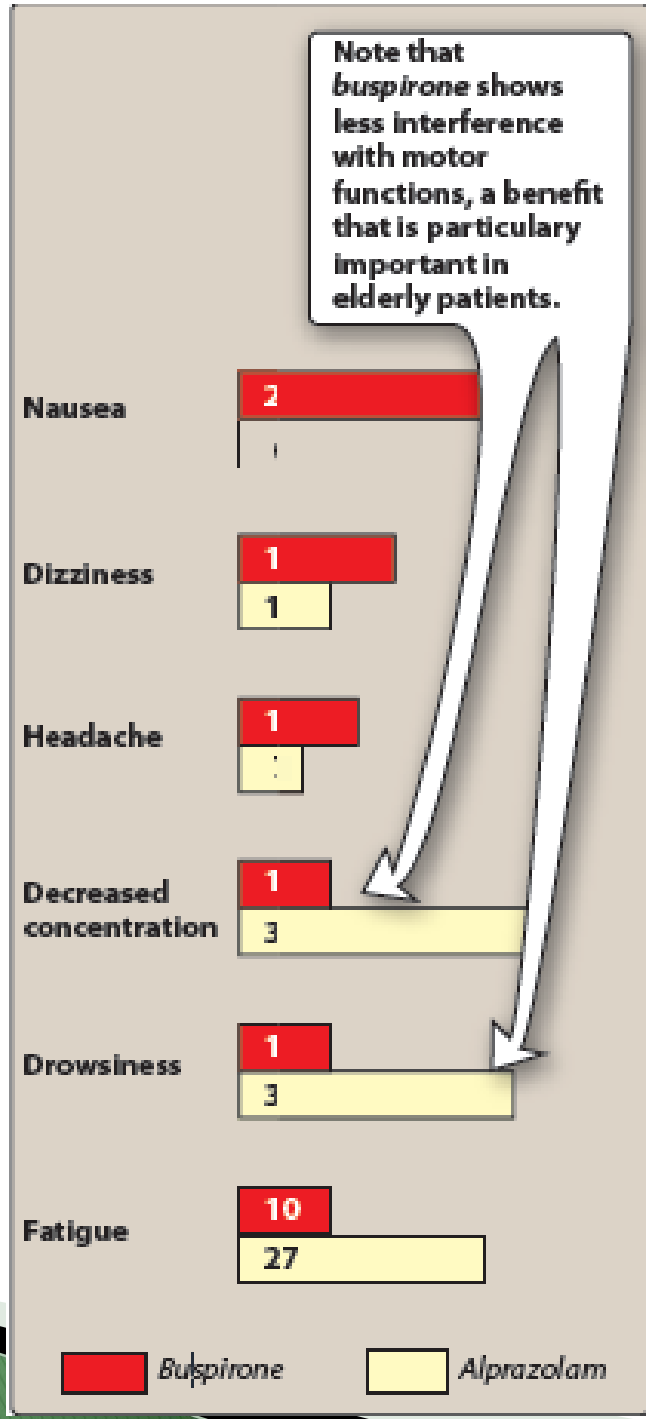


Figure 9.6
Treatment guideline for persistent anxiety.

Buspirone

- Useful for chronic treatment of GAD
- Not effective for short-term or as needed treatment of acute anxiety
- Acts through dopamine and serotonin ($5\text{-}HT_{1A}$) receptors
- More selective for anxiety
- Less sedation than benzodiazepines
- No anticonvulsant or muscle relaxant activity
- No dependence
- Less side effects than benzodiazepines


Note that buspirone shows less interference with motor functions, a benefit that is particulary important in elderly patients.
Nausea
2
Dizziness
1
1
Headache
1
Decreased concentration
1
3
Drowsiness
1
3
Fatigue
10
27
Bulspirone
Alprazolam

Barbiturates

- Sedative
- Being replaced by benzodiazepines because
  - Barbiturates cause more tolerance
  - Barbiturates induce drug metabolizing enzymes
  - Barbiturates are associated with severe withdrawal symptoms
  - Barbiturates can cause coma in toxic doses
- Thiopental, a very short acting barbiturate, used to induce anesthesia

Barbiturates

- Thiopental
- Pentobarbital
- Phenobarbital
- Amobarbital
- Secobarbital

Barbiturates

- Mechanism of action
  - Bind to $GABA_A$ 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

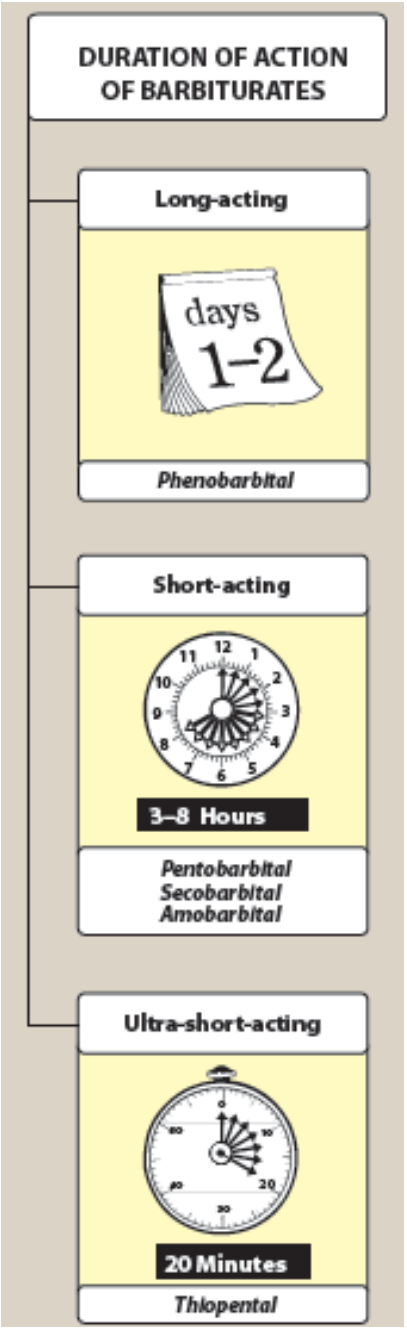
Barbiturates

- 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 CO_2

    (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

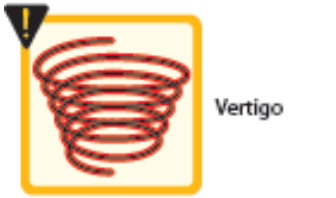
Barbiturates

- Uses
  - Anesthesia (Thiopental is an ultra short acting barbiturate that is used to induced anesthesia)
  - Anticonvulsant: Phenobarbital (Long acting barbiturate)
  - Anxiety (Being replaced by benzodiazepines)



Barbiturates

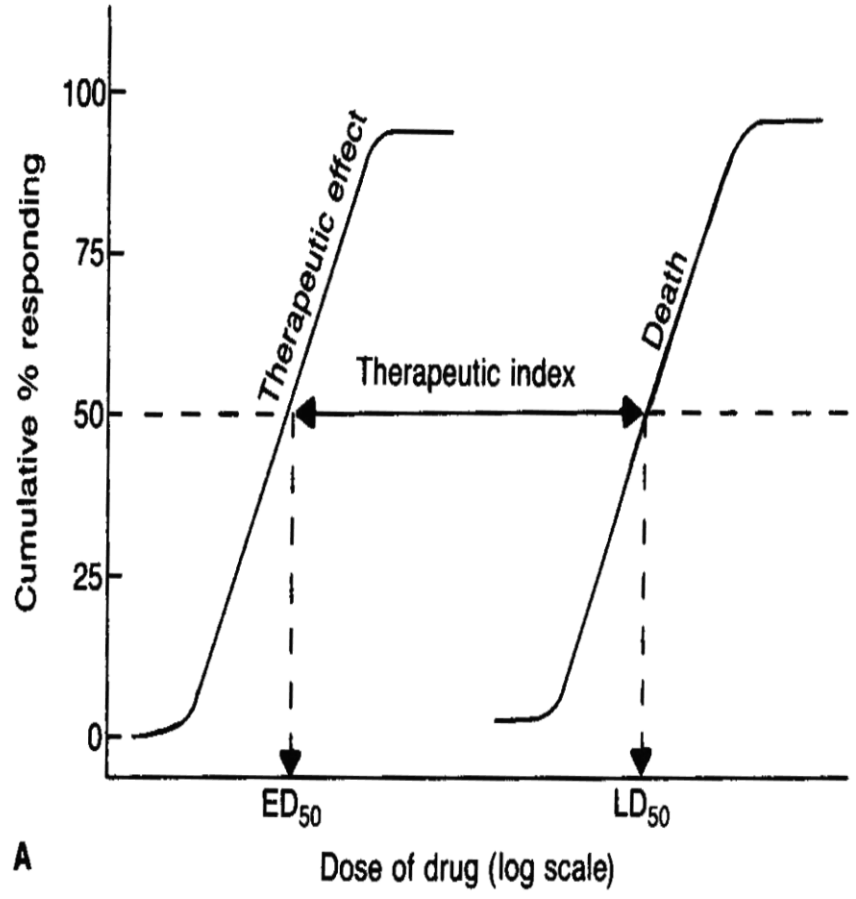
- Adverse effects
  - Drowsiness and impaired concentratio
  - Addiction potential
  - Nausea
  - Vertigo
  - Tremors
  - Physical dependence
  - Poisoning

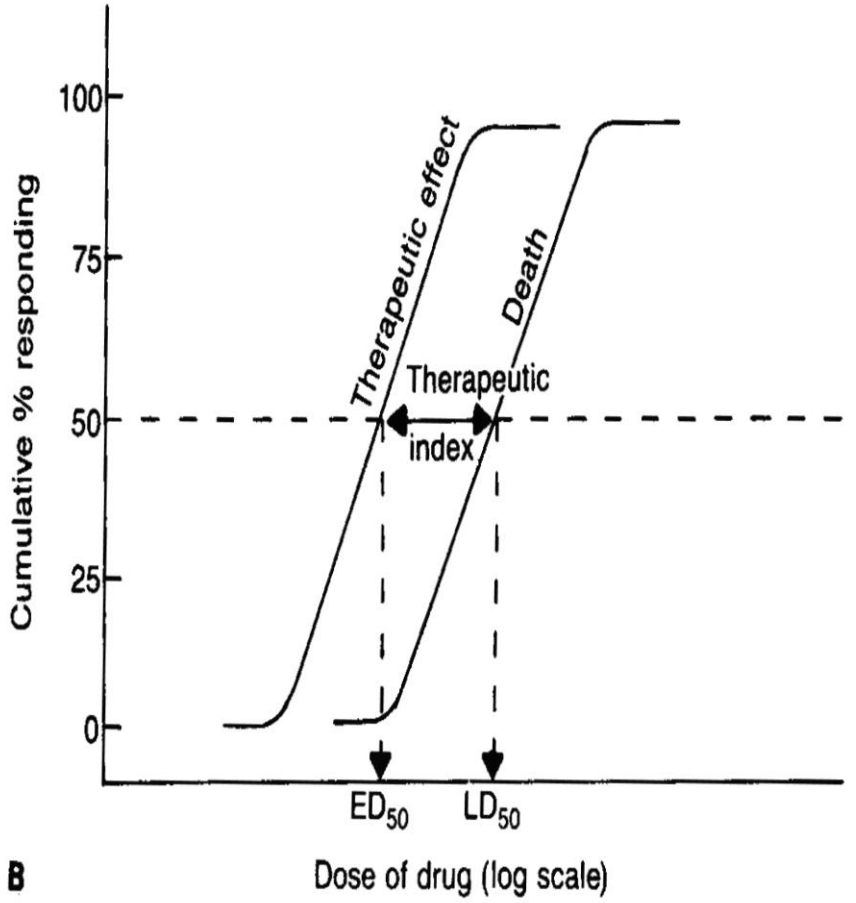


Barbiturates

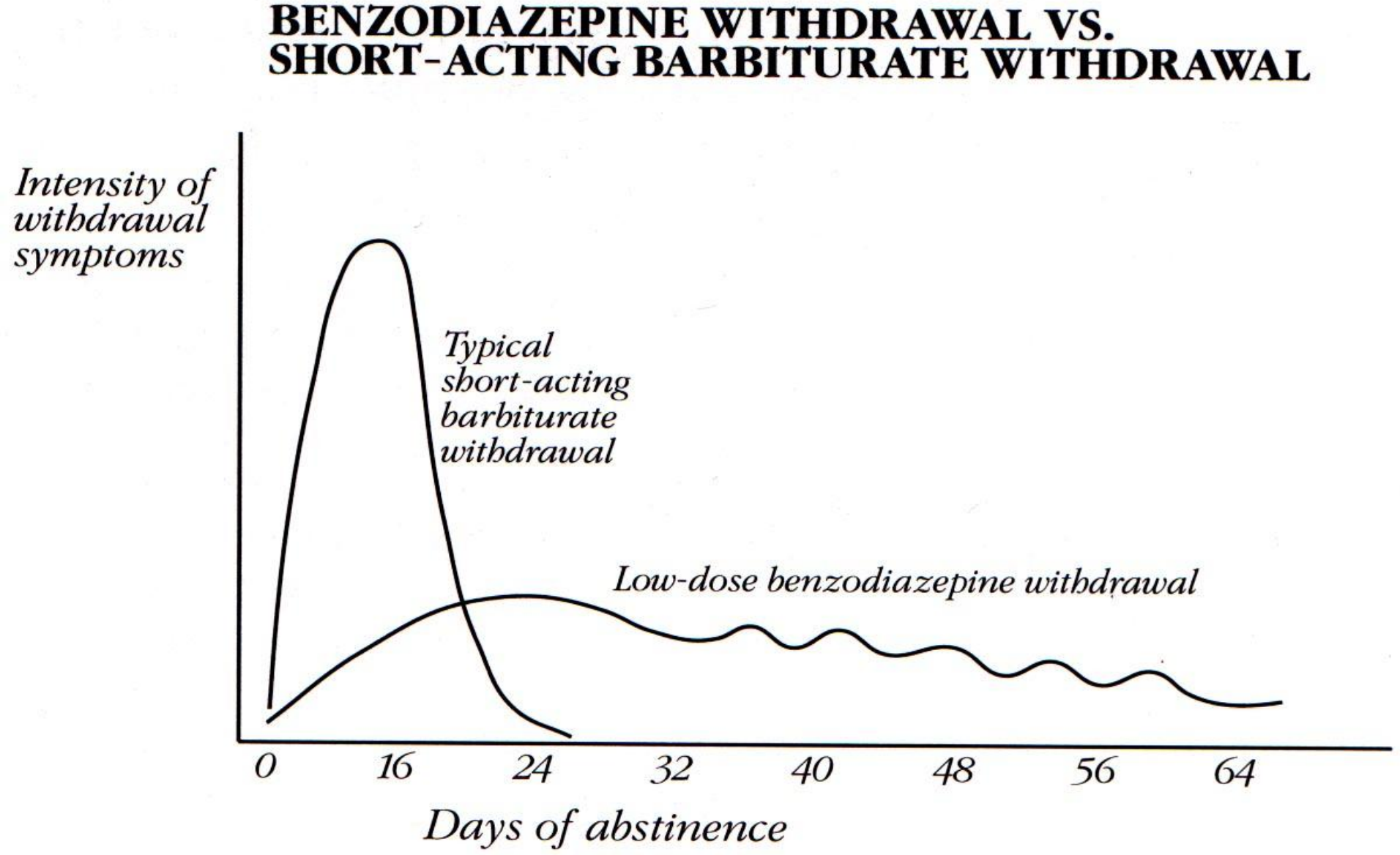
- Precautions: can cause enzyme induction, drug interactions
- Abrupt withdrawal causes tremors, anxiety, weakness, restlessness, nausea, seizures, delirium and cardiac arrest
- Toxicity: (Can cause respiratory and cardiovascular depression)
  - There is no specific antidote available
  - Artificial 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: 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

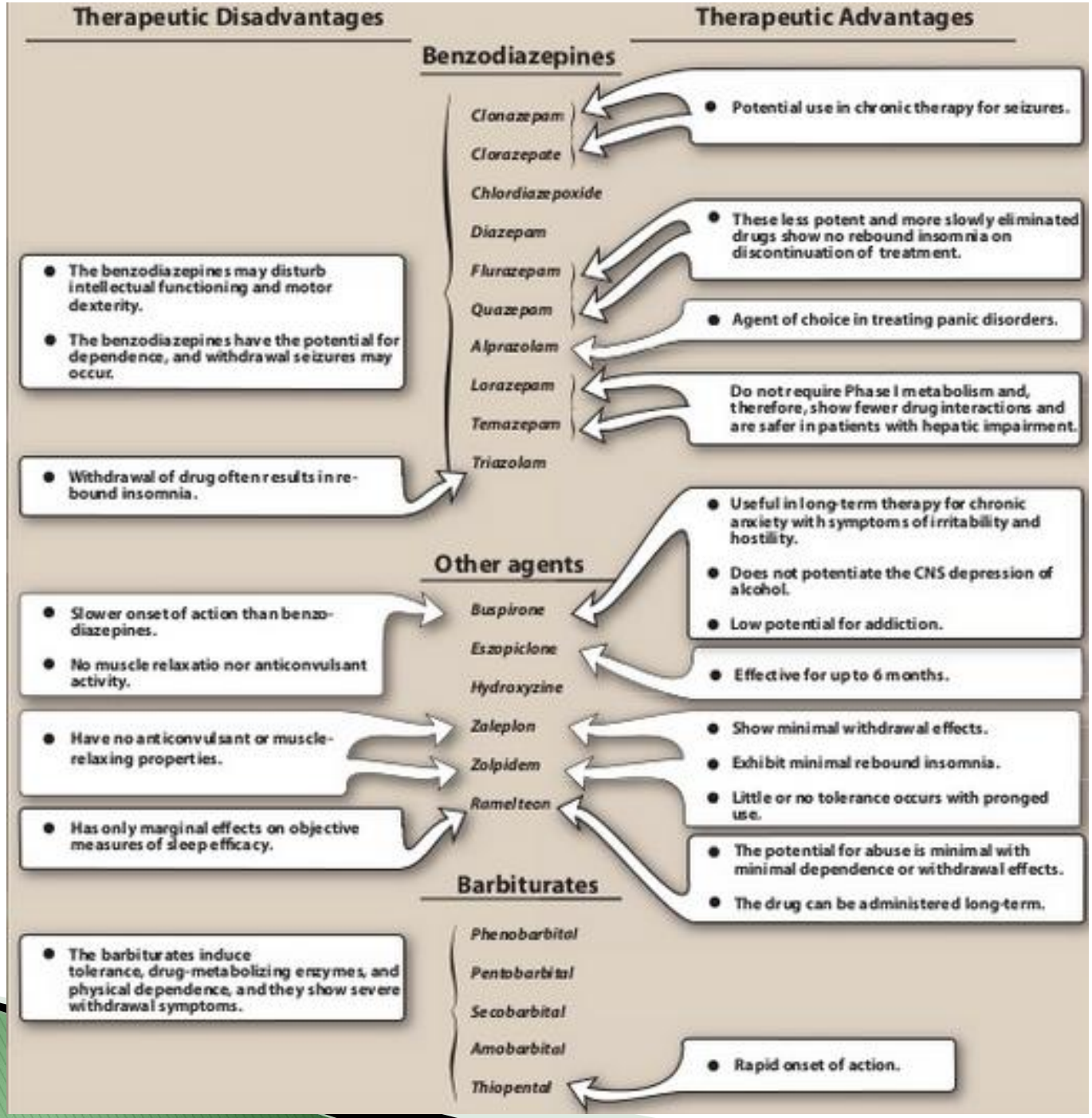
Other hypnotic agents

- Ramelteon
  - Selective agonist at the MT1 and MT2 subtypes of melatonin receptors
  - Light stimulates the retina which transmits a signal to the suprachiasmatic nucleus of the hypothalamus that passes a signal to the pineal gland to inhibit melatonin release
  - During the dark, light stops to affect the retina and melatonin release is no longer inhibited
  - Useful as a sleep-inducer
  - No tolerance, dependence, rebound hyperinsomnia, or abuse liability

Figure 9.10
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
  - Anticholinergic side effects


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 rebound 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 benzodiazepines.
No muscle relaxatio 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.