

ANTIANSXIETY AGENTS

- **Is there distinction between antianxiety drugs and sedatives?**
 - Major therapeutic use and not the structure or mechanism of action determines classification. If used for the treatment of insomnia, they are sedative-hypnotic drugs; and if used for the therapy of anxiety, they are antianxiety agents.
 - Most sedative-hypnotic agents have anxiolytic effect but not all antianxiety agents produce sedation. Thus, anxiety is likely a specific disorder not directly related to mechanisms producing sedation.
 - Animal models: antianxiety agents, but not antidepressants and antipsychotic agents abolish punishment suppressant behavior.
 - Distinguish between anxiety as primary disorder and anxiety as secondary reaction to disease (post-traumatic stress, ulcer, myocardial infarct) or situation (panic, phobias – social, claustrophobia, agoraphobia, agitated depression)
 - Effects are dose-related progressing from sedation, hypnosis, anesthesia to coma.

- **Major Uses**

- **Anxiety state**
- **Insomnia**
- **Epilepsy**
- **Muscle spasticity**
- **Induction of amnesia**
- **As preanesthetic medication**
- **Adjunct in alcohol withdrawal**
- **For differential psychiatric diagnosis**

- **Classification**

- **Benzodiazepines: Chlordiazepoxide, diazepam, oxazepam**
- **Non-benzodiazepines: Buspirone, β -adrenergic blocker-propranolol, some antidepressants (imipramine, fluoxetine, MAOIs), zolpidem, zaleplon, clonidine**
- **Older and less commonly used: Barbiturates, meprobamate, chloral hydrate**

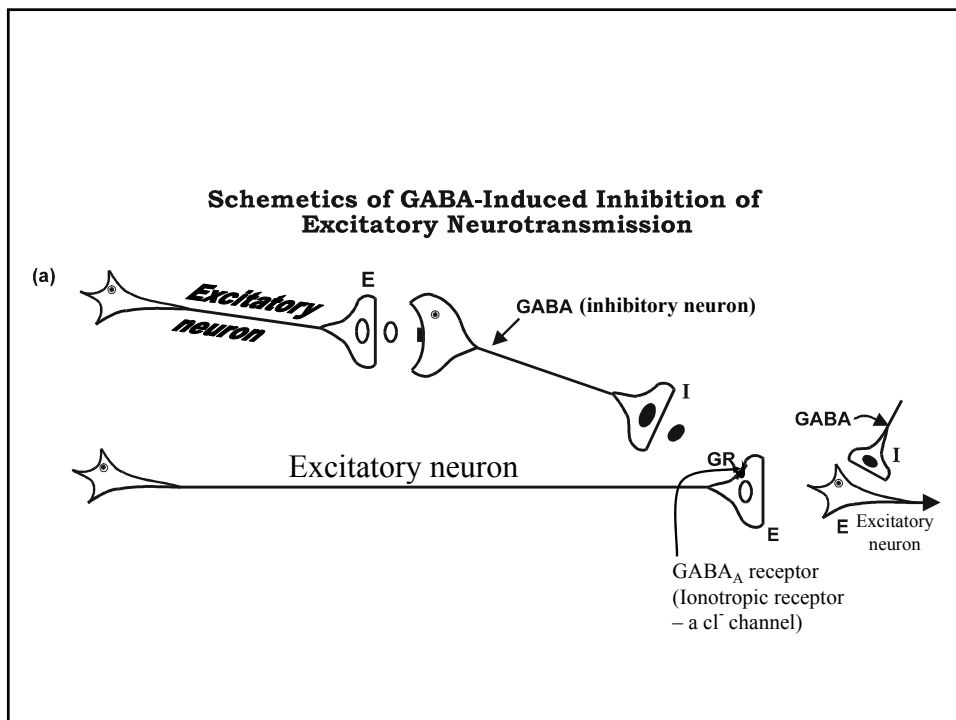
- **Benzodiazepines**

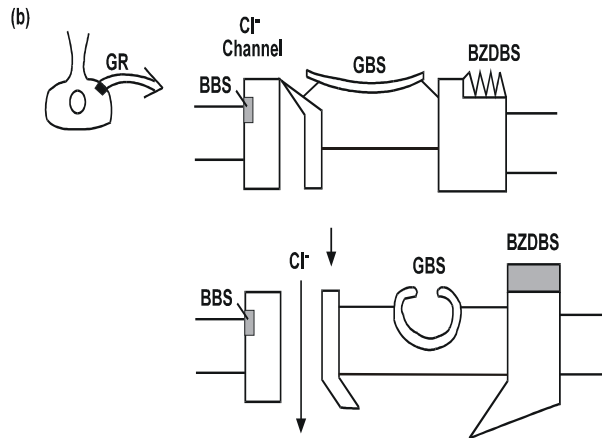
Benzodiazepines are the most commonly used antianxiety agents. They are neither analgesics nor anesthetics.

- **mechanism of action**

- **act on limbic system**

- **potentiate GABA-induced inhibition (GABA is the major inhibitory neurotransmitter in the CNS)**

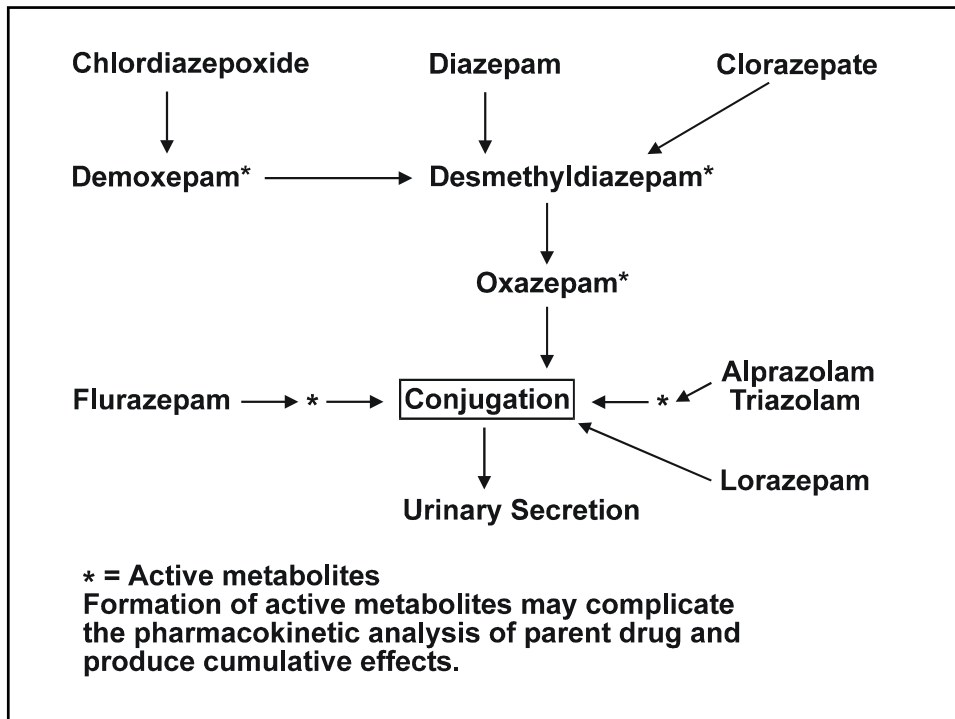




E = Excitatory Neuron
 I = Inhibitory Neuron
 GR = GABA receptor
 BZDBS = Benzodiazepine Binding Site
 BBS = Barbiturate Binding Site
 GBS = GABA Binding Site

- **Benzodiazepines**

- absorption
- **distribution & redistribution of benzodiazepines is effected by**
 - blood flow: brain, heart, kidney > skeletal muscles >> fat tissue
 - concentration gradient
 - Lipophilicity – more lipophilic drugs have faster onset of action and short duration of action
- **biotransformation: benzodiazepines form**
 - active compounds



- **Chlordiazepoxide: pharmacology & uses**

- **antianxiety: treatment of prolonged anxiety, long duration of action, no tolerance to antianxiety effects**
- **anticonvulsant: limited use for prolonged treatment as tolerance develops to anticonvulsant effects**
- **muscle relaxant**
- **sedative - hypnotic**
 - **modifies sleep pattern**
- **withdrawal delayed (withdrawal symptoms are a sign of physical dependence and with long-acting drugs withdrawal symptoms are delayed)**
- **forms active compounds**
- **used for treatment of prolonged anxiety**
- **used as adjunct in alcohol withdrawal and as premedication to anesthesia**

- **Diazepam**
 - anticonvulsant
 - amnesic agent
 - alcohol withdrawal
 - status epilepticus
- **Oxazepam**
 - metabolite of diazepam
 - short duration of action

- **Adverse Effects**
 - tolerance and physical dependence
 - develops to all drugs of this class
 - cross-tolerance
 - pharmacokinetic tolerance – rate of inactivation changes
 - pharmacodynamic tolerance – change in responsiveness
 - withdrawal symptoms: insomnia, tremors, anxiety, loss of appetite, perception disorders
 - severity of withdrawal symptoms related to severity of physical dependence; also shorter the $t_{1/2}$ more severe is the physical dependence
 - habituation

- **Drug Interactions**

- **additive with CNS depressants such as alcohol, opioids, antihistamines, phenothiazines**
- **cimetidine decreases diazepam metabolism**

(Daytime sedation and drowsiness, synergistic depression of CNS with other sedatives and alcohol, likelihood of physical and psychological dependence has led to the development of non-benzodiazepine antianxiety agents)

- ◆ **Nonbenzodiazepines**

- **Buspirone**

- **antianxiety effect without marked sedation or euphoria**
- **5-HT_{1A} receptor antagonist at postsynaptic sites and agonist at 5-HT_{1A} presynaptic receptors**
- **no direct effect on GABA system**
- **little interaction with depressants except alcohol**
- **not anticonvulsant**
- **not a muscle relaxant**
- **no effect on cognitive function**
- **not a sedative-hypnotic**
- **no cross tolerance with antianxiety drugs**
- **no physical dependence and little abuse liability**

- **β -Adrenergic blocker**
 - propranolol
 - reduces autonomic symptoms of anxiety
- **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

- **Antidepressants**
 - imipramine in panic disorder. The dose is higher than used in the treatment of depression
 - MAO inhibitors in agoraphobia, panic disorder, social phobia, post-traumatic stress
 - selective serotonin reuptake inhibitors (SSRI_s) and TCA_s such as clomipramine in obsessive compulsive disorder

- **Special Considerations Concerning Antianxiety Agents :**

- **Choice of drug should be based on:**
 - **Desired onset of action.**
 - **Desired duration of action.**
 - **Desired period of treatment.**
 - **Presence or absence of pain.**
 - **Personality of patient including age.**
 - **Risk of drug interactions.**
- **Avoid**
 - **Use of short-acting agents for long periods.**
 - **Combine with other sedative-hypnotic agents, alcohol, antihistamines, anticholinergics, and phenothiazines.**

- **Benzodiazepines possess certain advantages over barbiturates**
 - **less depression of respiration**
 - **safer, because higher therapeutic index**
 - **less induction of hepatic drug-metabolism enzymes**
 - **lower risk of physical dependence, withdrawal usually not severe**
 - **less depression of REM sleep**
 - **all are anticonvulsants**

However, benzodiazepines are more prone to produce psychological dependence, they form active metabolites, may produce unwanted amnesia, their cost is high, and they produce additive effects with several sedative agents and may impair judgment.