Anxiolytic and Hypnotic Drugs

Anxiolytics are drugs used to treat anxiety and hypnotics are drugs used to treat insomnia (sleep inducing drugs).

Anxiety is an unpleasant state of tension, apprehension, or uneasiness (Figure 1), it is a fear response that arises from either a known or an unknown source. The physical symptoms of severe anxiety are similar to those of fear including tachycardia, sweating, trembling, palpitations (Figure 2) 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 (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 agents.

There is some overlap between anxiolytics and hypnotics, reflecting the fact that (older) anxiolytic drugs commonly caused a degree of sedation and drowsiness. Newer anxiolytic drugs show much less sedative effect and other hypnotic drugs have been introduced that lack specific anxiolytic effects. In high doses, all these drugs cause unconsciousness, and eventually death from respiratory and cardiovascular depression.

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. Benzodiazepines include Alprazolam (XANAX), Chlordiazepoxide (LIBRIUM), Clonazepam, Clorazepate, Diazepam (VALIUM), Estazolam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Quazepam, Temazepam, Triazolam, nitrazepam.

Mechanism of action

The targets for benzodiazepine actions are the γ -aminobutyric acid (GABA) receptors. $GABA_A$ is the major inhibitory neurotransmitter in the CNS. The $GABA_A$ receptors are composed of a combination of five subunits (α, β, and γ) that span the postsynaptic membrane (Figure 3). For each subunit, many subtypes exist. Binding of GABA to its receptor triggers an opening of the ion channel, allowing chloride influx through the pore causing hyperpolarization of the neuron and decreasing 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 on the $GABA_A$ receptor. These binding sites are sometimes labeled "benzodiazepine (BZ) receptors. Common BZ receptor subtypes in the CNS are designated as BZ1 or BZ2 depending on whether the binding site includes an α1 or α2 subunit, respectively.

Benzodiazepines act by increase the frequency of channel openings produced by GABA and increase the affinity of GABA for the GABA-binding site (Figure 4). Benzodiazepines do not affect receptors for other amino acids like glycine or glutamate.

Actions and therapeutic uses of benzodiazepines

Benzodiazepines have neither antipsychotic activity nor analgesic action, and they do not affect the autonomic nervous system. Benzodiazepines have the following actions:

1- Reduction of anxiety (Anxiolytic action): At low doses, benzodiazepines are anxiolytic, they reduce anxiety and aggression. They are thought to reduce anxiety by selectively enhancing $GABA_A$ receptors having the α2 subunit, thereby inhibiting neuronal circuits in the limbic system of the brain.

Benzodiazepines are effective for the treatment of the anxiety symptoms of various types. These drugs should be reserved for severe anxiety only and not used to manage the stress of everyday life. Because of their addiction potential, they should only be used for short periods of time. The longer-acting agents, such as clonazepam, lorazepam and diazepam, are often preferred in those patients with anxiety that may require prolonged treatment. Tolerance occurs when used for more than 1 to 2 weeks. Tolerance to anxiolytic effect is less likely to develop than the sedative effects. Cross-tolerance exists between the benzodiazepines and ethanol.

2- Sedation and hypnotic actions: 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 α1 -$GABA_A$ receptors. Benzodiazepines decrease the time taken to get to sleep, and increase the total duration of sleep (Figure 5).

A few of the benzodiazepines are useful as hypnotic agents. Both REM sleep and slow-wave sleep are decreased (Figure 6). In the treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation ("hangover") upon awakening. Commonly prescribed benzodiazepines for sleep disorders include intermediate-acting (e.g. temazepam) and short-acting (e.g. triazolam). Long-acting (e.g. flurazepam) is rarely used, due to its extended half-life, which may result in excessive daytime sedation and accumulation of the drug, especially in the elderly (Figure 5).

Temazepam is useful in patients who experience frequent wakening and inability to stay sleep, whereas short-acting triazolam is effective in treating individuals who have difficulty in going to sleep. Tolerance to triazolam frequently develops within a few days, and withdrawal of the drug often results in rebound insomnia. Therefore, this drug is not a preferred agent, and it is best used intermittently. In general, hypnotics should be given for only a limited time, usually less than 2 to 4 weeks.

3- Muscle relaxant: At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing inhibition in the spinal cord, where the α2 -$GABA_A$ receptors are largely located. Baclofen is a muscle relaxant that is believed to affect GABA receptors at the level of the spinal cord.

Benzodiazepines reduce muscle tone by a central action as increased muscle tone is a common feature of anxiety states in humans and may contribute to the aches and pains, including headache, that often trouble anxious patients (Figure 7). The relaxant effect of benzodiazepines may therefore be clinically useful. A reduction of muscle tone appears to be possible without appreciable loss of coordination. However, with intravenous administration in anesthesia and in overdose when these drugs are being abused, airway obstruction may occur.

Diazepam is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain, and in

treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

4- Anticonvulsant: Several benzodiazepines have anticonvulsant activity. This effect is partially, although not completely, mediated by α1 -$GABA_A$ receptors. Lorazepam and diazepam (and to lesser extent clonazepam) are used to treat epilepsy, they can be given intravenously to control life-threatening seizures in status epilepticus.

5- Aterograde amnesia: Temporary impairment of memory with use of the benzodiazepines is also mediated by the α1 –$GABA_A$ receptors. The ability to learn and form new memories is also impaired. Benzodiazepines prevent memory of events experienced while under their influence, an effect not seen with other CNS depressants. Minor surgical or invasive procedures can thus be performed without leaving unpleasant memories.

The shorter-acting agents are often employed as premedication for anxiety-provoking and unpleasant procedures, such as endoscopy, dental procedures, and angioplasty. They cause a form of conscious sedation, allowing the person to be receptive to instructions during these procedures. Midazolam used to facilitate amnesia while causing sedation prior to anesthesia.

Pharmacokinetics

Benzodiazepines are lipophilic drugs. They are rapidly and completely absorbed after oral administration, distribute throughout the body and penetrate into the CNS.

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 (Figure 8). The longer-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 active metabolites, t 1/2 of diazepam and its active metabolites about 50 hrs while the duration of action about 4-6 hrs). This may be due to receptor dissociation rates in the CNS and subsequent redistribution to fatty tissues and other areas.

Most benzodiazepines, including chlordiazepoxide and diazepam, are metabolized by the hepatic enzymes to compounds that are also active (Figure 9). For these benzodiazepines, the apparent half-life of the drug represents the combined actions of the parent drug and its metabolites. Drug effects are terminated not only by excretion but also by redistribution. The benzodiazepines are excreted in the urine as glucuronides or oxidized metabolites. All benzodiazepines cross the placenta and may depress the CNS of the newborn if given before birth, thus are not recommended for use during pregnancy. Nursing infants may also be exposed to the drugs in breast milk.

Unwanted effects
These may be divided into:
• Toxic effects resulting from acute overdosage
• Unwanted effects occurring during normal therapeutic use
• Tolerance and dependence

Toxic effects resulting from acute overdosage:

Benzodiazepines in acute overdose are considerably less dangerous than other anxiolytic/hypnotic drugs. In overdose, benzodiazepines cause prolonged sleep, without serious depression of respiration or cardiovascular function. However, in the presence of other CNS depressants, particularly alcohol, benzodiazepines can cause severe, even life-threatening, respiratory depression. The availability of an effective antagonist, flumazenil (competitive antagonist of benzodiazepine receptor), means that the effects of an acute overdose can be counteracted, which is not possible for most CNS depressants.

Unwanted effects occurring during normal therapeutic use:
The main side effects of benzodiazepines are drowsiness, confusion, amnesia and ataxia (impaired coordination), which considerably impair manual skills such as driving performance. Benzodiazepines enhance the depressant effect of other drugs, including alcohol.

Tolerance and dependence
Tolerance (i.e. a gradual escalation of dose needed to produce the required effect) occurs with all benzodiazepines, as does dependence, which is their main drawback. They share these properties with other sedatives. Tolerance appears to represent a change at the receptor level, but the mechanism is not well understood. It is thought that tolerance is associated with a decrease in GABA receptor density. Tolerance develops when benzodiazepines are used continuously whereas less tolerance occurs to the sleep-inducing effect when the subject is relatively drug free during the day.

Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given for a prolonged period. Abrupt discontinuation of the benzodiazepines 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 (Figure 10). It is recommended that benzodiazepines be withdrawn gradually by stepwise lowering of the dose.

Benzodiazepines should be used cautiously in patients with liver disease. These drugs should be avoided in patients with acute angle closure glaucoma. Alcohol and other CNS depressants enhance the sedative–hypnotic effects of the benzodiazepines. Benzodiazepines are, however, considerably less dangerous than the older anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal unless other central depressants, such as alcohol, are taken concurrently.

Benzodiazepine antagonist

Flumazenil is a GABA receptor competitive antagonist that can rapidly reverse 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. Dizziness, nausea, vomiting, and agitation are the most common side effects.

Other anxiolytic drugs
Buspirone

It is useful for the treatment of various chronic anxiety types (GAD generalized anxiety disorder), phobias, social anxiety disorder and post-traumatic stress disorder) and has an efficacy comparable to that of the benzodiazepines. It has a slow onset of action and is not effective for short-term or "as-needed" treatment of acute anxiety states. The actions of buspirone appear mainly to be mediated by activation of serotonin (5-HT1A) receptors. 5-HT1A receptors are expressed on the serotonin containing neurons, where they function as inhibitory autoreceptors. Buspirone also displays some affinity for blocking D2 dopamine receptors and activating 5-HT2A serotonin receptors but these effects thought to have little effect on its anxiolytic action. Buspirone takes days or weeks to produce its effect in humans, suggesting a more complex mechanism of action than simply activation of 5-HT1A receptors. In addition, buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines. Sedation, psychomotor dysfunction and cognitive dysfunction are minimal. Tolerance and dependence is unlikely. Buspirone does not potentiate the effect of CNS depressants and alcohol.
The frequency of adverse effects is low, with the most common effects being headache, dizziness, nervousness, nausea, and light-headedness.

Antidepressant drugs

Many antidepressants are effective in the treatment of chronic anxiety disorders and should be considered as first-line agents, especially in patients with concerns for addiction or dependence. Selective serotonin reuptake inhibitors (SSRIs, such as escitalopram or paroxetine) or serotonin/norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine or duloxetine) may be used alone or prescribed in combination with a low dose of a benzodiazepine at first, then when the antidepressant begins to produce an anxiolytic effect, the benzodiazepine dose can be tapered. SSRIs and SNRIs have a lower potential for physical dependence than the benzodiazepines and have become first-line treatment for GAD.

Barbiturates

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. Today, they have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance and physical dependence and are associated with very severe withdrawal symptoms. All barbiturates are controlled substances. Certain barbiturates, such as the very short-acting thiopental, have been used to induce anesthesia but are infrequently used today due to the advent of newer agents with fewer adverse effects.
Barbiturate drugs include Amobarbital, Pentobarbital, Phenobarbital, Secobarbital, Thiopental.

Mechanism of action

The sedative–hypnotic action of the barbiturates is due to their interaction with $GABA_A$ receptors,

which enhances GABAergic transmission. The binding site of barbiturates on the GABA receptor is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings. In addition, barbiturates can block excitatory glutamate receptors. Anesthetic concentrations of pentobarbital also block high-frequency sodium channels. All of these molecular actions lead to decreased neuronal activity.

Actions

1- Depression of CNS: Barbiturates depress CNS in dose dependent manner. At low doses, they produce sedation (have a calming effect and reduce excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and, finally, coma and death. Barbiturates do not raise the pain threshold (do not impair pain sensation) and have no analgesic properties. They may even exacerbate pain at low doses.

2- Respiratory depression: Barbiturates suppress the hypoxic and chemoreceptor response to CO2. Death due to overdosage resulted from respiratory depression.

Therapeutic uses:

1- Anesthesia: The ultra–short-acting barbiturates, such as thiopental, have been used intravenously to induce anesthesia but have largely been replaced by other agents.

2- Anticonvulsant: Phenobarbital has specific anticonvulsant activity. It is used in long-term management of tonic–clonic seizures and refractory status epilepticus. However, phenobarbital can depress cognitive development in children and decrease cognitive performance in adults, and it should be used only if other therapies have failed.

3- Sedative and hypnotic: Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. When used as hypnotics, they suppress REM sleep and slow wave sleep more than other stages. However, the use of barbiturates for insomnia is no longer generally accepted, given their adverse effects and potential for tolerance.

Pharmacokinetic

Barbiturates are classified according to their duration of action (Figure 11). Ultra–short-acting thiopental acts within seconds and has duration of action of about 30 minutes. In contrast, long-acting phenobarbital has duration of action greater than a day. Pentobarbital, secobarbital , amobarbital, and butalbital are short-acting barbiturates

Barbiturates are well absorbed after oral administration and distribute throughout the body. All barbiturates redistribute from the brain to the splanchnic areas, to skeletal muscle, and, finally, to adipose tissue. This movement is important in causing the short duration of action. Barbiturates readily cross the placenta and can depress the fetus. These agents are metabolized in the liver, and inactive metabolites are excreted in urine (Figure 12).

Barbiturates strongly induce hepatic microsomal CYP450 and conjugating enzymes and thus increasing the rate of metabolic degradation of its own leading to pharmacokinetic tolerance. Barbiturates also enhance the rate of metabolism of other drugs giving rise to a number of important drug - drug interactions.

Adverse effects

Barbiturates cause drowsiness, impaired concentration, and mental and physical sluggishness. The CNS depressant effects of barbiturates synergize with those of ethanol. Hypnotic doses of barbiturates produce a drug "hangover" that may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur.
Barbiturates cause tolerance and dependence, therefore, abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opiates or benzodiazepines and can result in death. Severe depression of respiration is coupled with central cardiovascular depression and results in a shock-like condition.

Other hypnotic drugs
Zolpidem, Zaleplon, zopiclone and Eszopiclone

They are not structurally related to benzodiazepines, but they selectively binds to the benzodiazepine receptor subtype BZ1 (enhance $GABA_A$). They have no anticonvulsant or muscle-relaxing properties. They show few withdrawal effects, exhibits minimal rebound insomnia, and little tolerance occurs with prolonged use. They are rapidly absorbed from the gastrointestinal (GI) tract, and they have rapid onset of action and short elimination half-life (1-6 hrs) and thus short duration of action.
They undergo hepatic oxidation by the CYP450 system to inactive products. Unlike the benzodiazepines, at usual hypnotic doses, the nonbenzodiazepine drugs zolpidem, zaleplon, zopiclone and eszopiclone, do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics. This may be due to their relative selectivity for the BZ1 receptor. All three agents are controlled substances.

Ramelteon
It is a selective agonist at the MT1 and MT2 subtypes of melatonin receptors. Melatonin is a hormone secreted by the pineal gland that helps to maintain the circadian rhythm underlying the normal sleep–wake cycle. Stimulation of MT1 and MT2 receptors by ramelteon is thought to induce and promote sleep. Ramelteon is indicated for the treatment of insomnia characterized by difficulty falling asleep (cause decrease in sleep latency). It has minimal potential for abuse, and no evidence of dependence or withdrawal effects has been observed. Therefore, ramelteon can be administered long term.
Common adverse effects of ramelteon include dizziness, fatigue, and somnolence. Ramelteon may also increase prolactin levels.

Antihistamines
Some antihistamines with sedating properties, such as diphenhydramine, hydroxyzine, and doxylamine, are effective in treating mild types of situational insomnia. However, they have undesirable side effects (such as anticholinergic effects) that make them less useful than the

benzodiazepines and the nonbenzodiazepines.

Antidepressants

The use of sedating antidepressants with strong antihistamine profiles has been ongoing for decades. Doxepin, trazodone, mirtazapine used at low doses for the management of insomnia.

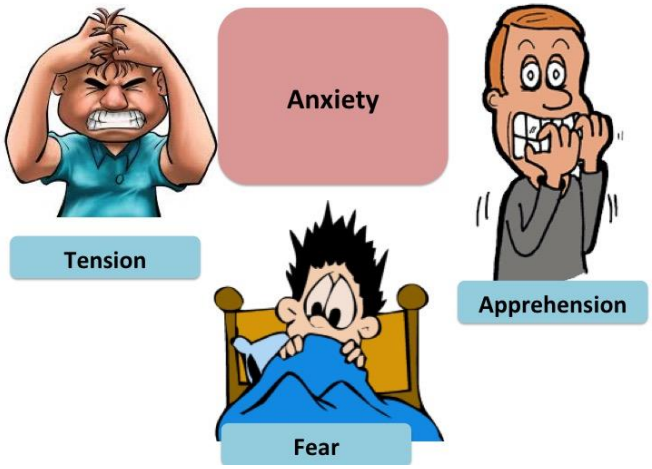

Figure 1: anxiety

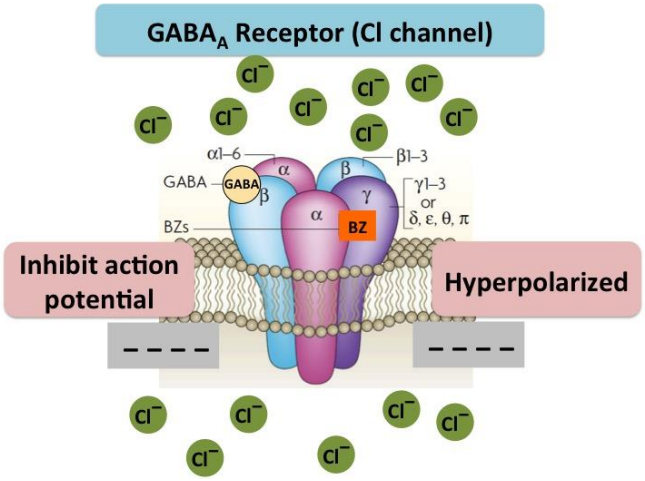

Figure 3: Mechanism of action of BZ

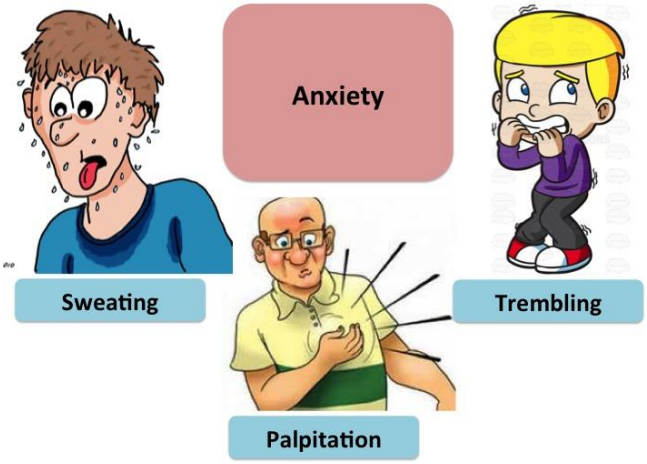

Figure 2: Symptoms of anxiety

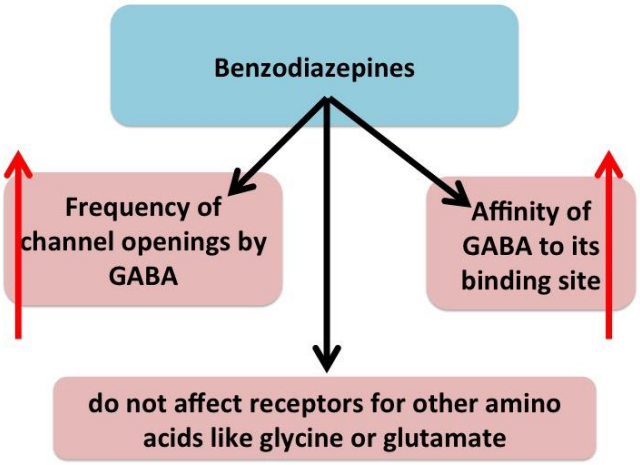

Figure 4: effects of BZ on GABA receptors

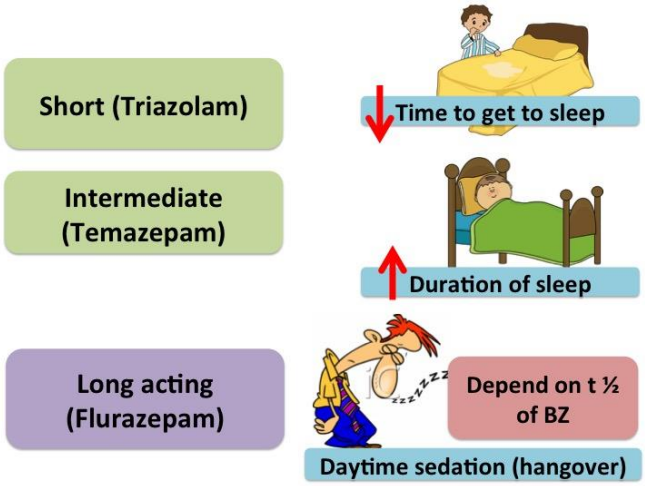

Figure 5: Hypnotic effects of BZ

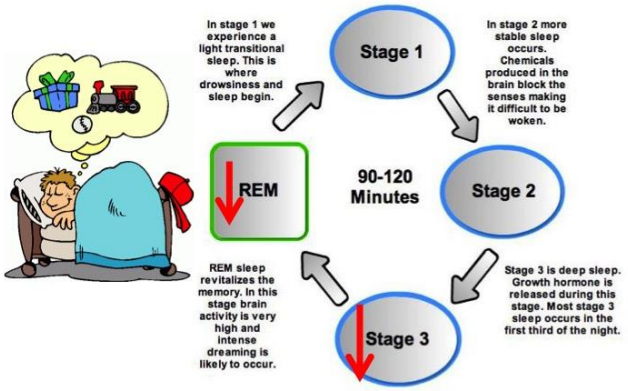

Figure 6: Effects of BZ on sleep stages

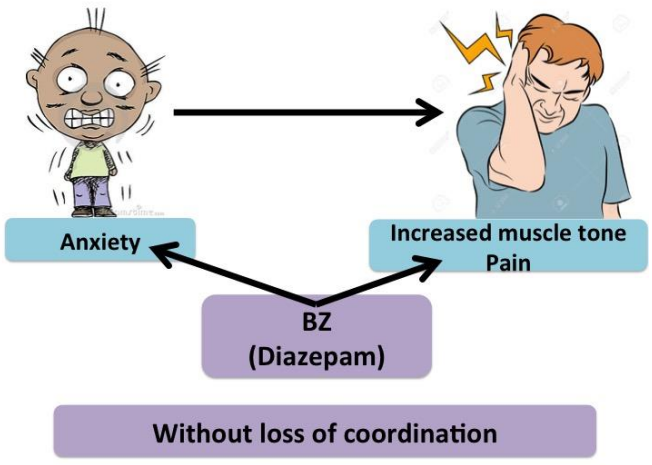

Figure 7: muscle relaxant effect of BZ

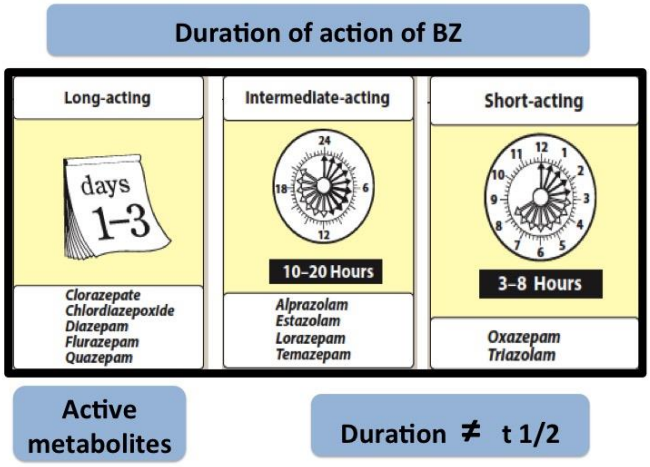

Figure 8: Duration of action of BZ

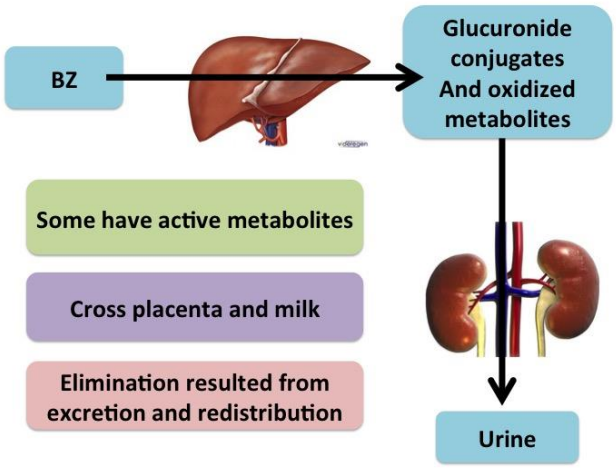

Figure 9: Pharmacokinetic of BZ

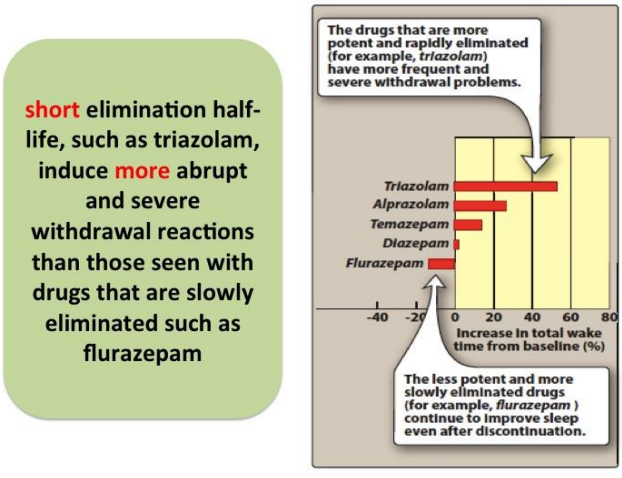

Figure 10: Duration of action of BZ in relation to withdrawal symptoms.

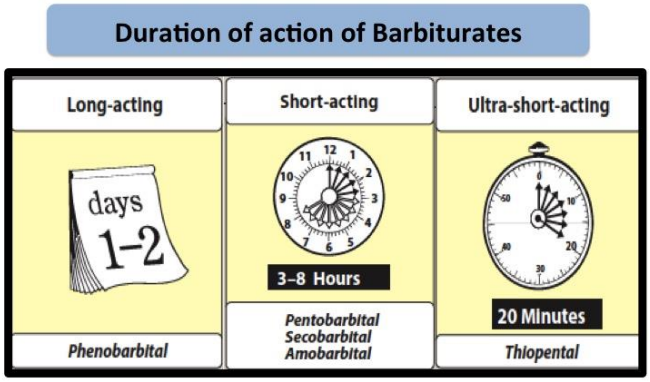

Figure 11: Duration of action of Barbiturates

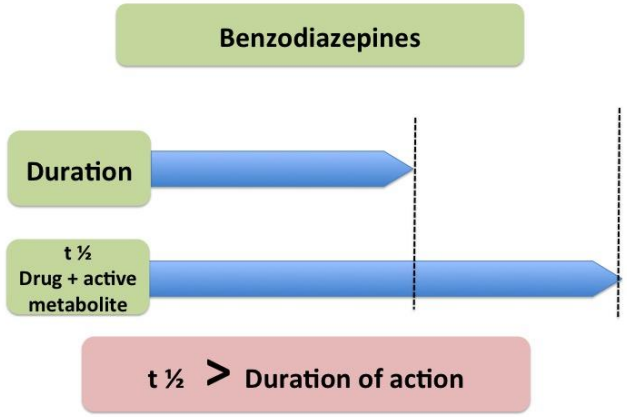

Figure: Benzodiazepine duration of action not correlated with t ½.

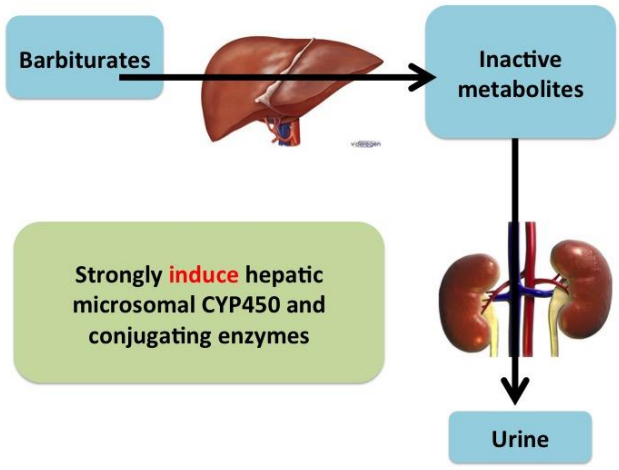

Figure 12: Barbiturate's pharmacokinetics

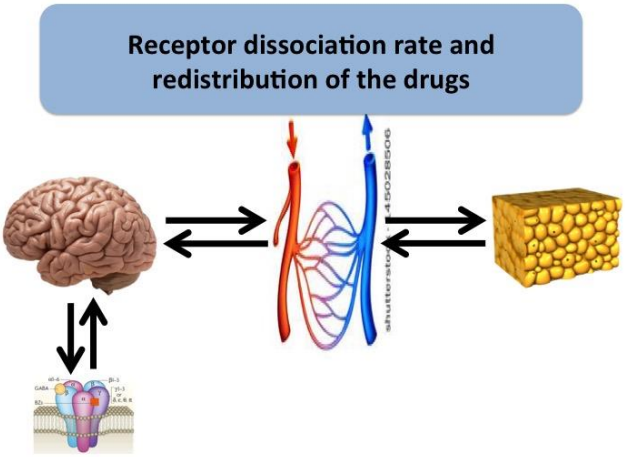

Figure: Redistribution of the drug between lead to short duration of action.

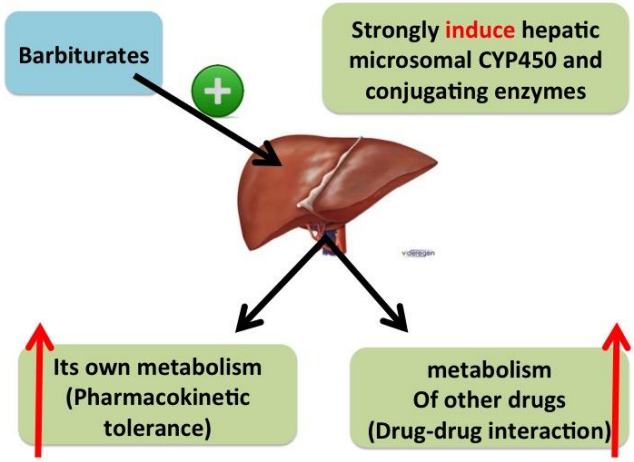

Figure: Barbiturates pharmacokinetics.