Benzodiazepines

All benzodiazepines exhibit following actions (to greater or lesser extent):

1. **Anxiety reduction** (by selectively inhibiting neuronal circuits in limbic system) - at low doses.
2. **Sedative & hypnotic**: at higher doses, certain benzodiazepines produce hypnosis (artificially-produced sleep), but not general anesthesia (safe drugs!).
   - benzodiazepines suppress REM sleep (as do barbiturates); after drug discontinuation - rebound of REM sleep (usually in form of nightmares)
   - antianxiety effect is more subject to tolerance than sedative-hypnotic effect!
3. **Anticonvulsant**: by increasing seizure threshold
4. **Skeletal muscle relaxant** (by presynaptic inhibition in spinal cord) - relax muscle spasticity

### MECHANISM OF ACTION

Benzodiazepines bind to specific, high affinity **BENZODIAZEPINE RECEPTORS** (found only in CNS) - sites on cell membrane, which are **separate from but adjacent to GABA receptor** (allosteric sites of GABA, receptor).

- binding of benzodiazepines **enhances GABA receptor affinity for GABA** → more frequent opening of adjacent Cl channels → **enhanced hyperpolarization** → **inhibition of neuronal excitability**.

*Benzodiazepines and GABA mutually increase affinity of their binding sites.

**Clinical effects** of various benzodiazepines correlate well with each drug's binding affinity for GABA's receptor–Cl channel complex.

### PHARMACOLOGIC ACTIONS

Benzodiazepines have no antipsychotic activity, no analgesic activity, and do not affect autonomic nervous system (e.g. minimal effect on CV system)

### PHARMACOKINETICS

- **benzodiazepines are lipophilic**: rapidly and completely absorbed after oral administration widely distributed throughout body, cross BBB (plasma levels reflect brain levels).
- highly lipid-soluble benzodiazepines produce more rapid effect (experienced as "high")
- metabolized by hepatic microsomes; long-acting benzodiazepines form active metabolites (prolong drug effect duration).
- excreted in urine as glucuronides or oxidized metabolites.
- duration of action is very important clinically - determines therapeutic use.

### LONG-ACTING benzodiazepines (T1/2: 1–4 days)

- have active metabolites with long half-lives.
- may accumulate.

### CHLORZEPAXONE (T1/2: 2–4 days) - low potency; first developed benzodiazepine.

**DIAZEPAM** (T1/2 = 2–4 days) - intermediate potency.

**FLUZAPAZEM** (T1/2 = 2–3 days = 40–100 hours) - classical hypnotic.

**CLONAPAZEM** (T1/2 = 2–3 days = 20–80 hours) - classical antiepileptic.

**CLOBAZAM** (T1/2 = 10–50 hours) - non-standard benzodiazepine (80% reduced anxiety effect + 4–10-fold decreased sedative effects) - used as antiepileptic.

**CLORAZEPATE** (T1/2 = 2–4 days)*

**HALAZEPAM** (T1/2 = 2–4 days)*

**PRAZEPAM** (T1/2 = 2–4 days)*

**NITRAZEPAM** (T1/2 = 1–1.5 days)

**QUAZEPAM** (T1/2 = 1–2 days) - benzodiazepine derivative selective for subtype 1 of benzodiazepine receptor.

*DIAPZEPAM prodrg (must be metabolized to DIAZEPAM, to become active).

### INTERMEDIATE-ACTING benzodiazepines (10–20 hours)

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**INTERMEDIATE A**

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**PHARMACOKINETICS**

- **duration of action** is very important clinically - determines therapeutic use.

### BENZODIAZEPINES

- most widely used **ANXIOLYTICS** (s. MINOR TRANQUILIZERS).

N.B. since all anxiolytics also cause some sedation, same drugs often function clinically as both anxiolytics and hypnotics.

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**INTERMEDIATE A**

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**PHARMACOKINETICS**

- **duration of action** is very important clinically - determines therapeutic use.


SHORT-ACTING benzodiazepines (3-8 hours)

THALIDOMIDE (T1/2 = 1-3 hours) – classical hypnotic

BENZODIAZEPINES – longer acting than short-acting

• individual benzodiazepines show small differences in their relative anxiety, anticonvulsant-sedative, anxiolytic properties; variable pharmacokinetic features are important in drug choice.

• benzodiazepines have largely replaced barbiturates and neuroleptics, since benzodiazepines are more effective and safer.

1. Anxiety disorders – benzodiazepines are most effective anxiolytics!!!

• do not use to alleviate normal stress of everyday life.

• use only for short periods (addiction potential).

• longer acting agents (e.g. DIAZEPAM) at low doses are preferred.

• ALPRAZOLAM is most effective for panic disorders.

2. Sleep disorders – benzodiazepines are preferred drugs (not all of benzodiazepines are useful as hypnotics, although all have sedative effects) – drug should be given for only limited time (usually <2-4 weeks); use higher doses than for anxiety, most commonly prescribed:

   SHORT-ACTING benzodiazepines (e.g. TRIAZOLAM) – useful for sleep induction.

   INTERMEDIATE-ACTING benzodiazepines (e.g. TEMAZEPAM) – useful for frequent awakenings;

   LONG-ACTING benzodiazepines – useful for sleep induction and frequent awakenings; also increase sleep duration; may result in daytime sedation.

   FLURAZEPAM causes less suppression of REM sleep (than other benzodiazepines), no rebound insomnia; with continued use, maintains effectiveness for up to 4 weeks.

3. Seizures:

   chronic treatment of epilepsy – CLONAZEPAM, LORAZEPAM, CLOBAZAM; terminating grand mal epileptic seizures and status epilepticus – DIAZEPAM (drug of choice), LORAZEPAM.

4. Muscular disorders (skeletal muscle spasms in muscle strain, spasticity from neurodegenerative disorders) – DIAZEPAM.

5. Acute treatment of alcohol withdrawal – CYPROHEXAMIDE, CLOBAZAM, DIAZEPAM, LORAZEPAM.

ADVERSE EFFECTS

1. Drowsiness - most common side effect.

2. Cognitive impairment (es. memory problems - decreased long-term recall and acquisition of new knowledge); may cause or aggravate depression!

3. Impaired psychomotor performance; cause falls in elderly; anxia occurs at high doses.

4. Tolerance to sedative effects (but not to anxiolytic or impaired performance effects).

5. Dependence (psychological and physical) – generally rare; develops if high doses are given over prolonged period; abrupt discontinuation – withdrawal symptoms: confusion, anxiety, agitation, rebound insomnia, influenza-like muscle aches, seizures.

   N.B. in long-acting benzodiazepines, withdrawal may not occur until number of days after discontinuation and abstinence symptoms may last up to 1 year!

   (leading to prolonged use of benzodiazepine to suppress withdrawal);

   short-acting benzodiazepines induce more abrupt, more severe, but shorter withdrawal reactions.

   Do not prescribe benzodiazepines for patients with history of substance dependence!

6. Potentiation of other CNS depressants (incl alcohol).

   N.B. benzodiazepines per se are very safe.

BENZODIAZEPINE OVERDOSE

• frequent, but very rarely fatal unless other CNS depressants are taken concurrently (benzodiazepines have high therapeutic index).

• CNS depression (up to coma) from ethanol intoxication is hallmark.

   diagnosis:

   • ECG
   • EEG – widespread high-voltage beta activity
   • serum levels are unhelpful
   • always screen for CNS depressant co-ingestions!

   treatment (most people recover without intervention)

   • activated charcoal
   • specific antidote – FLUMAZENIL (see below) – has adverse effects, so indicated not in every case.

   • dialysis ineffective (benzodiazepines have high protein binding).

LORAZEPAM (T1/2 = 10-20 hours) see also p. Rx3 >>

TEMAZEPAM (T1/2 = 6-15 hours) – classical hypnotic

ALPRAZOLAM (T1/2 = 14 hours) – high potency, high lipid solubility, no active metabolites.

ESTAZOLAM (T1/2 = 16-18 hours)

OXAZEPAM (T1/2 = 6-10 hours)

THERAPEUTIC USES

• individual benzodiazepines show small differences in their relative anxiety, anticonvulsant-sedative, anxiolytic properties; variable pharmacokinetic features are important in drug choice.

• benzodiazepines can be used to treat insomina as well as anxiety!!!

• benzodiazepines have largely replaced barbiturates and neuroleptics, since benzodiazepines are more effective and safer.

Diagnosis: See below. Always screen for CNS depressant co-ingestions!
**BENZODIAZEPINES**

**BENZODIAZEPINE ANTAGONISTS**

**FLUMAZENIL** - GABA receptor antagonist (competitively blocks benzodiazepine receptors) - can rapidly reverse effects of benzodiazepines.

- available only for IV administration. see p. S30 >>
- rapid onset but short duration ($T_{1/2} \approx 1$ hour);
  - frequent administration may be necessary for reversal of long-acting benzodiazepines.
- adverse effects:
  1) dizziness, nausea & vomiting, agitation - most common side effects.
  2) may precipitate withdrawal in dependent patients.
  3) may cause seizures if benzodiazepine is used to control seizure activity or if patient co-ingested epileptogenic agents (e.g. cyclic antidepressants).
  4) ICP↑ in head trauma

- contraindications:
  1) epilepsy controlled with benzodiazepine
  2) benzodiazepine dependency
  3) co-ingestion of epileptogenic agents (e.g. cyclic antidepressants)
  4) anticholinergic or sympathomimetic toxidrome.

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