Benzodiazepines

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Benzodiazepines are most widely used **ANXIOLYTICS** (s. **MINOR TRANQUILIZERS**).

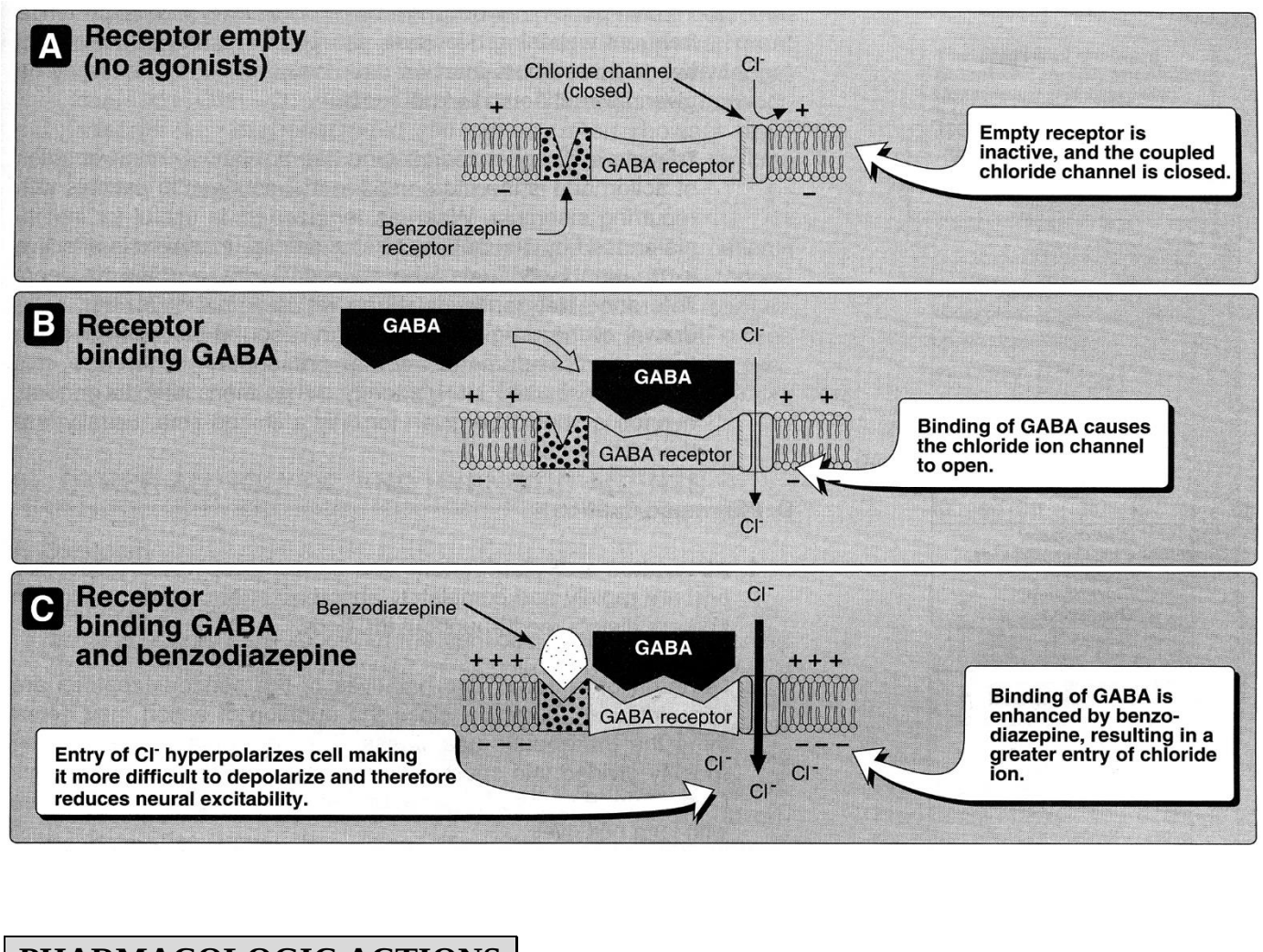
N.B. since all anxiolytics also cause some sedation, same drugs often function clinically as both ***anxiolytics*** and ***hypnotics***.

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 $GABA_A$ receptor (allosteric sites of $GABA_A$ receptor).

- binding of benzodiazepines **enhances $GABA_A$ 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 **$GABA_A$ 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 c/v system).

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 supress REM sleep (as do barbiturates); after drug discontinuance - rebound of REM sleep (usually in form of nightmares).
   - antianxiety effect is less subject to tolerance than sedative-hypnotic effect!
3. **Anticonvulsant** (by increasing *seizure threshold*) - only several benzodiazepines. see p. E3 >>
4. **Skeletal muscle relaxant** (by increasing presynaptic inhibition in *spinal cord*) - relax muscle spasticity.

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 ($T_{1/2}$ – 1-4 days)

- have active metabolites with long half-lives.
- may accumulate.
- usually administered ×2/d (to minimize oversedating peaks).

CHLORDIAZEPOXIDE ($T_{1/2}$ – 2-4 days) – low potency; first developed benzodiazepine.
DIAZEPAM ($T_{1/2}$ = 2-4 days) – intermediate potency.
FLURAZEPAM ($T_{1/2}$ = 2-3 days ≈ 40-100 hours) – classical **hypnotic**.
CLONAZEPAM ($T_{1/2}$ = 2-3 days ≈ 20-80 hours) – classical **antiepileptic**. see p. E3 >>
CLOBAZAM ($T_{1/2}$ = 10-50 hours) – non-standard benzodiazepine (80% reduced anxiolytic activity + 10-fold decreased sedative effects) – used as **antiepileptic**. see p. E3 >>
CLORAZEPATE ($T_{1/2}$ = 2-4 days)*
HALAZEPAM ($T_{1/2}$ = 2-4 days)*
PRAZEPAM ($T_{1/2}$ = 2-4 days)*
NITRAZEPAM ($T_{1/2}$ = 1-1,5 days)
QUAZEPAM ($T_{1/2}$ = 1-2 days) - benzodiazepine derivative selective for **subtype 1 of benzodiazepine receptor**.

*DIAZEPAM **prodrug** (must be metabolized to DIAZEPAM, to become active)

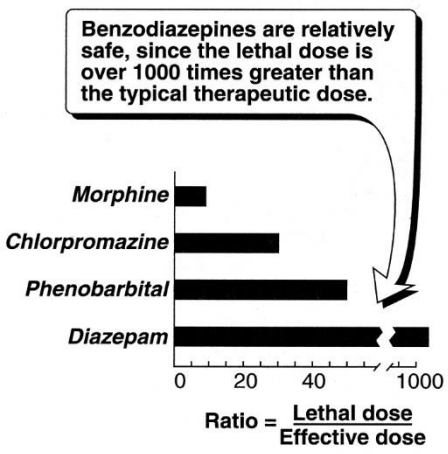
INTERMEDIATE-ACTING benzodiazepines (10-20 hours)

LORAZEPAM ($T_{1/2}$ = 10-20 hours) see also p. Rx3 >>
TEMAZEPAM ($T_{1/2}$ = 8-15 hours) – classical **hypnotic**
ALPRAZOLAM ($T_{1/2}$ = 14 hours) – high potency; high lipid solubility, no active metabolites.
ESTAZOLAM ($T_{1/2}$ =16-18 hours)
OXAZEPAM ($T_{1/2}$ = 6-10 hours)

SHORT-ACTING benzodiazepines (3-8 hours)
TRIAZOLAM ($T_{1/2}$ =1,5-3 hours) – classical **hypnotic**
MIDAZOLAM – shortest acting ($T_{1/2}$ =1.5-2.3 hours), high potency; used as **amnestic** in premedication. see also p. Rx3 >>

THERAPEUTIC USES

- individual benzodiazepines show *small differences* in their relative anxiolytic-anticonvulsant-sedative properties; variable pharmacokinetic features are important in drug choice.
  Any benzodiazepine can be used to treat **INSOMNIA** as well as **ANXIETY**!!!
- benzodiazepines have largely replaced **barbiturates** and *MEPROBAMATE*, 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**.
   *tolerance develops within few days (drug withdrawal → rebound insomnia!!!).

   INTERMEDIATE-ACTING **benzodiazepines** (e.g. TEMAZEPAM) - useful for frequent **awakenings**; do not affect sleep latency.

   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.

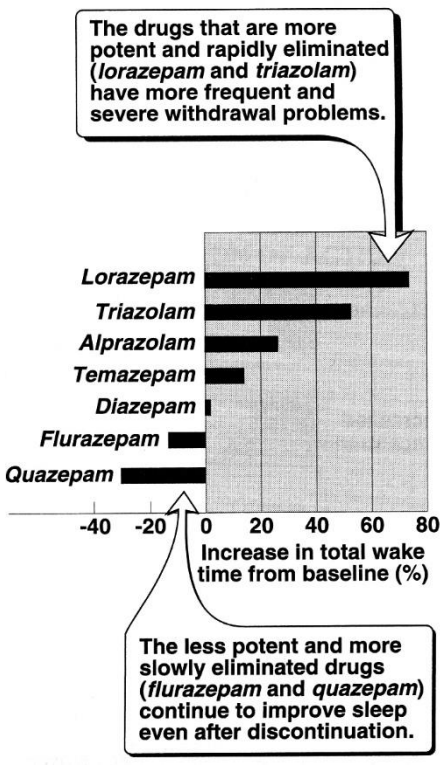
3. **Seizures**:
   chronic treatment of epilepsy – CLONAZEPAM, CLOBAZAM, CLORAZEPATE;
   terminating grand mal epileptic seizures and status epilepticus - DIAZEPAM (drug of choice), LORAZEPAM.

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

5. Acute treatment of **alcohol withdrawal** - CHLORDIAZEPOXIDE, CLORAZEPATE, DIAZEPAM, OXAZEPAM, LORAZEPAM.

ADVERSE EFFECTS

1. **Drowsiness** - most common side effect.
2. **Cognitive impairment** (esp. memory problems - decreased long-term recall and acquisition of new knowledge); may cause or aggravate depression!
3. **Impaired psychomotor performance**; cause falls in elderly; ataxia 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 ≈ ethanol intoxication) is hallmark. also see p. Psy23 >>
- 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).

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);
  - in benzodiazepine overdose, flumazenil will reverse coma within 1-2 minutes.
  - 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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