Tranquilizers & Sedative-Hypnotics
Tranquilizer or anxiolytic:
Drugs used therapeutically to treat agitation or anxiety

Sedative-Hypnotic:
drugs used to sedate and aid in sleep

Original sedatives (before development of barbiturates):
- brandy, chloral hydrate, bromides, opium
  - only marginally effective, unwanted side-effects.

Barbiturates (1860s) Derivatives of barbituric acid
- 1000s of different barbiturates developed
- ultra short acting, short acting, medium acting and long acting.
- 50 marketed.

By 1990s, barbiturates replaced by benzodiazepines - exceptions: phenobarbital – seizures.
BARBITURATES

Classification

(1) Ultra-short-acting:
   act in seconds, duration 30min.
   **Thiopental**: anesthesia

(2) Short-acting
   duration 2h. **Secobarbital** hypnotic

(3) Intermediate-acting
   duration 3-5h. **Amobarbital** hypnotics.

(4) Long-acting
   duration greater than 6h. **Phenobarbital**.

Therapeutic uses: antiepileptic agents at low doses.
Barbiturates depress the CNS at all levels in a dose-dependent fashion. Now it mainly used in **anesthesia** and treatment of **epilepsy**. Use as sedative-hypnotic agents is no longer recommended.

**Reasons:**
(1) have a narrow therapeutic-to-toxic dosage range.
(2) suppress REM sleep.
(3) Tolerance develops relatively quickly.
(4) have a high potential for physical dependence and abuse.
(5) potent inducers of hepatic drug-metabolizing enzymes.
MECHANISM OF ACTION
Barbiturates prolong the duration of the opening of GABA-activated chloride channels. (2) At high doses, barbiturates can inhibit the release of the Ca$^{2+}$-dependent neurotransmitter.

Pharmacokinetics
High lipid solubility (Ultra-short, short) Rapid transport across BBB, short onset. Removal from the brain by redistribution to the other tissues results in short duration of action. Barbiturates and their metabolites are excreted via the renal route. Alkalization of the urine expedites the excretion of barbiturates.
Therapeutic uses
Sedative-hypnotic agents (No longer used)
Used in the emergency treatment of convulsions as in \textit{status epileptics}.
Anesthetic (or be given before anesthetic)
Treatment of \textit{hyperbilirubinemia and kernicterus} in the neonate. (Barbiturates enhance the conjugation and excretion of bilirubin).
Adverse effects

- **After effect:** hangover---dizzy, drowsiness, amnesia, impaired judgment, disorientation.
- **Tolerance:** due to down-regulation of receptors and induction of hepatic drug-metabolizing enzymes.
- **Dependence:** psychologic & physiologic dependence.

Withdrawal symptoms: excitation, insomnia, tremor, anxiety, hallucinations and sometimes convulsions.

- **Depressant effect on respiration.**
- can cross the placental barrier during pregnancy and secrete to breast milk.
- **Others:** Skin eruptions and porphyria (problem with the production of haem)
Treatment of acute overdosage

- An overdose can result in coma, diminished reflexes, severe respiratory depression, hypotension leading to cardiovascular collapse, and renal failure.

- Treatment:
  - supporting respiration and circulation.
  - (2) alkalinizing the urine and promoting diuresis.
  - (3) Hemodialysis or peritoneal dialysis.
Benzodiazepines
The first, chlordiazepoxide synthesized by accident in 1961. Derivative of 1,4- benzodiazepines. About 20 are available for clinical use. Similar in their pharmacological actions, with some degree of selectivity. Difference in pharmacokinetic behavior are more important than difference in profile of activity.
PHARMACOLOGICAL EFFECTS

1. Reduction of anxiety and aggression
2. Sedation and induction of sleep:
   (1) sleep onset is decreased.
   (2) Duration of stage 2 NREM sleep is increased.
   (3) Duration of slow-wave sleep is decreased.

Reasons for their extensive clinical use:
(1) great margin of safety.
(2) little effect on REM sleep.
(3) little hepatic microsomal drug-metabolizing enzymes.
(4) slight physiologic and psychologic dependence & withdrawal syndrome.
(5) less adverse effects.
3. Anticonvulsant and antiseizure
Highly effective anticonvulsant agents. **Diazepam & lorazepam** are used to treat **status epilepticus**.
**Clonazepam** is used to treat **Petit mal epilepsy**.
**Nitrazepam** is used in **Infantile Spasms**.

4. Muscle relaxation
Relax contracted muscle in joint disease or muscle spasm.

5. Other effects
Lead to temporary **amnesia**, decrease the dosage of anesthetic so decrease their depressant effects on respiratory & cardiovascular functions.
MECHANISM OF ACTION

Enhance the response to GABA, by increasing in the frequency of channel opening, but no change in the conductance or mean open time.

Bind specifically to a regulatory site on the receptor, distinct from the GABA binding site, and enhanced receptor affinity for GABA.

The GABAA-receptors is a ligand -gated ion channel consisting of a pentameric assembly of subunits.
PHARMACOKINETIC ASPECTS

Well absorbed orally.
They bind strongly to plasma protein
High lipid solubility, accumulate gradually in body fat. Distribution volumes is big.
Metabolism in the liver, some metabolites are active. Excreted as glucuronide conjugates in the urine.
Vary in duration & can be roughly divided into
1. Short-acting: **Triazolam, Oxazepam**
   (15-30min, t1/2 2-3 h)
2. Medium-acting: **Estazolam, Nitrazepam**
   (40min, t1/2 5-8 h)
3. Long-acting: **Diazepam** (20-100h), **Flurazepam** (50h).
Acute toxicity:
less dangerous than other sedative-hypnotic drugs. Cause prolonged sleep, without serious depression of respiration or cardiovascular system. 

**Flumazenil** is an effective antagonist

**Side-effects:**
drowsiness, confusion, amnesia, impaired coordination.

**Main disadvantages**
interaction with alcohol.
long-lasting hangover.
the development of dependence.
OTHER BENZODIAZEPINE RECEPTOR AGONISTS

Zolpidem & Zaleplon

Structurally unrelated to the benzodiazepines
Bind to benzodiazepine receptors and
Facilitate GABA-mediated inhibition.

Zolpidem

Preserves deep sleep (stages 3 & 4)
& has minor effects on REM sleep.

Weak anxiolytic, anticonvulsant,& skeletal muscle relaxant properties at therapeutic doses.
Rapid onset & short duration. Half-life is 2.5 hours, sufficient to provide for a normal 8 hours of sleep.

**Side effects:**
drowsiness, dizziness, and diarrhea.
Increase the depressant effects of other sedatives.

**Zaleplon**
Rapid onset & a half-life of 1 hour,
Used for treatment of *sleep onset insomnia*,
but does not ensure a full 8 hours of sleep.
Extensively metabolized by aldehyde dehydrogenase, so less than 1% of a dose is excreted unchanged.
Buspirone
Partial agonist at the serotonin 5-HT1A receptor.

**Pharmacokinetics**
well absorbed from GIT peak in 1 to 1.5 hours
95% bound to plasma proteins, extensively metabolized. Half life, 2-3 hours
One of the metabolic products is biologically active.

**Pharmacological Actions**
as effective as the benzodiazepines in the treatment of general anxiety disorder (GAD).
full anxiolytic effect takes several weeks to develop,
little or **no sedative** effect & lacks the muscle relaxant & anticonvulsant properties of the benzodiazepines.

No potentiation of the CNS depressants.

**Clinical Uses**
General anxiety & in anxiety with depression.

**Adverse Effects**
Safe even in very high doses.
Dizziness, light-headedness, and headache.
Not addictive.
Increases BP in patients taking MAO inhibitors.
may increase plasma levels of haloperidol
SEDATIVES AND ANXIOLYTICS
WITH OTHER MAJOR USES

Antihistamines

Diphenhydramine, promethazine, & hydroxyzine
Used as sedative–hypnotics, since they produce some sedation sufficient for treatment of anxiety and sleep disturbance

Hydroxyzine is the antihistamine with the greatest use in the treatment of anxiety.
Often used to reduce the anxiety associated with anesthesia and surgery.

Produces sedation, dries mucous membranes (via an anticholinergic effect), & has antiemetic activity.
β- Adrenoceptor Blocking Agents

Propranolol

Useful in some forms of anxiety, particularly those that are characterized by somatic symptoms or by performance anxiety (stage fright).

They can lessen the severity & prevent many of the autonomic responses associated with anxiety, such as tremors, sweating, tachycardia, and palpitations.
Antidepressants

Tricyclic antidepressants & the selective serotonin reuptake inhibitors (SSRIs)

Effective when used in the treatment of several anxiety disorders:

General anxiety, obsessive-compulsive disorder, and several phobias, including agoraphobia (a fear of being in situations where escape might be difficult, or help wouldn't be available if things go wrong).

SSRIs are less toxic than the tricyclic antidepressants, so, their use in the treatment of anxiety is safer and less likely to produce serious side effects.
OLDER SEDATIVE–HYPNOTIC & ANXIOLYTIC AGENTS
Most of these compounds are no longer widely used. The barbiturates: **Pentobarbital, Amobarbital, Meprobamate, Glutethimide.**

**Chloral hydrate**
Developed in the late 1800s and is still used as a sedative–hypnotic agent. Has a disagreeable smell and taste. Rapidly reduced to **trichloroethanol**, which is the active metabolite. Produces a high incidence of gastric irritation and allergic responses. Occasionally causes cardiac arrhythmias.
NONPRESCRIPTION DRUGS
Most of these over-the-counter products have antihistamines, such as diphenhydramine, or promethazine.

Ethanol
widely used to relieve anxiety & produce sedation. Its effects are additive with other CNS depressants.

Symptoms of acute alcohol intoxication:
increase self-confidence, loss of inhibitions, euphoria, and loss of judgment.

With increasing doses motor and intellectual impairment become prominent.

Chronic abuse of ethanol leads to severe liver impairment.