

## ANTIANSXIETY DRUGS

### Introduction

Frequently no distinction is made between antianxiety drugs and sedative-hypnotic drugs. Major therapeutic use determines classification of these drugs and not the similarities of their chemical structure or their mechanism of action. If they are used for treatment of insomnia they are sedative-hypnotics and if they are used for treating anxiety they are antianxiety agents. Since most sedatives have anxiolytic property but not all anxiolytics have sedative property, it would suggest that anxiety and antianxiety action of drugs may be specific.

A distinction should be made between anxiety as a primary pathological disorder and anxiety as a secondary reaction to organic disease (post-traumatic stress, ulcer, myocardial infarct), panic situations, phobias (e.g., social phobias, claustrophobia, agoraphobia), or the presence of both anxiety and depression in the patient. Anxiety is best treated with antianxiety drugs. However, panic situations, phobias or coexistence of anxiety and depression (agitated depression) may be best managed by other classes of drugs, such as  $\beta$ -adrenergic blockers and antidepressants.

Animal models of anxiety for screening antianxiety drugs are often used. For example, antianxiety drugs but not antipsychotic or antidepressant drugs abolish punishment-suppression behavior in animal models.

### Major Uses

- A. **Anxiety state**
- B. **Insomnia**
- C. **Epilepsy**
- D. **Muscle spasticity**
- E. Induction of amnesia
- F. Adjunct in alcohol withdrawal
- G. For differential psychiatric diagnosis

### Classification

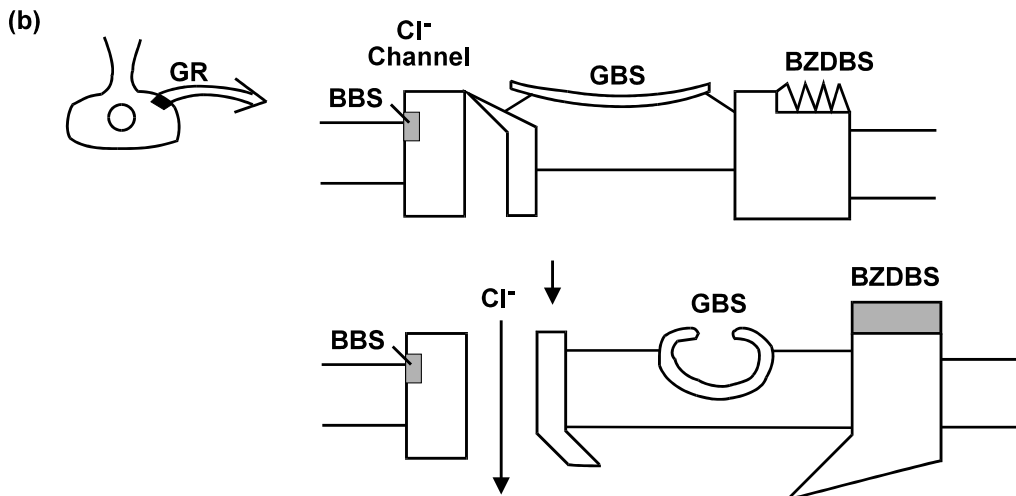
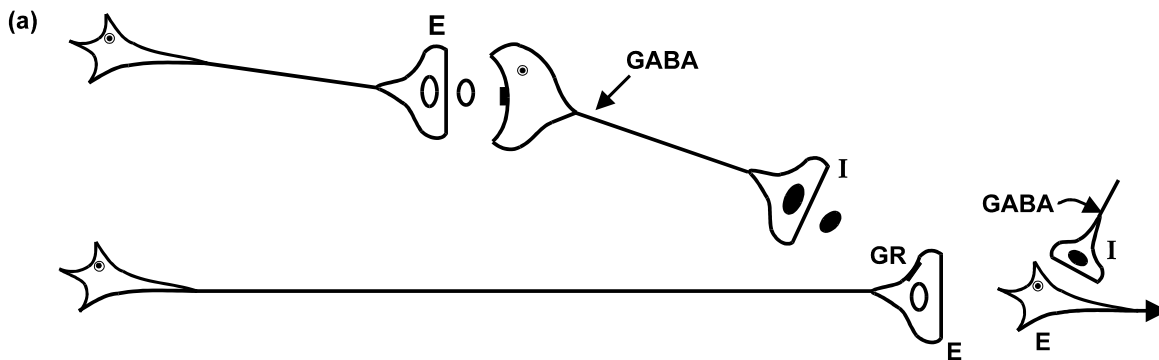
- A. Benzodiazepines
  - 1. **Chlordiazepoxide**
  - 2. **Diazepam**
  - 3. **Oxazepam**
  - 4. Others (**alprazolam**, clorazepate, **flurazepam**, **lorazepam**, prazepam, **temazepam**, **midazolam**, halazepam and **clonazepam**)
  - 5. Newer benzodiazepines
- B. Nonbenzodiazepines
  - 1. Buspirone
  - 2.  $\beta$ -adrenergic antagonists: propranolol
  - 3. Antidepressants: imipramine, MAOIs, fluoxetine, clomipramine
- C. Benzodiazepine antagonist – Flumazenil

Benzodiazepines are the most commonly used anxiolytic drugs. They are not general anesthetics and are not analgesics.

A. Benzodiazepines

1. Mechanism of action. They preferentially act on the limbic system of the brain where they potentiate inhibitory neurotransmission in those systems where  $\gamma$ -aminobutyric acid (GABA) is a neurotransmitter.  $GABA_A$  receptor subtype is selectively effected by benzodiazepines. They enhance  $Cl^-$  influx and produce postsynaptic membrane hyperpolarization.

**Schematics of GABA-Induced Inhibition of Excitatory Neurotransmission**



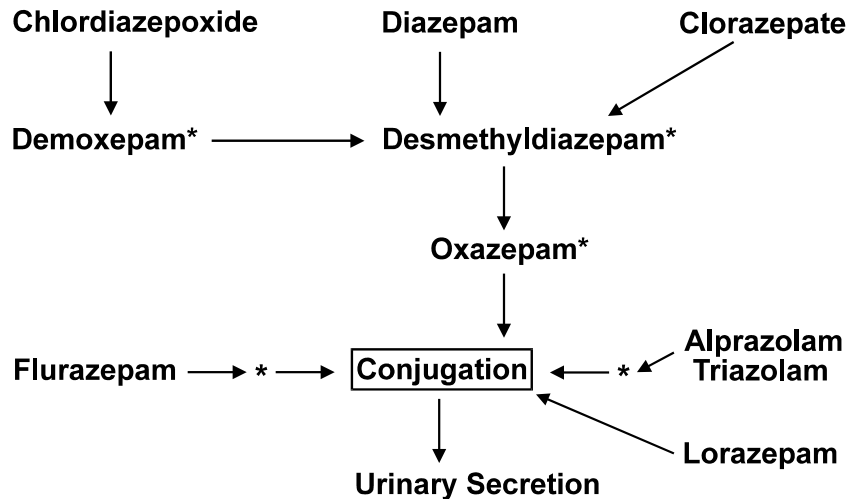
E = Excitatory Neuron  
I = Inhibitory Neuron  
GR = GABA receptor  
BZDBS = Benzodiazepine Binding Site  
BBS = Barbiturate Binding Site  
GBS = GABA Binding Site

Benzodiazepines allow the **frequency** of GABA-induced chloride channel opening to increase and barbiturates allow the **duration** of GABA-induced chloride channel opening to increase.

2. Absorption, distribution and biotransformation. Several benzodiazepines are metabolized to many active compounds with short or long half-lives. Benzodiazepines are weakly basic chemicals and are therefore better absorbed in the duodenum. Some inactive benzodiazepines, e.g., clorazepate, are converted to active compounds in the stomach. They are well absorbed orally, distributed widely in body and all are metabolized in liver and excreted in urine.
- a. Distribution. The distribution and **redistribution** of benzodiazepines is effected by blood flow to organs, their concentration gradients across membranes and their lipophilicity. More lipophilic drugs (e.g., diazepam) have faster onset and shorter duration of action than lesser lipophilic drugs (e.g., chlordiazepoxide, oxazepam).

The redistribution of benzodiazepines from brain and other highly perfused tissues to poorly perfused tissues depends on their lipophilicity. Several benzodiazepines bind avidly to plasma proteins and may displace drugs like warfarin that is bound to plasma proteins.

b. Biotransformation



\* = Active metabolites

Formation of active metabolites may complicate the pharmacokinetic analysis of parent drug and produce cumulative effects.

3. Pharmacological properties

(a) Chlordiazepoxide

- i. possess anticonvulsant, muscle relaxing properties, sedative and hypnotic effects. Frequently produces drowsiness and impairs psychomotor performance. Used primarily in anxiety and muscular-skeletal disorders, and alcohol withdrawal syndromes. Also used in pre-medical treatment to anesthesia. When used for hypnosis (sleep), it reduces the latency of onset of sleep, duration of REM phase of sleep, and duration of stages 3 and 4 of non-REM sleep, and increases the duration of stage 2 of non-REM sleep.
- ii. is used for treatment of prolonged anxiety, because of its long duration of action. It is metabolized to several active compounds such as oxazepam and a desmethyl derivative(s).

(b) Diazepam

- i. used as an anticonvulsant and in treating status epilepticus.
- ii. used as an amnesic agent in dental surgery and for possible amnesic effects in procedures such as endoscopy and bronchoscopy.
- iii. useful in acute alcohol withdrawal.

(c) Oxazepam

- i. is a metabolite of diazepam with short duration of action.

4. Adverse effects

Tolerance and physical dependence occur with benzodiazepines. Tolerance develops within 2-3 weeks. **Cross-tolerance** also occurs between benzodiazepines and sedative-hypnotics including ethanol. Both pharmacokinetic (**dispositional or metabolic**) and pharmacodynamic (**adaptive**) tolerances develop. Benzodiazepines produce more pharmacodynamic tolerance than pharmacokinetic tolerance.

Severity of physical dependence, as characterized by the severity of withdrawal symptoms upon discontinuance of the drug, depends on the specific drug and its dose. Usually, higher the dose and shorter its plasma half-life, more severe is the physical dependence. Abruptness of onset of withdrawal symptoms of a drug depends on the severity of physical dependence and its plasma half-life. **Sudden withdrawal** in a person physically dependent on these drugs may cause **weakness, insomnia, tremor, anxiety, loss of appetite, perception disorders**. **Severe withdrawal** symptoms may include: **agitation, depression, panic, paranoia, convulsions and muscle twitches**. Drug withdrawal or switching of drugs of markedly different plasma half-life should be done gradually (over several weeks to months).

Habituation is common and overdoses are frequent. However, serious consequences are rare. Treatment includes support of respiration and cardiovascular functions.

5. Drug interactions

Depressant effects are additive with other drugs producing CNS depression such as alcohol, narcotics, phenothiazines and antihistamines, as well as antidepressants and some antihypertensives. Cimetidine decreases the metabolism of diazepam.

B. Nonbenzodiazepines

1. Buspirone

Buspirone belongs to a class of agents called azapirones. It is an effective antianxiety drug and is a 5-HT<sub>1A</sub> receptor antagonist. It also interacts with dopamine and norepinephrine receptors. Buspirone:

- a. has no effect on GABA benzodiazepine receptor complex
- b. has little interaction with CNS depressants but caution must be exercised with alcohol
- c. possesses no anticonvulsant properties
- d. does not produce significant sedation
- e. has little effect, if any, on cognitive functions
- f. has low risk of dependence
- g. has no effect on panic disorder
- h. elicits no cross tolerance with other antianxiety drugs
- i. does produce nervousness, lightheadedness, dizziness

2.  $\beta$ -adrenergic antagonists

Anxiety, particularly anxiety related to social phobias and performance, may produce somatic manifestations such as sympathetic autonomic arousal (palpitations, tremor, sweating). In such cases propranolol is useful as the effects of anxiety-induced excess of catecholamines are blocked by propranolol. However, at least part of the "antianxiety effects" of propranolol may be by its actions in the brain.

3. Antidepressants

Some antidepressants have specific uses.

- a. Imipramine in panic disorder. The dose is higher than used in the treatment of depression.
- b. MAO inhibitors in agoraphobia, panic disorder, social phobia, post-traumatic stress.
- c. Selective serotonin reuptake inhibitors and TCA such clomipramine in obsessive-compulsive disorder.

4. Zolpidem, zaleplon—non-benzodiazepine but interact with benzodiazepine receptors; produce less amnesia; in high doses, may produce insomnia; potentiate ethanol effect; little anticonvulsant and muscle relaxant effects

C. Benzodiazepine antagonists – Flumazenil, given intravenously, will quickly reverse the benzodiazepine-induced respiratory depression

Special Considerations Concerning Antianxiety Agents

Use of these agents should be limited to treatment causing severe and disabling anxiety state and used only when these conditions prevail. Thus, one would not normally prescribe these drugs on a prolonged basis, but rather for brief periods for relief of a particular episode when it occurs. Short-acting agents should not be administered for prolonged treatment of anxiety due to their dependence and withdrawal liabilities.

Benzodiazepines possess certain advantages over barbiturates

- a. less depression of respiration
- b. safer, because of higher therapeutic index
- c. less induction of hepatic drug-metabolism enzymes
- d. lower risk of physical dependence, withdrawal usually not severe
- e. less depression of REM sleep
- f. all are anticonvulsants

Choice of drug should be based on:

1. Desired onset of action.
2. Desired duration of action.
3. Desired period of treatment.
4. Personality of patient including age.
5. Risk of drug interactions.