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 (Diazepam)
  - 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 = anxiolytic = minor tranquilizer
- Benzodiazepines
  - Alprazolam
  - Clonazepam
  - Diazepam
  - Lorazepam
  - Triazolam
- Barbiturates
  - Pentobarbital
  - Phenobarbital
  - Thiopental

- Other anxiolytic drugs
  - Antidepressants
  - Buspirone

- Other hypnotic agents
  - Antihistamines
  - Zaleplon
  - Zolpidem
  - Ramelteon

Benzodiazepines

- Most widely used anxiolytic drugs
- Safer and more effective than barbituates
- Mechanism of action: (GABA agonist)
  - 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, inhibiting formation of action potentials

Benzodiazepines

- Alprazolam
- Clonazepam
- Diazepam (Assival®)
- Lorazepam
- Triazolam
- Midazolam

Benzodiazepines

- Actions
  - Reduce anxiety at low doses
  - Sedative and hypnotic at higher doses
  - Anticonvulsant
  - Muscle relaxant
- Uses
  - Anxiety
  - Muscular disorders (Diazepam)
  - Seizures (Clonazepam, diazepam, lorazepam)
  - Sleep disorders (Triazolam is used for insomnia, it has a short duration of action)

Benzodiazepines

- Can cause dependence if given over a prolonged period of time
- Abrupt discontinuation of benzodiazepines causes withdrawal symptoms
  - Confusion
  - Anxiety
  - Agitation
  - Insomnia
  - Tension

Benzodiazepines

- Adverse effects
  - Drowsiness and confusion
  - Over dose (Respiratory depression, cardiovascular side effects)
- 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)

Antidepressants

- Antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs like escitalopram) or Selective serotonin and norepinephrine reuptake inhibitors (SNRIs like venlafaxine) maybe used alone or with a benzodiazepine for chronic anxiety

Buspirone

- Useful for chronic treatment of generalized anxiety disorder.
- Not effective for short-term or as needed treatment of anxiety disorders
- Acts through dopamine and serotonin receptors
- More selective for anxiety
- Less sedation than benzodiazepines
- No anticonvulsant or muscle relaxant activity
- No dependence
- Less side effects than benzodiazepines

Barbiturates

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

Barbiturates

- Thiopental
- Pentobarbital
- Phenobarbital

Barbiturates

- Mechanism of action: (GABA agonist)
  - Bind to $GABA_A$ receptors enhancing GABA transmission by prolonging the duration of chloride channel opening
  - Block excitatory glutamate receptors

Barbiturates

- Actions
  - CNS depressant (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 depressants (overdose causes respiratory depression and death)

Barbiturates

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

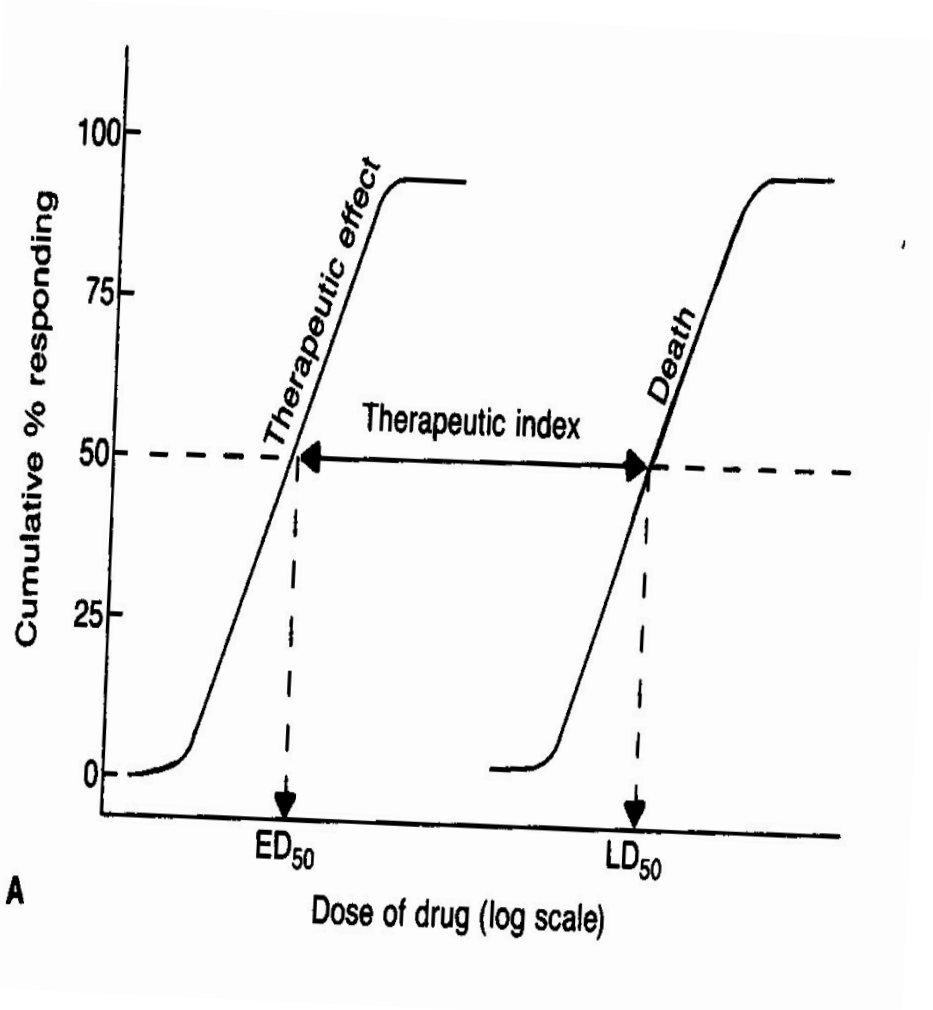
Barbiturates

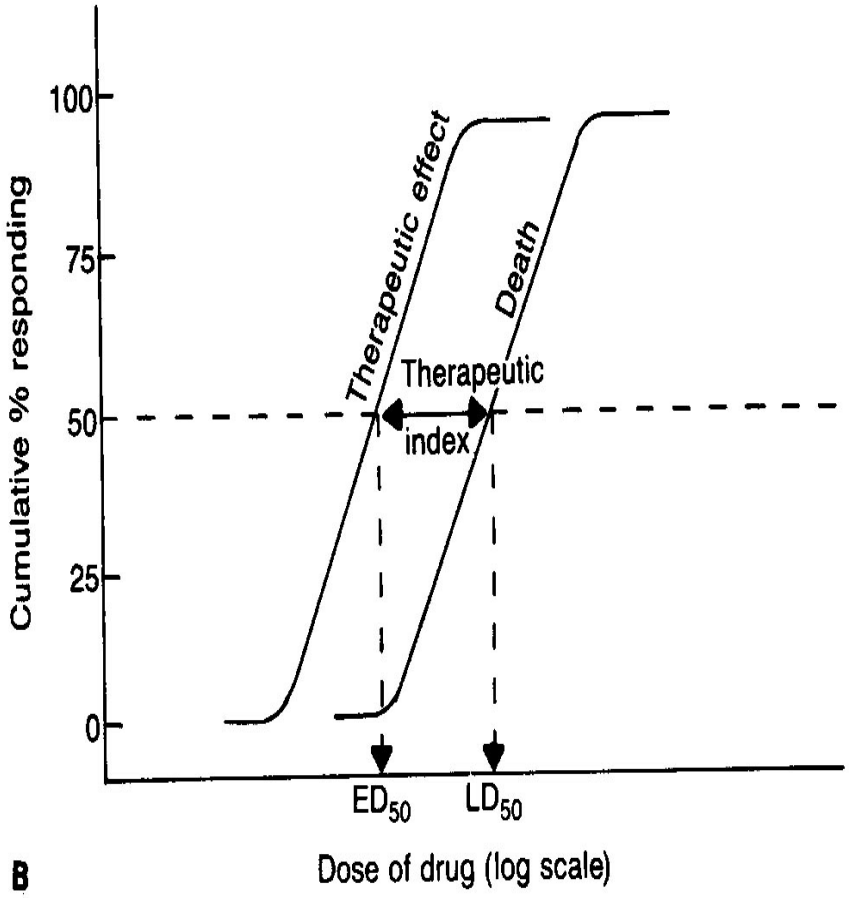
- Adverse effects
  - Drowsiness and impaired concentration
  - Addiction
  - Nausea
  - Vertigo
  - Tremors
- Precautions: can cause enzyme induction, drug interactions
- Abrupt withdrawal causes tremors, anxiety, weakness, restlessness, nausea, seizures, delirium and cardiac arrest
- Toxicity: There is no specific antidote available.

  Artificial respiration, purging the stomach of its contents, hemodialysis may be necessary

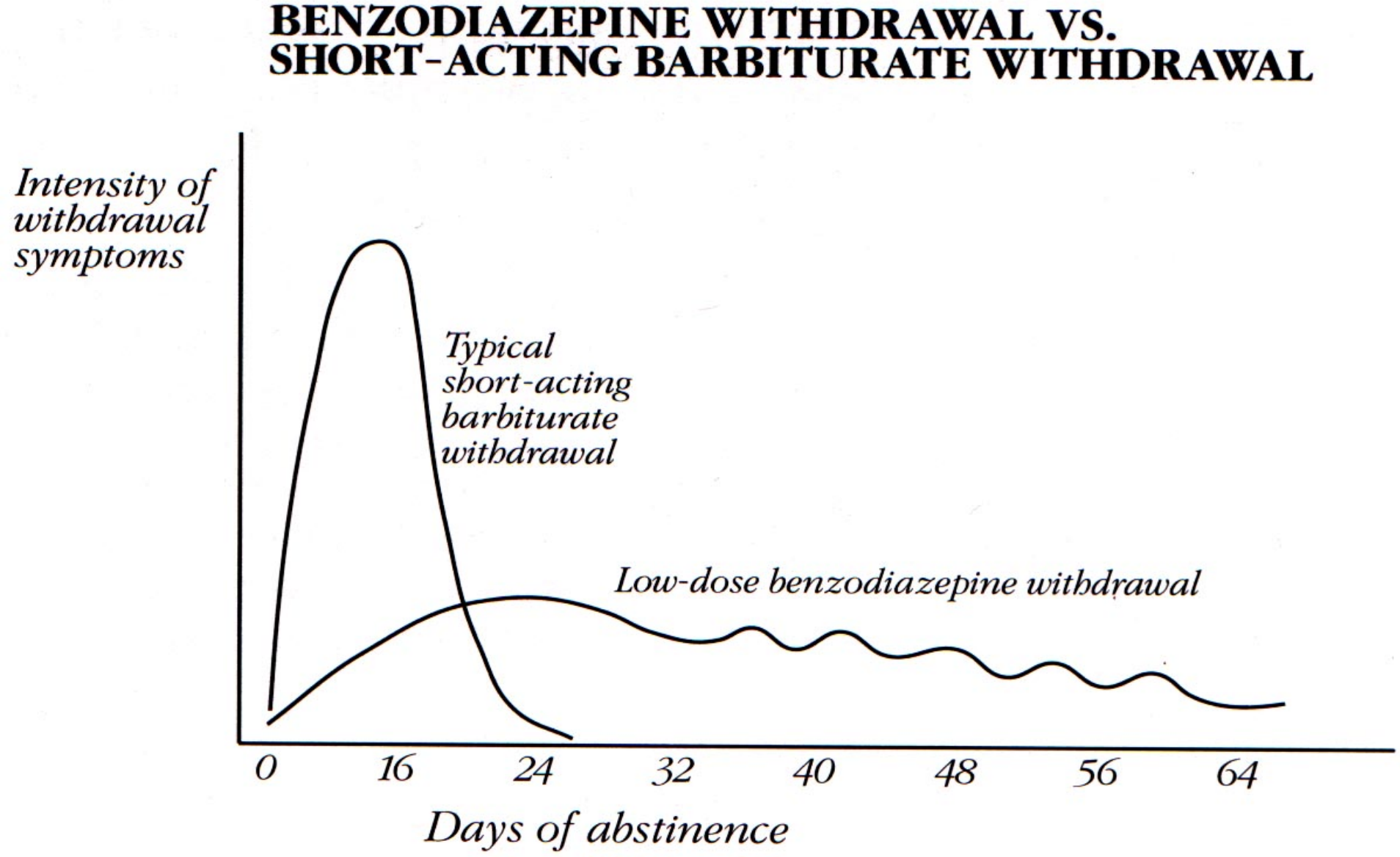
Acidification of urine

TI's for Benzodiazepines vs. Barbiturates





Relative Abuse Liability



Other hypnotic agents

- Antihistamines
  - Diphenhydramine
  - Effective for mild insomnia
  - Low risk
- Zolpidem
  - Binds to benzodiazepine receptor (not a benzodiazepine)
  - No anticonvulsant or muscle relaxing effects
  - Adverse effects: day time drowsiness, nightmares
- Zaleplon
  - Similar to zolpidem
  - Fewer adverse effects

- Ramelteon
  - Melatonin Receptor Agonist
  - Useful as a sleep-inducer
  - No tolerance, dependence, rebound hyperinsomnia, or abuse liability