# Anti-anxiety &Sedative-Hypnotic Drugs

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**Reference:** Basic & Clinical Pharmacology: Bertrum G. Katzung and Anthony J. Treveror, 13th edition,2015, chapter 22, p.369-383

**Learning Objectives:**

**At the end of session, the student should be able to:**

1. Define anti-anxiety, sedative and hypnotic terms.
2. Classify anti-anxiety and sedative-hypnotic drugs.
3. List advantages of benzodiazepines over barbiturates as sedative-hypnotic drugs.
4. Explain the mechanism of action of benzodiazepines
5. Explain pharmacokinetics of benzodiazepines.
6. State the clinical importance of benzodiazepines' pharmacokinetics.
7. Describe clinical uses of benzodiazepines.
8. Explain side effects of benzodiazepines.
9. Identify important drug interactions of benzodiazepines.
10. Identify the mechanism of action of buspirone.
11. Explain advantages and disadvantages of buspiron in comparison to benzodiazepines.
12. State the clinical indication of zolpidem and zaleplone
13. Explain the differences between zolpidem, zaleplon and older benzodiazepines.
14. Specify antihistamines used as sedative-hypnotic drugs.
15. Describe the use of antidepressants as anti-anxiety drugs.
16. Explain the indication of beta blockers in anxiety disorders.

Anti-anxiety & Sedative-Hypnotic Drugs

Anxiety states and sleep disorders are common problems, and sedative-hypnotics are widely prescribed drugs worldwide.Assignment of a drug to the sedative-hypnotic class indicates that it is able to cause sedation (with concomitant relief of anxiety) or to encourage sleep (hypnosis). Because there is considerable chemical variation within the group, this drug classification is based on clinical uses rather than on similarities in chemical structure.

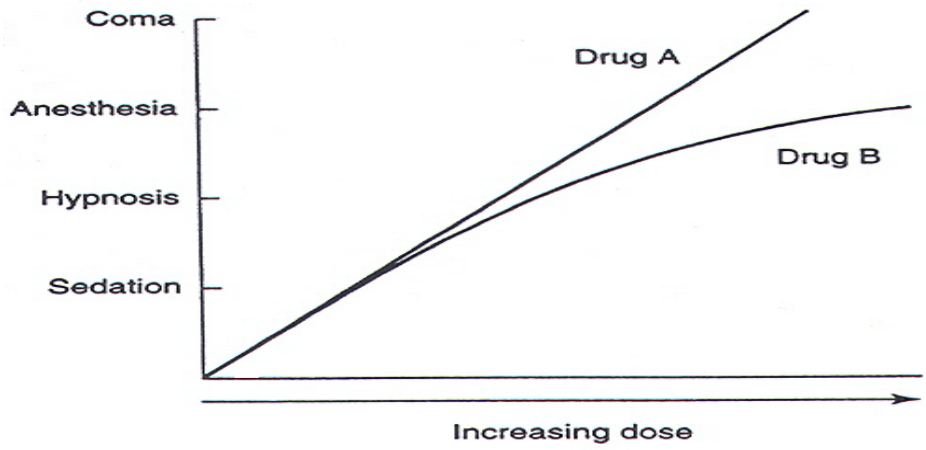
**DEFINITION OF SEDATIVE-HYPNOTICS**

A **sedative** (anxiolytic) agent should reduce anxiety and exert a calming effect. The degree of central nervous system (CNS) depression caused by a sedative should be the minimum consistent with therapeutic efficacy.

A **hypnotic** drug should produce drowsiness and encourage the onset and maintenance of a state of sleep.Hypnotic effects involve more pronounced depression of the CNS than sedation, and this can be achieved with many drugs in this class simply by increasing the dose.

Graded dose-dependent depression of CNS function is a characteristic of most sedative-hypnotics. However, individual drugs differ in the relationship between the dose and the degree of CNS depression. Two examples of such dose response relationships are shown in Figure 1. The linear slope for drug A is typical of many of the older sedative-hypnotics, including the barbiturates and alcohols. With such drugs, an increase in dose higher than that needed for hypnosis may lead to a state ofgeneral anesthesia. At still higher doses, these sedative-hypnotics may depress respiratory and vasomotor centers in the medulla, leading to coma and death. Deviations from a linear dose-response relationship, as shown for drug B, require proportionately greater dosage increments to achieve CNS depression more profound than hypnosis. This appears to be the case for benzodiazepines and for certain newer hypnotics that have a similar mechanism of action.

**Figure 1. Dose-response Curves for Sedative-hypnotics**




Benzodiazepines and Barbiturates are two main classes of sedative-hypnotics. However, benzodiazepines are currently the most widely used agents as sedative-hypnotics due to their advantages over barbiturates which include the followings:

1. **Safer:** Benzodiazepines have relatively higher Therapeutic index as sedative-hypnotic agents than barbiturates as mentioned above (Figure 1).

2. **Availability of flumazenil**which is a benzodiazepine receptor antagonist. Barbiturates do not have a pharmacological antagonist. Flumazenil is used for treatment of benzodiazepines' overdose. It reverses the sedative actions of benzodiazepines, however, its duration of action is short and its antagonism of respiratory depression is unpredictable. Consequently, the use of flumazenil in benzodiazepine overdose mustbe accompanied by adequate monitoring and support of respiratory function.

3. **Fewer drug interactionsbased on liver enzyme induction:** Barbiturates (especially phenobarbital) are enzyme inducers and are most likely to cause drug interactions involving changes in the activity of hepatic drugmetabolizingenzyme systems, which may result in an increased biotransformation of other pharmacologic agents. In contrast, benzodiazepines do not change hepatic drug-metabolizing enzyme activity with continuous use.The most common drug interactions involving benzodiazepines are interactions with other CNS depressant drugs, leading to additiveeffects. Additive effects can be predicted withconcomitant use of alcoholic beverages, opioid analgesics, anticonvulsants,phenothiazines, antihistamines, antihypertensiveagents, and tricyclic antidepressants.

**4. Lower potential for abuse:** Benzodiazepines are less likely to cause psychological dependence and to be abused in comparison to barbiturates.

**Pharmacodynamics**

The benzodiazepines and the barbiturates bind to molecular components ofthe GABA-A receptor in neuronal membranes in the CNS. This receptor, which functions as a chloride ion channel, is activated by the inhibitory neurotransmitter GABA. However, GABA-A receptors in different areas of the CNS consist of various combinations of the essential subunits, and the benzodiazepines bind tomany of these subunits. Barbiturates also bind to multiple isoforms of the GABA-A receptor but at different sites from those with which benzodiazepines interact. The heterogeneity of GABA-A receptors may constitute the molecular basis for the varied pharmacologic actions of benzodiazepines and related drugs. GABA is a major inhibitory neurotransmitter in the CNS. Benzodiazepines appear to increase the efficiency of GABAergicsynaptic inhibition. The benzodiazepines enhance GABA's effects allosterically withoutdirectly activating GABA-A receptors or opening the associatedchloride channels leading to an increase in the frequencyof channel-opening events.Barbiturates also facilitate the actions of GABA at multiple sitesin the CNS, increasing the durationof the GABA-gated chloride channel openings.At high concentrations, the barbiturates may also be GABAmimetic, directly activating chloride channels. The multiplicity of sites of action of barbiturates may be the basis fortheir ability to induce full surgical anesthesia andfor their more pronounced central depressant effects (which resultin their low margin of safety) compared with benzodiazepines.

**Pharmacokinetics**

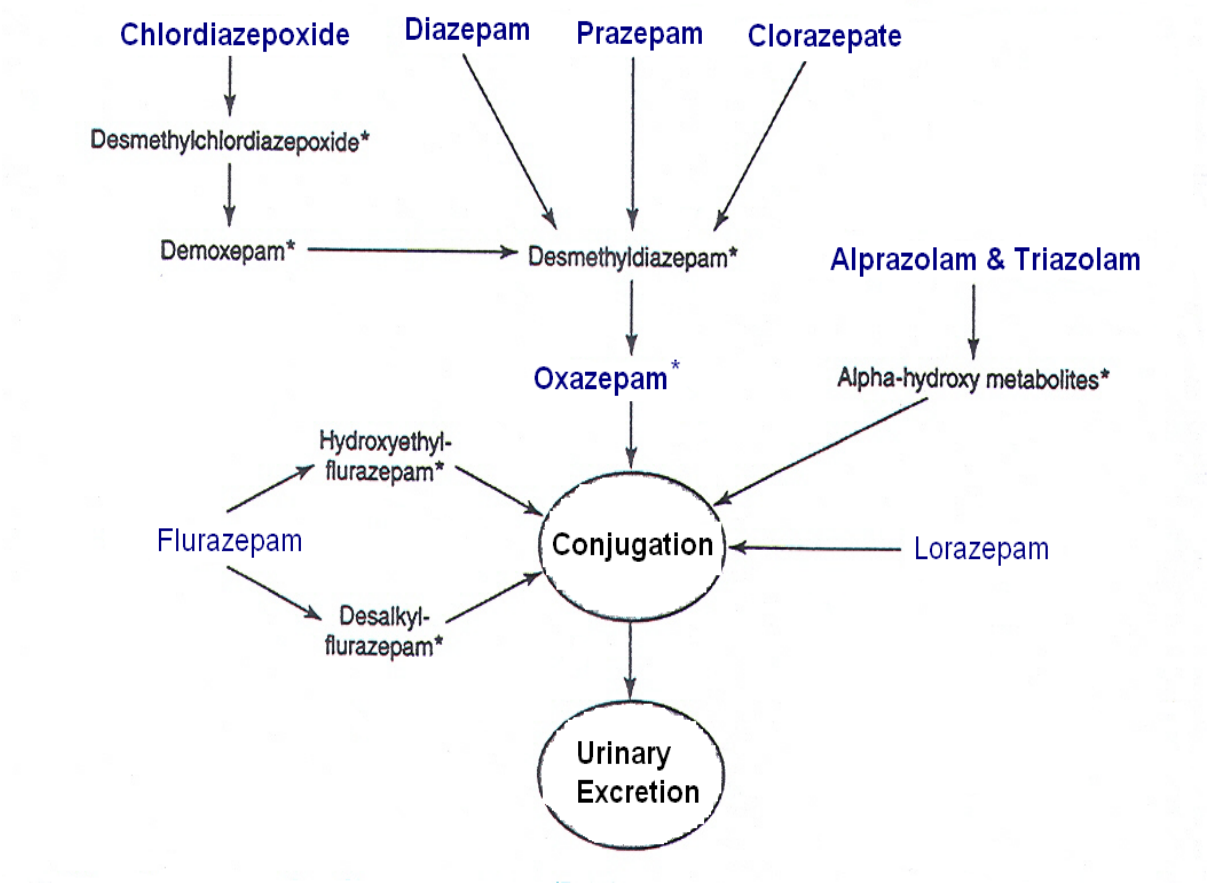
**Absorption and Distribution:** Lipid solubility plays a major role in determining the rate atwhich a particular benzodiazepine enters the CNS. For example,the absorption of triazolam is extremely rapid, and that of diazepamis more rapid thanother commonly used benzodiazepines.

**Biotransformation:** Hepatic metabolism accounts for theclearance of all benzodiazepines. The patterns and rates of metabolism depend on the individual drugs. Most benzodiazepinesundergo microsomal oxidation (phase I reactions), by cytochromeP450 isozymes, especially CYP3A4. The metabolites aresubsequently conjugated (phase II reactions) to form glucuronidesthat are excreted in the urine. However, many phase I metabolitesof benzodiazepines are pharmacologically active, some with longhalf-lives (Figure 2). For example, desmethyldiazepam, whichhas an elimination half-life of more than 40 hours, is an activemetabolite of chlordiazepoxide, diazepam, prazepam, and clorazepate.Alprazolam and triazolam undergo □-hydroxylation, andthe resulting metabolites appear to exert short-lived pharmacologiceffects because they are rapidly conjugated to form inactiveglucuronides. The short elimination half-life of triazolam (2–3hours) favors its use as

a hypnotic rather than as a sedative drug.The formation of active metabolites has complicated studies onthe pharmacokinetics of the benzodiazepines in humans becausethe elimination half-life of the parent drug may have little relationto the time course of pharmacologic effects. Benzodiazepines forwhich the parent drug or active metabolites have long are more likely to cause cumulative effects with multiple doses.Cumulative and residual effects such as excessive drowsinessappear to be less of a problem with such drugs as estazolam, oxazepam,and lorazepam, which have relatively short half-lives andare metabolized directly to inactive glucuronides.

**Excretion:** The water-soluble metabolites of sedative-hypnotics, mostly formedvia the phase II conjugation of phase I metabolites, are excretedmainly via the kidney. In most cases, changes in renal function do nothave a marked effect on the elimination of parent drugs.

**Figure 2.Metabolism of Benzodiazepines**




**Clinical Uses of Benzodiazepines**

**Anxiolytic or anti-anxiety:** Anxiety is often secondary to organic disease states—acute myocardial infarction, angina pectoris, gastrointestinal ulcers, etc—which themselves require specific therapy.Another class of secondary anxiety states (situational anxiety) results from circumstances that may have to be dealt with only once or a few times, including anticipation

of frightening medical or dental procedures and family illness or other stressful event. Even though situational anxiety tends to be self-limiting, the short-term use of benzodiazepines may be appropriate for the treatment of this and certain disease-associated anxiety states. Clinical anxieties such as excessive or unreasonable anxiety about life circumstances (generalizedanxiety disorder, GAD), panic disorders, and agoraphobiaare also amenable to drug therapy, sometimes in conjunction withpsychotherapy.

The benzodiazepines continue to be widely used forthe management of acute anxiety states and for rapid control ofpanic attacks. They are also used, though less commonly, in thelong-term management of GAD and panic disorders with no tolerance developing to their anxiolytic effects. Anxietysymptoms may be relieved by many benzodiazepines, but it is notalways easy to demonstrate the superiority of one drug overanother. Therefore, the choice of benzodiazepines for anxiety is based on several pharmacokinetic properties including Onset of action, duration of action and tendency to accumulate with repeated daily dosing. Alprazolam is an exception andappears to be more selective in the treatment of panic disordersand agoraphobia than other benzodiazepines.

**Sedative:**Benzodiazepines exert calming effects (sedation) with concomitant reductionof anxiety at relatively low doses. They are used for sedative and possible amnestic effects during medical or surgical procedures such as endoscopy and bronchoscopy—as well as for premedication prior to anesthesia.

**Hypnotic:**Benzodiazepines inducesleep if high enough doses are given. However, benzodiazepines can alter the structure and pattern of normal sleep as follows:(1) the latency of sleep onset is decreased (time to fall asleep);(2) the duration of stage 2 NREM (non-rapid eye movement) sleepis increased; (3) the duration of REM (rapid eye movement) sleep isdecreased; and (4) the duration of stage 4 NREM slow-wave sleepis decreased.

The choice of benzodiazepines as a hypnotic drug is dependent on individual's sleep problem. For example, for patients who have difficulty in falling asleep, the selected drug should provide sleep of fairly rapid onset (decreased sleep latency); and for those with repeated awaking during night, the drug should have sufficient duration of action, with minimal "hangover" effects such as drowsiness, dysphoria, and mental or motor depression the following day. If benzodiazepines are used nightly (for more than 1–2 weeks), tolerance can occur, which may lead to dose increases by the patient to produce the desired effect. In addition, anterograde amnesia occurs to some degree with all benzodiazepines used for hypnosis. Generally, long-term use of benzodiazepines as hypnotics is an irrational and dangerous medical practice.

**Anesthetic:** Benzodiazepines—including diazepam, lorazepam, andmidazolam—are used intravenously as a component of balanced anesthesia in combination with other agents.
**Anticonvulsant:** Several benzodiazepines—including clonazepam, nitrazepam,lorazepam, and diazepam—are sufficiently selective to beclinically useful in the management of seizures. Benzodiazepines at anticonvulsant doses can cause sedation and tolerance will develop to their anticonvulsant effects. Benzodiazepines are mainly used in status epilepticus.
**Muscle relaxant:** benzodiazepines exert inhibitory effects on polysynapticreflexes andinternuncial transmission and at high doses may alsodepress transmission at the skeletal neuromuscular junction. The benzodiazepines have frequently beenused as central muscle relaxants, though evidence for general efficacy without accompanying sedation is lacking. A possibleexception is diazepam, which has useful relaxant effects in skeletalmuscle spasticity of central origin.
**Alcohol withdrawal:** Long-acting benzodiazepines such as chlordiazepoxide and diazepamare administered in progressivelydecreasing doses to patients during withdrawal from physiologicdependence on ethanol.

**Adverse Effects of benzodiazepines**

**CNS depression**: The Most common adverse effects of benzodiazepines are dose-related depression of the CNS. Relatively low dosesmay lead to drowsiness, impaired judgment, and diminishedmotor skills, sometimes with a significant impact on driving ability (psychomotor impairment),job performance, and personal relationships. Sleep driving andother somnambulistic behavior with no memory of the event hasoccurred with the benzodiazepines used in sleep disorders. At higher doses, toxicity may present as lethargy or a state of exhaustion or, alternatively, as gross symptoms equivalent to those of ethanol intoxication. Because elderly patients are more sensitive to the effects of benzodiazepines, doses approximately half of those used in younger adults are safer and usually as effective. Benzodiazepines have behavioral disinhibitory effects (i.e. the disinhibition of previously suppressed behavior) including euphoria, impaired judgment, and loss of self-control. Disinhibitory reactions during benzodiazepine treatment are more clearly associated with the use of very high doses and the pretreatment level of patient hostility. However, this effect can occur at dosages in the range of those used for management of anxiety.The physician should be aware of variability among patients in terms of doses causing adverse effects.
**Anterograde amnesia**(inability to remember events occurring during the drug's duration of action): Benzodiazepines may cause significant dose-relatedanterograde amnesia; they can significantly impair ability to learnnew information, particularly that involving effortful

cognitiveprocesses, while leaving the retrieval of previously learned informationintact. This effect is utilized for uncomfortable clinicalprocedures, eg, endoscopy, because the patient is able to cooperateduring the procedure but amnesic regarding it afterward. Thecriminal use of benzodiazepines in cases of “date rape” is based ontheir dose-dependent amnestic effects.

**Psychologic & Physiologic Dependence**

The perceived desirable properties of relief of anxiety, euphoria, disinhibition, and promotion of sleep have led to the compulsive misuse of virtually all sedative-hypnotics. For this reason, most sedative-hypnotic drugs are classified as Schedule III or Schedule IV drugs for prescribing purposes. However, the risk of psychological dependence and abuse with benzodiazepines are lower than other sedative hypnotics such as barbiturates.

Physiologic dependence can be described as an altered physiologic state that requires continuous drug administration to prevent an abstinence or withdrawal syndrome. Benzodiazepines are capable of causing physiologic dependence when used on a long-term basis. Benzodiapines withdrawal syndrome is characterized by states of increased anxiety, insomnia, tremor, sweating, hypertension and CNS excitability that may progress to convulsions.

**Effects on respiration and cardiovascular function:** At hypnotic doses in healthy patients, the effects of benzodiazepines on respiration are comparable to changes during natural sleep. However, even at therapeutic doses sedative-hypnotics can produce significant respiratory depression in patients with pulmonary disease. Effects on respiration are dose-related, and depression of the medullary respiratory center is the usual cause of death due to overdose of benzodiazepines when are given intravenously.

At doses up to those causing hypnosis, no significant effects on the cardiovascular system are observed in healthy patients. However, in hypovolemic states, heart failure, and other diseases that impair cardiovascular function, normal doses of benzodiazepines may cause cardiovascular depression, probably as a result of actions on the medullary vasomotor centers.

**Hypersensitivity reactions**: including skin rashes, occur only occasionally with most benzodiazepines.

**Teratogenicity:**Reports of teratogenicity leading to fetal deformationfollowing use of certain benzodiazepines have resulted inFDA assignment of individual benzodiazepines to either categoryD or X in terms of pregnancy risk.

**Other Anxiolytic, sedative-hypnotic Drugs**

**Buspirone:** is a partial 5HT1A serotonin receptor agonist. It has an anxiolytic effect with no adverse effects of benzodiazepines that is it causes **no sedation, memory or psychomotor impairment, and disinhibition phenomenon. It has no interaction with alcohol, abuse potential and the risk of physical or psychological dependence.**However, it has the disadvantage of slow onset of action. It takes several weeks to exert its anxiolytic action. It is useful in the management of generalized anxiety disorder. It is not effective for panic attacks.

**Antidepressants:**In the treatment of generalized anxiety disorders and certainphobias, newer antidepressants, including selective serotonin reuptakeinhibitors (SSRIs) and serotonin-norepinephrine reuptakeinhibitors (SNRIs), are now considered by many authorities to be drugs of first choice. However, these agents have aslow onset of action and thus minimal effectiveness in acute anxietystates.

**Zolpidem and Zaleplon:**Zolpidem and zaleplon are BZ1 receptor agonists and have efficacies similar to those of the hypnotic benzodiazepines in the management of sleep disorders. They have little effect on sleep pattern. Favorable clinical features of zolpidem and zaleplon include rapid onset of activity and modest day-after psychomotor depression with few amnestic effects. Zaleplon act rapidly and because of its short half-life, the drug appears to have value in the management of patients who awaken early in the sleep cycle. At recommended doses, Zaleplon appear to cause less amnesia or day-after omnolence than zolpidem or benzodiazepines. Muscle relaxation is not a characteristic action of zolpidem and zaleplon.Tolerance has been reported to occur with the extended use of zolpidem. Minimal tolerance was observed with the use of zaleplon over a 5-week period.The abrupt cessation of zolpidem or zaleplon may result in withdrawal symptoms, though usually of less intensity than those seen with benzodiazepines.

**Antihistamines:**First generation antihistamines with marked sedative effects including diphenhydramine, promethazine and hydroxyzine sometimes are used to reduce tension and anxiety associated with organic diseases.

**Beta blockers:** Propranolol is used for the management of stage or performance anxiety. It is useful for relieving the somatic manifestations of anxiety such as tachycardia, palpitation, tremor and sweating.