

Anxiolytic/Hypnotic Drugs 1

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BCPS

OVERVIEW

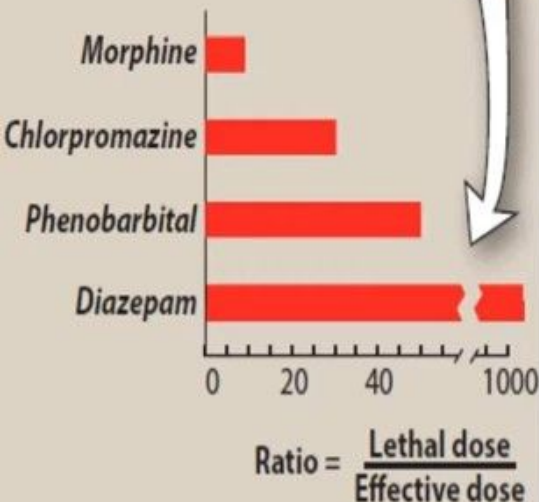
Disorders involving anxiety are among the most common mental disorders. Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that arises from either a known or an unknown source). The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, severe, chronic, debilitating anxiety may be treated with antianxiety drugs (sometimes called anxiolytics) and/or some form of psychotherapy. Because many antianxiety drugs also cause some sedation, they may be used clinically as both anxiolytic and hypnotic (sleep-inducing) agents. *Sedation* is characterized by decreased anxiety, motor activity, and cognitive acuity. *Hypnosis* is characterized by drowsiness and an increased tendency to sleep.

1. Generalized anxiety disorder (GAD) is characterized by 6 months or more of excessive worry or anxiety, generally with an unidentified cause.
2. Panic disorder is characterized by discrete periods of sudden, intense fear or terror, and feelings of impending doom. Usually, the precipitating cause is unknown, but the patient can become conditioned to believe it is attributable to some environmental cause.
3. Agoraphobia: Intense fear in two or more settings (mostly in the open or in public). These settings include using public transportation, being in open spaces, being in enclosed spaces, standing in line or being in a crowd, and being outside the home alone.
4. Social anxiety disorder is characterized by marked and persistent fear and anxiety in social or performance situations that are recognized as excessive or unreasonable. These situations are either avoided or endured with intense anxiety.
5. Specific phobias are characterized by intense fear or anxiety induced by a specific object.
6. OCD, which used to be classified as an anxiety disorder, now has its own designation. OCD is characterized by obsessive or intrusive thoughts that cannot be controlled and that are repetitive. Compulsions are ritualistic behaviors (e.g., washing the hands, combing the hair, cleaning the house).
7. PTSD, which also used to be classified as an anxiety disorder, has been moved to a category titled "Trauma- and Stressor-Related Disorders." PTSD follows a traumatic event. PTSD is characterized by increased arousal and avoidance of stimuli that approximate the original traumatic event.

BENZODIAZEPINES

Benzodiazepines are widely used anxiolytic drugs. They have largely replaced barbiturates and *meprobamate* in the treatment of anxiety and insomnia, because benzodiazepines are generally considered to be safer and more effective. Though benzodiazepines are commonly used, they are not necessarily the best choice for anxiety or insomnia. Certain antidepressants with anxiolytic action, such as the selective serotonin reuptake inhibitors, are preferred in many cases, and nonbenzodiazepine hypnotics and antihistamines may be preferable for insomnia.

Benzodiazepines are relatively safe, because the lethal dose is over 1000-fold greater than the typical therapeutic dose.



BENZODIAZEPINES

Long-acting

Chlordiazepoxide

Diazepam

Flurazepam

Intermediate-acting

Alprazolam

Clonazepam

Clorazepate

Estazolam

Lorazepam

Oxazepam

Quazepam

Temazepam

Short-acting

Triazolam

Midazolam

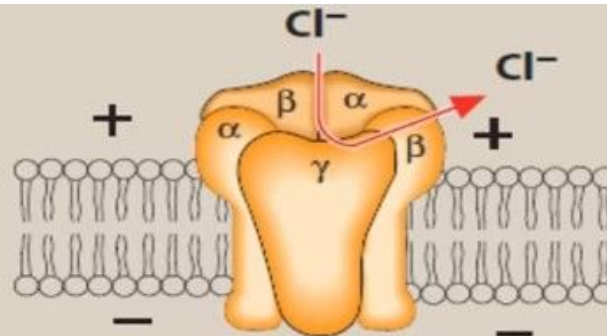
BENZODIAZEPINE ANTAGONIST

Flumazenil

Mechanism of action

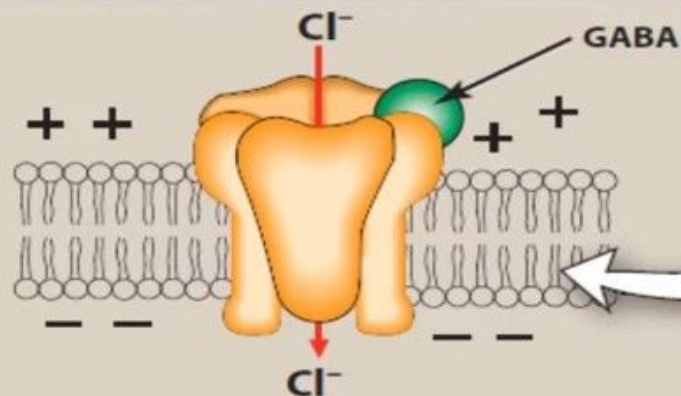
The targets for benzodiazepine actions are the γ -aminobutyric acid (GABAA) receptors. [Note: GABA is the major inhibitory neurotransmitter in the central nervous system (CNS).] The GABAA receptors are composed of a combination of five α , β , and γ subunits that span the postsynaptic membrane. For each subunit, many subtypes exist (for example, there are six subtypes of the α subunit). Binding of GABA to its receptor triggers an opening of the central ion channel, allowing chloride through the pore. The influx of chloride ions causes hyperpolarization of the neuron and decreases neurotransmission by inhibiting the formation of action potentials. Benzodiazepines modulate GABA effects by binding to a specific, high-affinity site (distinct from the GABA-binding site) located at the interface of the α subunit and the γ subunit on the GABAA receptor. Benzodiazepines increase the frequency of channel openings produced by GABA. The clinical effects of individual benzodiazepines correlate well with the binding affinity of each drug for the GABA receptor–chloride ion channel complex.

A Receptor empty
(no agonists)



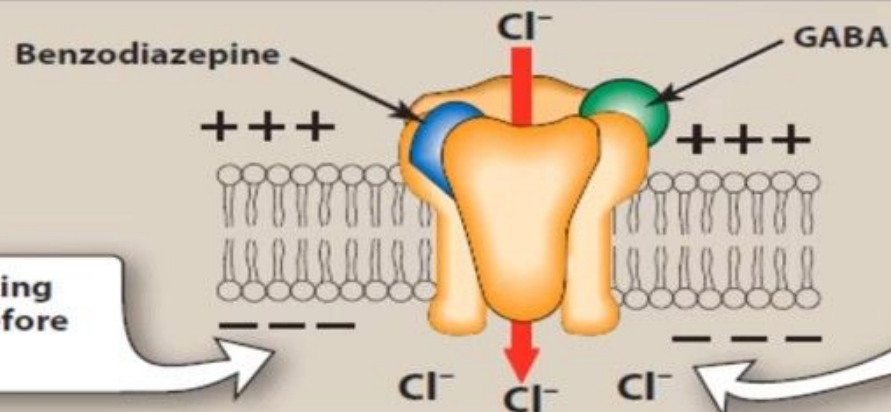
Empty receptor is inactive, and the coupled chloride channel is closed.

B Receptor binding GABA



Binding of GABA causes the chloride ion channel to open, leading to hyperpolarization of the cell.

C Receptor binding GABA and benzodiazepine



Entry of Cl^- hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.

Binding of GABA is enhanced by benzodiazepine, resulting in a greater entry of chloride ion.

Actions

Most benzodiazepines exhibit qualitatively similar therapeutic actions to some extent but differ in their relative lipid solubility, biotransformation, and elimination half-life.

1. **Reduction of anxiety:** At low doses, the benzodiazepines are anxiolytic. They reduce anxiety by selectively enhancing GABAergic transmission in neurons having the $\alpha 2$ subunit in their GABAA receptors, thereby inhibiting neuronal circuits in the limbic system of the brain.
2. **Sedative/hypnotic:** All benzodiazepines have sedative and calming properties, and some can produce hypnosis (artificially produced sleep) at higher doses. The hypnotic effects are mediated by the $\alpha 1$ -GABAA receptors.
3. **Anterograde amnesia:** Temporary impairment of memory with use of the benzodiazepines is also mediated by the $\alpha 1$ -GABAA receptors. The ability to learn and form new memories is also impaired.
4. **Anticonvulsant:** This effect is partially, although not completely, mediated by $\alpha 1$ -GABAA receptors.
5. **Muscle relaxant:** At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord, where the $\alpha 2$ -GABAA receptors are largely located. [Note: *Baclofen* is a muscle relaxant that is believed to affect GABA receptors at the level of the spinal cord.]
6. **Physical dependence:** Long-acting benzodiazepines (*diazepam*, *chlordiazepoxide*) are used to reduce the withdrawal symptoms of physical dependence associated with alcohol and long-term use of short-acting benzodiazepines and barbiturates

Pharmacokinetics

- 1. Absorption and distribution:** The benzodiazepines are lipophilic. They are rapidly and completely absorbed after oral administration, distribute throughout the body, and penetrate into the CNS. The onset of action of benzodiazepines is related to a relative degree of lipid solubility which can vary 50-fold or more. Highly lipid-soluble compounds (*midazolam*, *triazolam*, *diazepam*) have a rapid onset of action than relatively less lipid-soluble benzodiazepines. Most benzodiazepines are available in oral dosage forms; *diazepam* and *midazolam* can be given both parenterally and by the rectal route.
- 2. Duration of action:** The half-lives of the benzodiazepines are important clinically, because the duration of action may determine the therapeutic usefulness. The benzodiazepines can be roughly divided into short-, intermediate-, and long-acting groups. The long-acting agents form active metabolites with long half-lives. However, with some benzodiazepines, the clinical duration of action does not correlate with the actual half-life

(otherwise, a dose of *diazepam* could conceivably be given only every other day, given its long half-life and active metabolites). This may be due to receptor dissociation rates in the CNS and subsequent redistribution to fatty tissues and other areas. Short-acting benzodiazepines are more useful as they prevent preanesthetic anxiety and insomnia, without causing hangover on awakening. Long-acting benzodiazepines are generally more useful in managing anxiety, withdrawal states, seizures, and insomnia.

Tolerance, abuse, and dependence

Tolerance develops to the sedative, hypnotic, and anticonvulsant actions of benzodiazepines though to a lesser extent to the anxiolytic action. Cross-tolerance also occurs with other hypnotic and sedative agents, including alcohol and barbiturates. Psychological and physical dependence can develop if high doses of benzodiazepines are given for a prolonged period. All benzodiazepines are controlled substances. Abrupt discontinuation of these agents results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures. Benzodiazepines with a short elimination half-life, such as *triazolam*, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated such as *flurazepam*. The withdrawal reaction can be minimized by tapering the dose gradually or by substituting the long-acting benzodiazepines, for example, *diazepam* and *chlordiazepoxide*.

Benzodiazepines are differentiated by their half-life (plus or minus active metabolites) and potency. If they are thought of as short half-life/high-potency versus long half-life/lower-potency drugs, the following distinctions can be made:

i. Short half-life/high potency: These drugs are usually more rapid-acting agents that provide quicker symptom control. However, tolerance of the hypnotic effect develops rapidly, withdrawal problems are common, and interdose breakthrough symptoms can occur. These are often used for acute management and later replaced with longer half-life agents.

ii. Long half-life/low potency: These drugs produce longer-lasting effects throughout the day, and although withdrawal symptoms may be less pronounced, they do occur. Interdose breakthrough symptoms are less likely; however, more “hangover” symptoms occur in the morning. These agents can accumulate in older adult patients.

iii. Table compares the half-lives and potencies of the five main/most commonly prescribed benzodiazepines for anxiety disorders.

Agent	Half-life (hr)	Dose (mg)
Alprazolam (Xanax)	6–12	0.5
Chlordiazepoxide (Librium)	5–30 ^a	25
Clonazepam (Klonopin)	20–50	0.5
Diazepam (Valium)	20–100 ^a	10
Lorazepam (Ativan)	10–18	1

^aActive metabolite.

Adverse effects

Daytime drowsiness, sedation, and confusion are the most common adverse effects of the benzodiazepines. Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile, or tasks that require skill, particularly in the elderly and with long-acting benzodiazepines. Cognitive impairment (decreased recall and retention of new knowledge) can occur with use of benzodiazepines, especially in the elderly. Benzodiazepines should be used cautiously in patients with liver disease. They may depress respiration at higher doses than hypnotic doses and may be exaggerated in patients with obstructive sleep apnea and chronic obstructive pulmonary disease. Alcohol and other CNS depressants enhance the sedative–hypnotic effects of the benzodiazepines.

BENZODIAZEPINE ANTAGONIST

Flumazenil is a competitive GABA receptor antagonist that rapidly reverses the effects of benzodiazepines. The drug is available for intravenous (IV) administration only. Onset is rapid, but the duration is short, with a half-life of about 1 hour. Administration of *flumazenil* may precipitate withdrawal in dependent patients or cause seizures if a benzodiazepine is used to control seizure activity. Seizures may also result if the patient has a mixed ingestion with tricyclic antidepressants or antipsychotics.