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***.

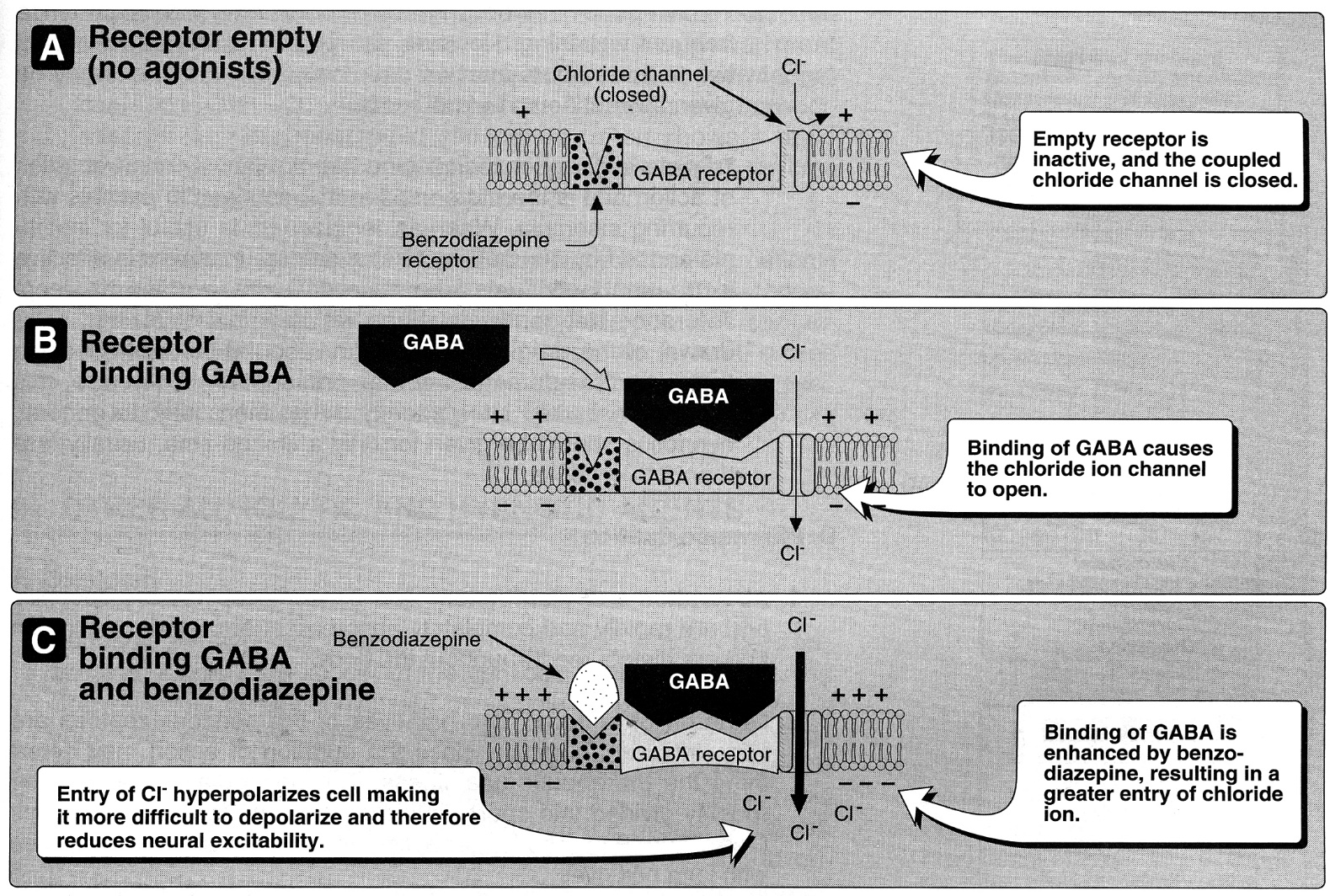
Mechanism of action

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

* binding of benzodiazepines **enhances GABAA 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 **GABAA 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 >>](http://www.neurosurgeryresident.net/E.%20Epilepsy%20and%20Seizures\E3.%20Antiepileptic%20Drugs.pdf)
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** (T1/2 –1-4 days)

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

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

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

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

**clonazepam** (T1/2 **=** 2-3 days ≈ 20-80 hours) – classical **antiepileptic**. [see p. E3 >>](http://www.neurosurgeryresident.net/E.%20Epilepsy%20and%20Seizures\E3.%20Antiepileptic%20Drugs.pdf)

clobazam (T1/2 = 10-50 hours) – non-standard benzodiazepine (80% reduced anxiolytic activity + 10-fold decreased sedative effects) – used as antiepileptic. [see p. E3 >>](http://www.neurosurgeryresident.net/E.%20Epilepsy%20and%20Seizures\E3.%20Antiepileptic%20Drugs.pdf)

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**.

\*diazepam prodrug (must be metabolized to diazepam, to become active)

**intermediate-acting** **benzodiazepines** (10-20 hours)

**lorazepam** (T1/2 **=** 10-20 hours)[see also p. Rx3 >>](http://www.neurosurgeryresident.net/Rx.%20Treatment%20Modalities\Rx3.%20Other%20Sedatives-Anxiolytics.pdf#Lorazepam)

**temazepam** (T1/2 **=** 8-15 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)

**short-acting** **benzodiazepines** (3-8 hours)

**triazolam** (T1/2 **=**1,5-3 hours) – classical **hypnotic**

**midazolam** – shortest acting (T1/2 **=**1.5-2.3 hours), high potency; used as **amnestic** in premedication. [see also p. Rx3 >>](http://www.neurosurgeryresident.net/Rx.%20Treatment%20Modalities\Rx3.%20Other%20Sedatives-Anxiolytics.pdf#Midazolam)

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. | D:\Viktoro\Neuroscience\Rx. Treatment Modalities\00. Pictures\benzodiazepine safety.jpg |

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**.

1. **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.

1. **Seizures:**

chronic treatment of epilepsy –clonazepam, clobazam, clorazepate;

terminating grand mal epileptic seizures and status epilepticus - diazepam(drug of choice), lorazepam.

1. **Muscular disorders** (skele­tal muscle spasms in muscle strain, spasticity from neurodegenerative disorders) - diazepam.
2. 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!   * 1. **Potentiation of other CNS depres­sants** (incl. alcohol).   N.B. *benzodiazepines per se are very safe*. | D:\Viktoro\Neuroscience\Rx. Treatment Modalities\00. Pictures\benzodiazepine withdrawal severity.jpg |

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 >>](http://www.neurosurgeryresident.net/Psy.%20Psychiatry\Psy23.%20Substance-related%20Disorders.pdf#Sedatives)
* 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 >>](http://www.neurosurgeryresident.net/S.%20Symptoms,%20Signs,%20Syndromes\S30-34.%20Alterations%20of%20Consciousness,%20Coma,%20Vegetative%20State,%20Brain%20Death\S30.%20Alterations%20in%20Level%20of%20Consciousness,%20Coma.pdf#Flumazenil)
* *rapid onset* but *short duration* (T1/2 ­≈ 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.

Bibliography for “Benzodiazepines” → follow this [link >>](http://www.neurosurgeryresident.net/Rx.%20Treatment%20Modalities\Rx.%20Bibliography.pdf)

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