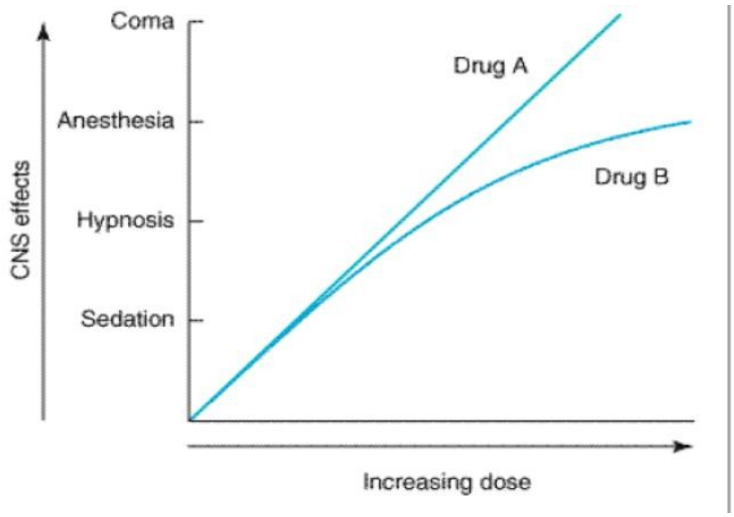
# Sedatives, Hypnotics, and Anxiolytics

***Terms:***
**Sedative**: a substance that induces sedation by reducing irritability and excitement.
**Hypnotic:** a drug which induces a state of drowsiness.
**Anxiolytic:** an agent which decreases worriness manifested as the psychic awareness of anxiety which is accompanied with increased vigilance, motor tension, and autonomic hyperreactivity.

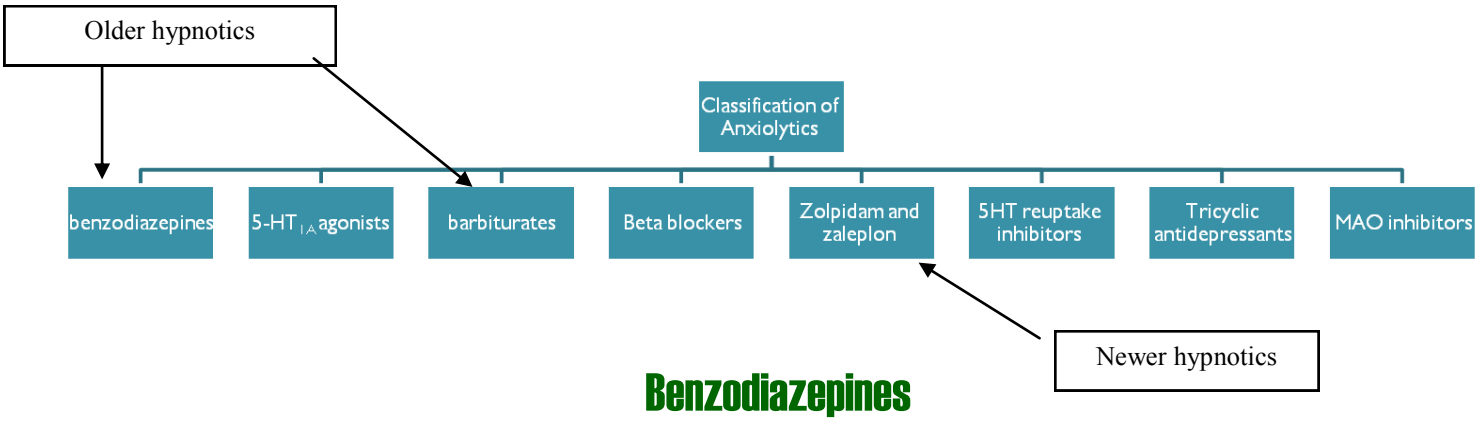
***Anxiety Disorders Are:***
- **Generalized anxiety disorder (GAD):** characterized by excessive, uncontrollable and often irrational worry about everyday things that is disproportionate to the actual source of worry.
- **Panic disorder**
- **Phobia:** A fear from a certain psychological irritant.
- **Post-traumatic stress disorder**
- **Obsessive compulsive disorder.**

***Introduction to Sedatives, Hypnotics, and Anxiolytics:***
With high doses of sedatives, more depression of central nervous system (CNS) occurs. However, individual drugs differ in relationship between the dose and the degree of central nervous system depression.




Take drug A in the above figure as an example. An increase in dose higher than that needed for hypnosis may lead to a state of general anesthesia. With higher doses, the drug will depress the respiratory and vasomotor centers which leads to coma. Drug A is an example of alcohol and barbiturates.

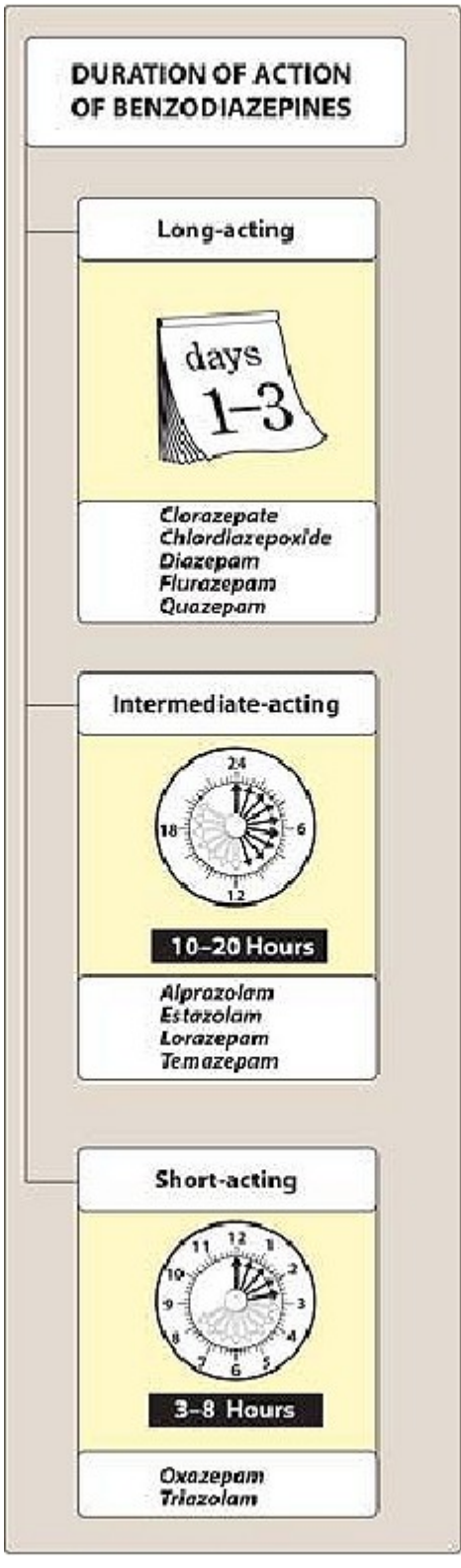
Drug B needs greater doses to achieve CNS depression. This appears to be the case for benzodiazepines and newer hypnotics.




# Benzodiazepines

## Pharmacokinetics:

- The rate of oral absorption varies depending on each drug's lipophilicity. Absorption of triazolam is extremely rapid. Diazepam and the active metabolite of clorazepate have more rapid absorption than other benzodiazepines. Clorazepate is a prodrug converted to the active metabolite (nordiazepam) by acid hydrolysis in the stomach. Peak plasma concentration for benzodiazepines in the plasma is reached in one hour.



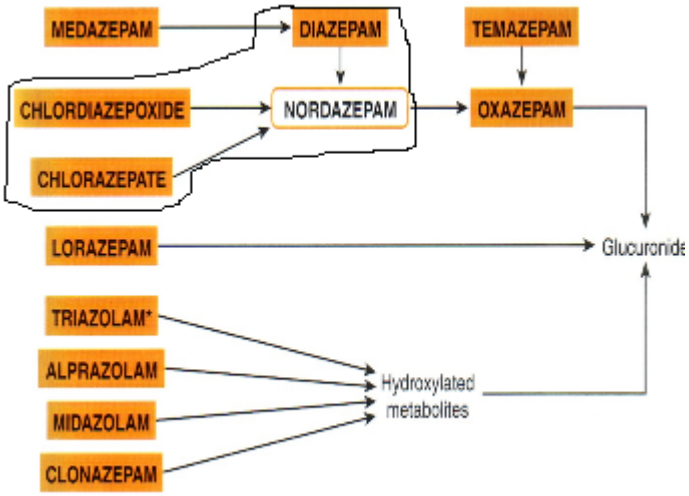

- Benzodiazepines bind strongly to plasma proteins. They also accumulate in body fats with high volume of distribution. They are commonly given by mouth, IM (with slow absorption to the circulation due precipitation with myocytes), or IV.

- All sedative-hypnotics cross the placental barrier during pregnancy. They are also detectable in breast milk.

- Benzodiazepines are metabolized by oxidation and hydroxylation by cytochrome P450 especially isoform CYP3A4 (phase I). The metabolites are subsequently conjugated (phase II) to form glucuronides that are excreted in the urine.

- The metabolism of diazepam, midazolam, and triazolam is affected by inhibitors and inducers of hepatic P450 isozymes.

- In very old patients and in patients with severe liver disease, the elimination half lives of sedative-hypnotics are increased significantly.




This figure illustrates the metabolism of several benzodiazepines. Note Diazepam, chlordizepoxide and chlorazepate are converted to nordazepam and oxazepam which extend their half lives.

## Pharmacodynamics:

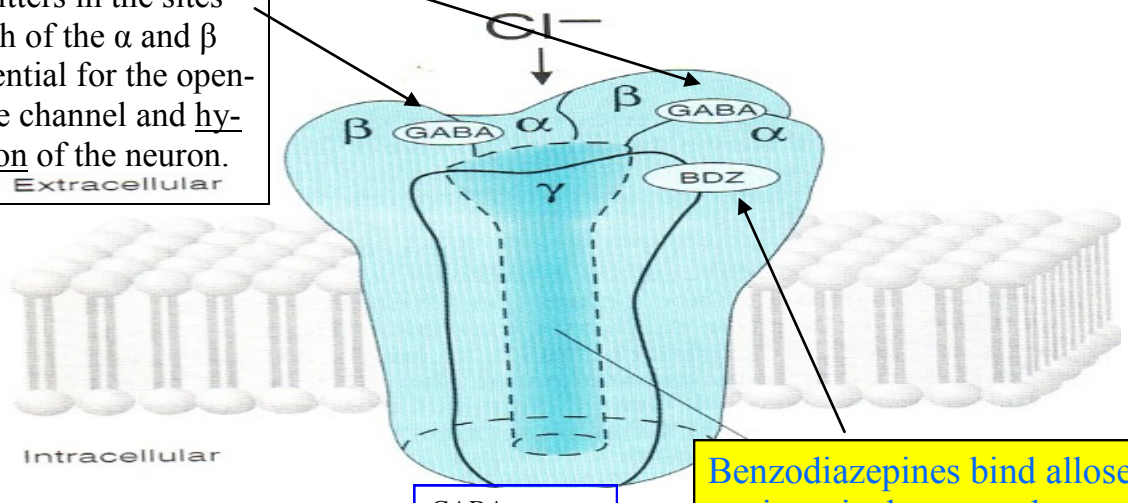
- Benzodiazepines exert their effect by selectively binding to $GABA_A$ receptors and enhancing its inhibitory effect on the CNS

- GABA receptor contains more than one isoform each with different subunits:
  1. α1-subunit→ sedation, amnesia and possibly antiseizure effects.
  2. α2 -subunit → anxiolytic and muscle relaxing action.
  3. α5-subunit→ memory impairment.

- Benzodiazepines bind to many isoforms of the GABA receptor at different areas of the brain.

- The GABA receptor is a pentameric receptor consisting from five subunits in variant isoforms. The major isoform is composed of five subunits comprising of 2α, 2β, and one γ subunits

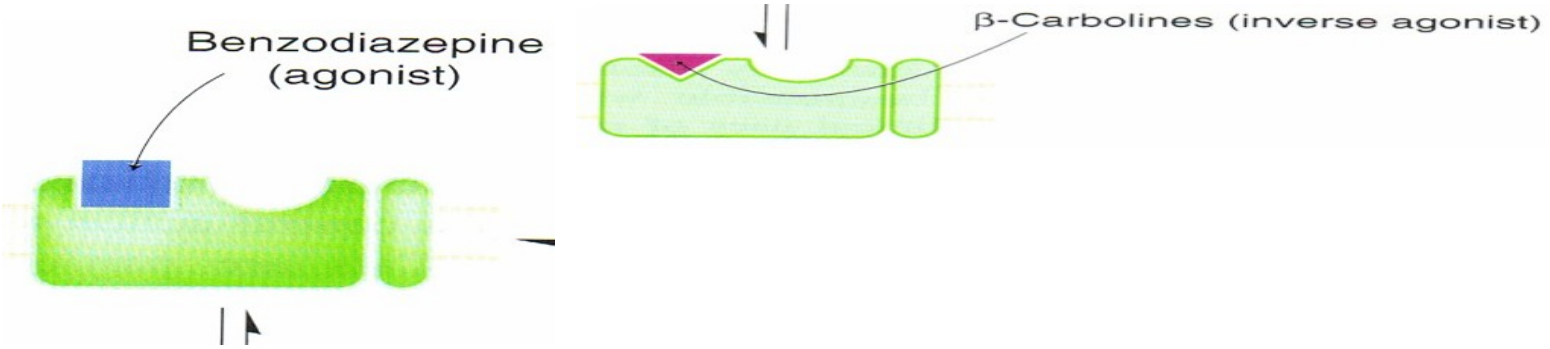
The binding of 2 GABA neurotransmitters in the sites between both of the α and β subunits is essential for the opening of chloride channel and hyperpolarization of the neuron.




GABA receptor

Benzodiazepines bind allosertically in a site between the α and γ subunits subsequently potentiating the opening of the chloride channel

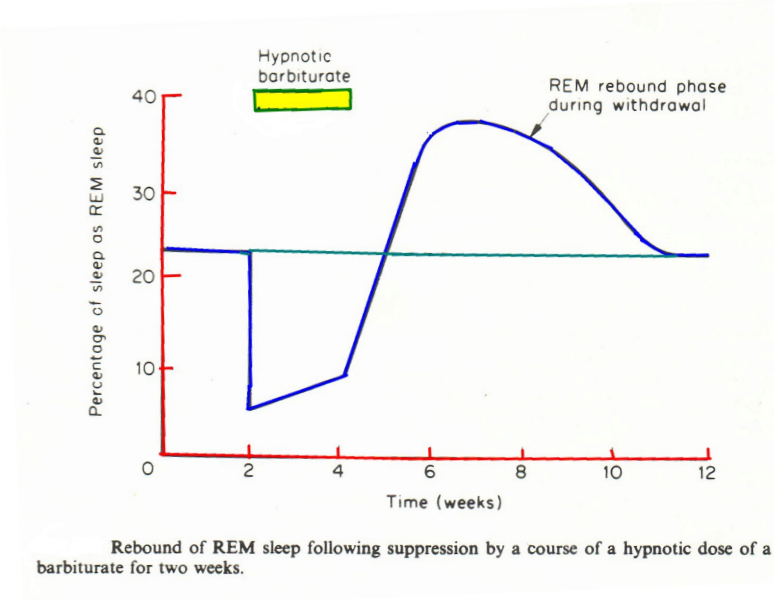
- Three types of ligand-benzodiazepine receptor interactions have been reported:
  1. **Agonists** facilitate GABA actions.
  2. **Antagonists** like **flumazenil** which blocks the action of benzodiazepines, escopiclone, zaleplon, and zolpidem but not barbiturates, meprobamate or ethanol.
  3. **Inverse agonists** act as a negative allosteric modulators of GABA receptor function. They produce anxiety and seizures. For example β-carbolines.




## Pharmacological Effects:

1. **Reduction of anxiety & aggression:**
   - active against all types of anxiety.
   - **Alprazolam** is an anxiolytic as well as an antidepressant
   - Because of the short half life of triazolam, severe rebound occurs after abrupt discontinuation

2. **Sedation:**
   - Exert calming effects.
   - In experimental animal models, benzodiazepines are able to disinhibit punishment-suppressed behavior.



Rebound of REM sleep following suppression by a course of a hypnotic dose of a barbiturate for two weeks.

3. **Induction of Sleep (Hypnotic)**
   - Effects of benzodiazepines older hypnotics on patterns of normal sleep:-
   A. decreases the time taken to fall to sleep (decrease sleep latency)
   B. increases total duration of sleep without the fluctuation of sleep and non-sleep alternating cycles throughout a night.
   C. The duration of stage 2 NREM sleep is increased.
   D. The duration of REM sleep is decreased
   E. The duration of stage 4 NREM slow-wave sleep is decreased.
   - In general: interruption of REM sleep causes anxiety and irritability followed by a rebound increase in REM sleep.
   - REM rebound can be detected following abrupt cessation of drug treatment with older sedatives

- No reports of disturbance in pituitary or adrenal hormones.

4. **Reduction of Muscle Tone and Coordination:**
   - Increased muscle tone is a common feature of anxiety which may contribute to muscle aches and headache .
   - Benzodiazepines exert inhibitory effects on polysynaptic reflexes and internuncial transmission.
   - At high doses, they may also depress transmission at the skeletal neuromuscular junction.
   - Muscle relaxation is not a characteristic action of zolpidem, zaleplon, and eszopiclone

5. **Anticonvulsant Effects:**
   - More effective against chemically induced convulsions caused by leptazol & bicuculline, but not strychnine due to the different mechanisms of action between the two.
   - Less effective against electrical- induced convulsions .
   - Some drugs of the benzodiazepines have greater selectivity for convulsion without marked CNS depression e.g. clonazepam, nitrazepam, lorazepam, and diazepam.
   - Zlpidem, zaleplon, and eszopiclone lack anticonvulsant activity.

6. **Anterograde Amnesia:**
- Benzodiazepines obliterate memory of events experienced under their influence.

7. **Effects on Respiration and Cardiovascular Functions:**
   - At therapeutic doses, sedatives-hypnotics can produce respiratory depression in patients with pulmonary disease.
   - In hypovolemic state and heart failure, normal doses of sedative-hypnotics can cause cardiovascular depression.
   - Respiratory and cardiovascular effects are marked when the doses given intravenously

**All of the above effects are considered clinical uses in addition to:**
**1. Initial management of mania**
**2. Control of drug-induced hyper excitability states e.g. phencyclidine intoxication**

# Individual Benzodiazepines:

| Drug | Half-life | Metabolism | Clinical uses |
|---|---|---|---|
| Triazolam & midazolam | 2-4 hr | To active metabolites | Hypnotic agents. Midazolam for prior induction of anesthesia |
| Lorazepam, oxazepam, and temazepam | 8-10 hr | They do not have any active metabolites | Anxiolytics and hypnotic agents |
| Diazepam and chlorodizepoxide | 20-40 hr | | Anxiolytics and to produce muscle relaxation. Diazepam as anticonvulsant |
| clonazepam | 50 hr | | Anticonvulsant in children and anxtiolytic in patients with mania |
| alprazolam | 6-12 hr | | Used for antidepression as an anxillytic |

# Unwanted Effects:

1. **Toxic Effects Resulting from Acute Over Dosage**

Severe overdoses resulting in sleep prolongation, but in the presence of other CNS depressants, such as alcohol, antihistamines, or anticholinergic drugs , severe respiratory depression may occur.

2. **Side Effects During Therapeutic Use:**

The clinical use of benzodiazepines are sometimes associated with unwanted symptoms such as drowsiness, confusion, anterograde amnesia, decrease in motor coordination, and decrease in psychomotor performances.

3. **Tolerance and Dependence:**

- Stopping benzodiazepines after weeks of use might cause an abrupt appearance of terrible rebound anxiety, tremor, insomnia, and dizziness.
- Benzodiazepines cause physical dependence when used for more than 2 weeks. The withdrawal symptoms are more pronounced with short acting benzodiazepines such as triazolam.

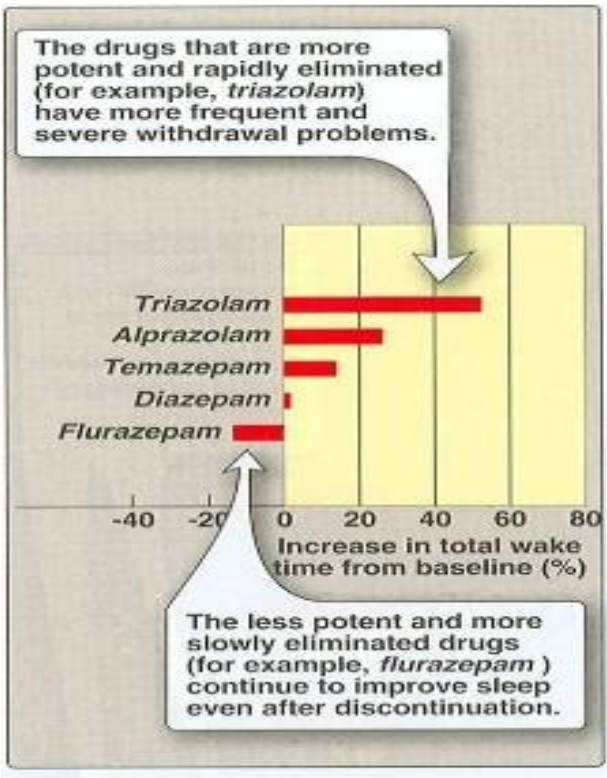
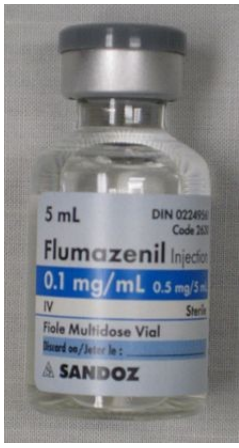



**Figure 9.5**
Frequency of rebound insomnia resulting from discontinuation of benzodiazepine therapy.

## Benzodiazepines Antagonists: Flumazenil

is a competitive antagonist of benzodiazepines.




**Pharmacokinetics:** when given intravenously, it has a short half life (0.7-1.3 hr) due to rapid hepatic clearance.

**Clinical Uses:** used for treating benzodiazepine overdose, in the reversal of deep sedative action of benzodiazepine when used during anesthesia, and to treat drowsiness and coma associated with alcohol intoxication and severe liver diseases such as hepatic encephalopathy

**Adverse Effects:** associated with adverse reactions such as agitation, confusion, dizziness, and nausea. Flumazenil may cause severe precipitated abstinence syndrome in patients who have previously developed physiologic benzodiazepine dependence.

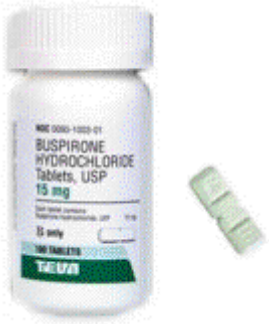
**Drug Interaction:** in patients who have ingested benzodiazepines with tricyclic antidepressants, seizures and cardiac arrhythmias may follow flumazenil administration.

## Benzodiazepines Drug Interactions:

Sedative-hypnotics interact with other CNS depressant drugs (alcoholoic baverages, opioid analgesics, anticonvulsants, and phenothiazines) which lead to additive effects. Nefazodone potentiates the action of triazolam by decreasing its metabolism by inhibiting P450 3A4. Diazepam may increase the plasma levels of digoxin and phenytoin.

## 5-HT agonists (Buspirone)

**Pharmacokinetics:** Buspirone is rapidly absorbed orally, undergoes extensive first-pass metabolism via hydroxylation and dealkylation reactions to form several active metabolites. Its t½ is 2-4h.




**Pharmacodynamics:** has high selectivity for the 5HT1A receptor resulting in selective anxiolytic effect without causing sedative, hypnotic, or anticonvulsant effects. The pharmacologic effects appear late only after two weeks from administration. Ipsapirone and gepirone are even more selective for the same receptor. It does not cause rebound anxiety or withdrawal signs. Buspirone does not affect driving skills or potentiate CNS depressant effects of other sedative hypnotic drugs.

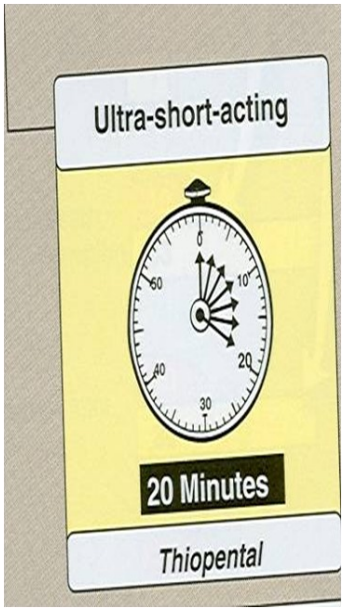
**Clinical Uses:** Used in generalized anxiety states, but is not very effective in panic disorders

**Side Effects:** nausea, dizziness, headache, restlessness, tachycardia, palpitations, gastrointestinal distress, and paraesthesias

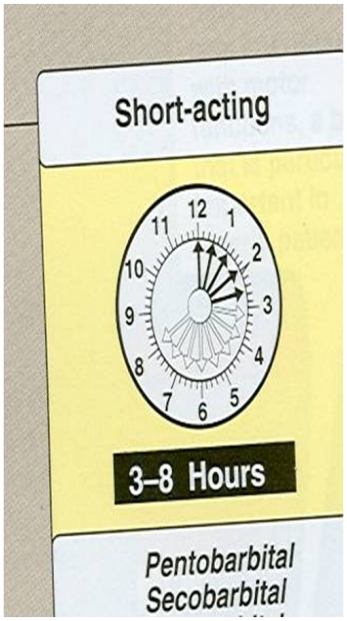
**Drug Interaction:** Blood pressure may be elevated in patients receiving MAO inhibitors. Rifampin decreases the half-life of buspirone. CYP3A3 inhibitors (erythromycin, ketoconazole) increase its plasma levels. The drug does not potentiate effects of sedative-hypnotics, ethanol, or tricyclic antidepressants.

## Barbiturates

**Pharmacokinetics:** Barbituratesare are absorbed rapidly into the blood following their oral administration. Phenobarbital is the only barbiturate excreted unchanged in the urine (20–30%), and its elimination rate can be increased significantly by alkalinization of the urine where it is considered a weak acid. Their metabolic pathway involves oxidation by hepatic enzymes to form substances which appears in the urine as glucuronide conjugates.




**Ultra Short Acting**
They have high lipid solubility with rapid tissue distribution




**Short Acting**
Used as sleeping pills and anxiolytics. This use is considered less safe.


**Long Acting**
They are effective in the treatment of generalized tonic-clonic seizures.

**Pharmacodynamics:** Barbiturates are able to enhance the action of GABA by prolonging the duration of chloride channel opening. At high doses, barbiturates can actually act directly on GABA's receptor. They have a depressant effect similar to general anesthetics due to their broad inhibitory effect on various CNS receptors.

**Adverse Effects:** high degree of tolerance and dependence. Barbiturates also induce the hepatic cytochrome P450 inducing increased metabolic degradation. Barbiturate, in relation to benzodiazepines, are more likely to causes cardiovascular and respiratory depression. Also, baribturates do aggravate porphyria crisis.

**Contraindication:** severe pulmonary insufficiency, hepatic failure, and porphyria.

## Zolpidem

**Pharmacokinetics:** Rapidly metabolized to inactive metabolites by oxidation and hydroxylation in the liver. t½ is1.5-3.5 hours.Clearance decreases in elderly patients with liver diseases or with concomitant use of cimetidine (a microsomal enzyme inhibitor). The clearance is increased by rifampin (a microsomal enzyme stimulator). It has a rapid onset and duration of action similar to triazolam.

**Pharmacodynamics:** It binds selectively to the BZ (benzodiazepine receptor). It has minimal muscle relaxing and anticonvulsant effects due to its selectivity to the GABA isoform with the α1 subunit.

**Clinical effects:** Amnesic effects have been reported with the use of doses greater than recommended. Has minor effects on sleep patterns at the recommended hypnotic dose but can suppress REM sleep at higher doses.

**Adverse effects:** It may cause rebound insomnia on abrupt discontinuance of higher doses. Lower risk of development of tolerance and dependence than benzodiazepines.

## Zaleplon

**Pharmacokinetics:** it is rapidly absorbed from the GIT. t½ is1 hour. Metabolized into inactive metabolites by hepatic aldehyde oxidase and CYP3A4 enzymes. Dosage should be reduced in the elderly and patients with hepatic impairment. Cimetidine prolongs zaleplon's peak plasma levels. Rifampin and liver microenzyme stimulators, decrease its plasma half-life.

**Clinical effects:** It is associated with the decrease of sleep latency. It carries less risk of developing amnesia or withdrawal symptoms.

## Beta Blockers

Beta-blocking drugs (eg, propranolol) may be used as antianxiety agents in situations such as **performance anxiety** (the anxiety, fear, or persistent phobia which may be aroused in an individual by the requirement toperform in front of an audience, whether actually or potentially).

## Tricyclic antidepressants (doxepin, imipramine, and desipramine)

**Pharmacodynamics:** Act by reducing the uptake of 5HT and norepinephrine

**Clinical uses:** Used for anxiety especially in those associated with depression. TCA are considered effective for panic attacks. They, however, have a delayed onset of action up to weeks.

**Side effects:** atropine-like effect (dry mouth and blurred vision), α-blocking activity (postural hypotension), sexual dysfunction, and weight gain.

## Selective serotonin reuptake inhibitors (fluoxetine)

**Pharmacokinetics:** The route of administration of fluoxetine is by the oral route. They have a long half life.

**Pharmacodynamics:** Acts by blocking the reuptake of 5HT. Weeks elapse before their onset of action starts to appear.

**Clinical uses:** It is used for panic disorders, obsessive compulsive disorder, generalized anxiety disorders (GAD), and phobia.

**Side Effects:** nausea, diarrhea, sexual dysfunction, dry mouth, seizures, sleep disturbance

## Monoamine oxidase (MAO) inhibitors (phenelzine)

**Pharmacodynamics:** Phenelzine acts by blocking the action of MAO enzyme which is essential in the degradation of norepinephrine , serotonin, and tyramine

**Clinical Uses:** used for panic attacks and phobia

**Side Effects:** dry mouth, constipation, diarrhea, restlessness, dizziness, postural hypotension, and weight gain

They require dietary restriction. Avoid the consumption of wine, beer, or fermented foods such as old cheese which contain tyramine.