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ANXIOLYTICS

ANXIETY

Anxiety is an emotional state combining fear and distress, expressed through psychological and physical symptoms. It is a normal component of human psychology but becomes pathological when it disrupts intellectual functioning.

There are different types of anxiety disorders:

- Generalized anxiety
- Post-traumatic stress disorder
- Social anxiety
- Obsessive-compulsive disorder (OCD)
- Specific phobias
- Panic disorder

- **ANXIOLYTICS: Minor tranquilizers**

Psychotropic drugs (psycholeptics and thymoleptics) that reduce anxiety in both its psychological and physical manifestations (reduce mental activity).

They include several classes:

1. Benzodiazepines (BZD) → most commonly used
2. BZD-like drugs
3. Carbamates → withdrawn from the market
4. Antihistamines
5. Others: antidepressants, beta-blockers, neuroleptics, buspirone

BENZODIAZEPINES

Etymology

- **Benzo**: addition of a benzene ring
- **Azepine**: heterocycle where carbon atoms are replaced by nitrogen
- **Di**: two carbon atoms replaced by nitrogen
- Structure includes an additional benzene ring (cycle C)
- Variations depend on substituents
- Nitrogen atoms may be in positions 1,4 – 1,5 – or 3,4

Structure-Activity Relationship

- Activity increases with electronegativity at R7:
  $CF_3 > Br > Cl > F > H$
- Nitroso derivatives: hypnotic or antiepileptic
- Halogenated derivatives: anxiolytic
- R1 (-CH_3) → increases activity
- R3 (-COOH) → prodrug
- Removing active group → loss of activity (Flumazenil)
- Halogen substitution increases activity

Physicochemical Properties

- Weak bases
- Liposoluble (especially hypnotics)
- Soluble in ethanol
- Conjugation due to double bond and nitrogen

Pharmacokinetics

Absorption

- Oral: rapid and complete (30 min to 6 hours)
- IM: slower and irregular
- Rectal: useful in pediatric seizures

Distribution

- Lipophilic → good tissue binding
- Cross BBB and placenta
- Plasma protein binding: 75–95%

Metabolism

- Hepatic metabolism
- Phase I + glucuronidation
- Main metabolite: **Nordiazepam (half-life 65h)** → converted to oxazepam

Elimination

- Mainly urinary (glucuronides)
- Minor biliary route
- Present in breast milk

Half-life:

- Short (<5h): Triazolam
- Intermediate (5–20h): Lorazepam, Bromazepam
- Long (>24h): Diazepam

Factors affecting kinetics: age, food, alcohol, liver/kidney disease

Mechanism of Action

a) CNS action

- Bind to GABA receptor
- Increase GABA affinity
- Increase chloride influx → hyperpolarization
  → **decreased neuronal excitability (anxiolysis)**

They have multiple effects:

- Anxiolytic
- Hypnotic
- Anticonvulsant
- Muscle relaxant

b) Respiratory effects

- Decrease respiratory rate and volume
- Risk of apnea

c) Cardiovascular effects

- Decreased cardiac output
- Decreased blood pressure
- Heart rate unchanged

d) Other effects

- Ocular hypotonia
- Vasodilation
- Slowed intestinal transit
- Increased heat loss
- Transient hyperglycemia

INDICATIONS

- Psychiatry: anxiety, alcohol withdrawal
- Neurology: epilepsy
- Anesthesiology: premedication

ADVERSE EFFECTS

- Sedation and drowsiness
- Memory impairment (anterograde amnesia)
- Tolerance and dependence
- Withdrawal syndrome
- Paradoxical effects
- Depression
- Muscle hypotonia
- Respiratory depression

CONTRAINDICATIONS

Absolute

- Severe respiratory failure
- Sleep apnea
- Severe hepatic failure
- Hypersensitivity

Relative

- Alcohol use
- Pregnancy and breastfeeding
- Depression
- Myasthenia
- Driving

INTERACTIONS

- Pharmacokinetic: enzyme inducers/inhibitors
- Pharmacodynamic: alcohol, opioids

ACUTE TOXICITY

Context

- Accidental or intentional overdose

Symptoms

- Agitation → sedation → coma
- Respiratory depression
- Hypotension

Prognosis

- Usually favorable

TREATMENT

- Symptomatic (ventilation)
- Activated charcoal
- Flumazenil (specific antidote)

CHRONIC TOXICITY

- Cognitive impairment
- Reduced performance
- Confusion (elderly)
- Depression

ANALYSIS

- Immunoassay screening
- Spectrophotometry
- Chromatography (HPLC, GC)

BZD-LIKE DRUGS

- Similar pharmacological effects
- Examples: Zopiclone, Zolpidem
- Low toxicity
- Minimal dependence

CARBAMATES

- First anxiolytics (1950)
- Example: Meprobamate

Mechanism

- Block spinal polysynaptic reflexes

Effects

- Sedative, anxiolytic, hypnotic
- Higher toxicity than BZD

ANTIHISTAMINES (Hydroxyzine)

Effects

- Sedative
- Anticholinergic

Toxicity

- Therapeutic dose: mild allergy
- Toxic dose: agitation, coma, convulsions

Treatment

- Gastric decontamination
- Ventilation
- Diazepam for seizures