

Sedative-Hypnotic Drugs

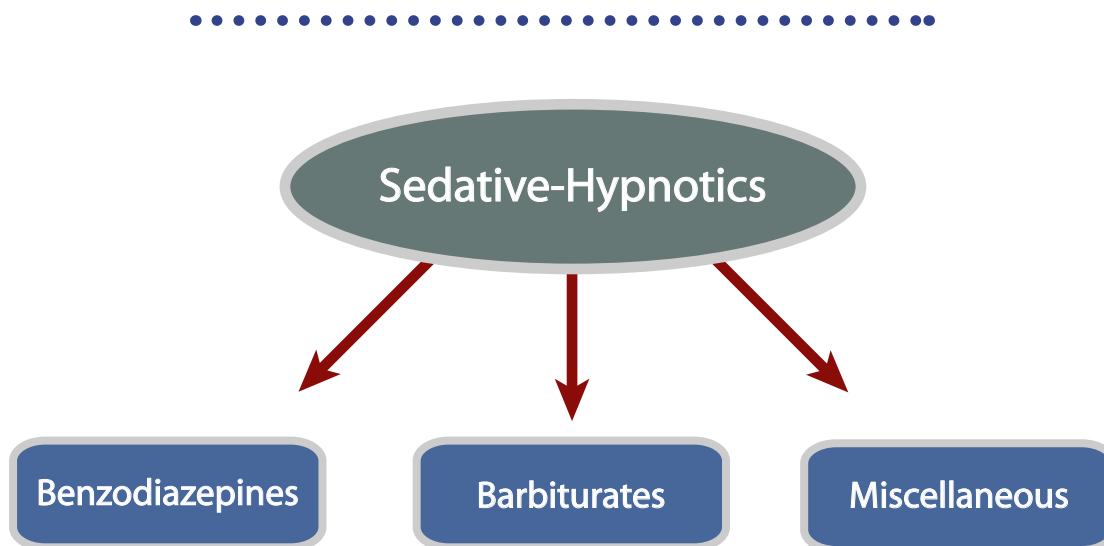
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Pharmacy 725: Principles of Drug Mechanisms
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In terms of drugs, *sedative* refers to a substance that moderates activity and excitement while inducing a calming effect, while *hypnotic* refers to a substance that causes drowsiness and facilitates the onset and maintenance of natural sleep. The term *anxiolytic* is sometimes applied to a sedative-hypnotic; however, be aware that many other drugs, especially the selective-serotonin reuptake inhibitors (SSRIs), are useful as chronic anxiolytics, as demonstrated by their efficacy in certain psychiatric disorders like generalized anxiety disorder.

Due to their pharmacodynamic actions, especially the sedative effects, many of the sedative-hypnotics are considered *potential drugs of abuse*, and are therefore regulated as controlled substances. Along these lines, several sedative-hypnotic drugs have developed an interesting and alarming niche in the group of “club drugs” that have become popular in the past decade. One such example is the widespread use of *alprazolam (Xanax®)* in combination with stimulant drugs of abuse, such as ecstasy or methamphetamine.

In clinical therapeutics, sedative-hypnotics are useful for treatment of a variety of diseases related to the central nervous system, such as acute and chronic anxiety, anesthesia, seizure control, and insomnia. The sedative-hypnotics may be divided into three major groups: (1) *benzodiazepines*, (2) *barbiturates*, and (3) other drugs that do not fall into either of the first two groups.



Chemistry & Molecular Pharmacology

Benzodiazepines

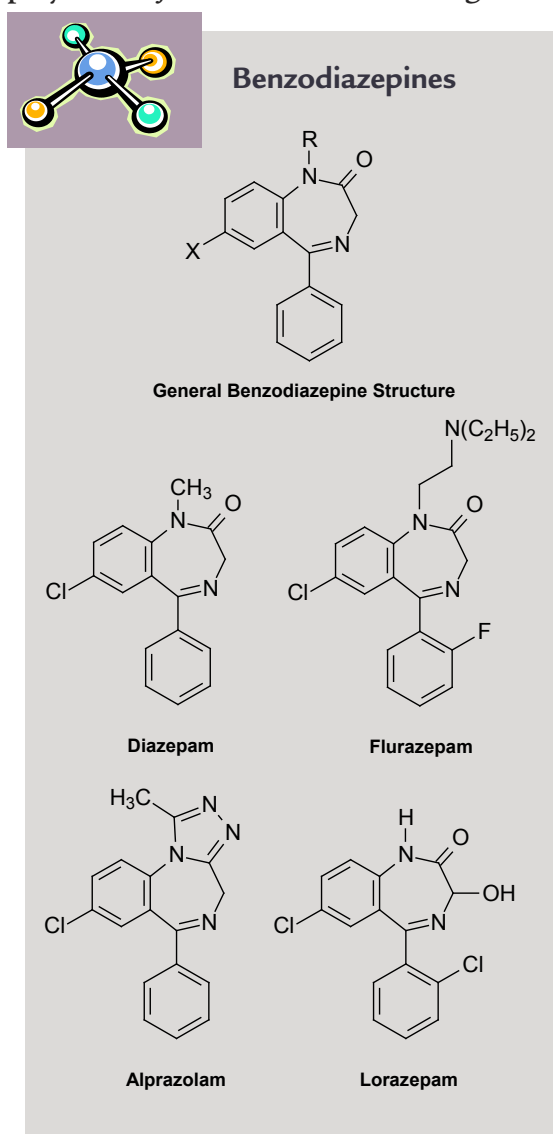
All of the *benzodiazepines have the same general chemical structure*, as shown below. Different benzodiazepine drugs have been developed through the years based on chemical substitutions at two major positions on the benzodiazepine structure. Therefore, all benzodiazepines are simply variations on the same core chemical structure.

The benzodiazepines are frequently classified into three groups: (1) *short-acting*, (2) *intermediate-acting*, and (3) *long-acting*. The *duration of action* for an individual benzodiazepine plays a major role in determining how that specific drug will be used clinically. The duration of action is dependent on two factors:

(1) *the half-life* and (2) *the metabolic fate* of the benzodiazepine.

The first factor, the drug half-life, is the time it takes for 50% of the drug to be eliminated. *The longer the half-life, the longer the duration of action.*

The second factor that determines the duration of action is the metabolic fate of the benzodiazepine after it enters the body. In many cases, a benzodiazepine will be metabolized by enzymes in the body to another benzodiazepine with the same pharmacodynamic effects (i.e.,



Benzodiazepine	Classification	Half-Life ¹
Midazolam *	Short-Acting	2-6
Triazolam *	Short-Acting	2-3
Alprazolam *	Intermediate-Acting	12-15
Estazolam	Intermediate-Acting	10-24
Lorazepam *	Intermediate-Acting	10-20
Temazepam	Intermediate-Acting	10-40
Clonazepam	Long-Acting	18-50
Clorazepate	Long-Acting	40-50
Diazepam *	Long-Acting	20-80
Flurazepam	Long-Acting	40-100

¹ Half-life includes parent drug and active metabolites

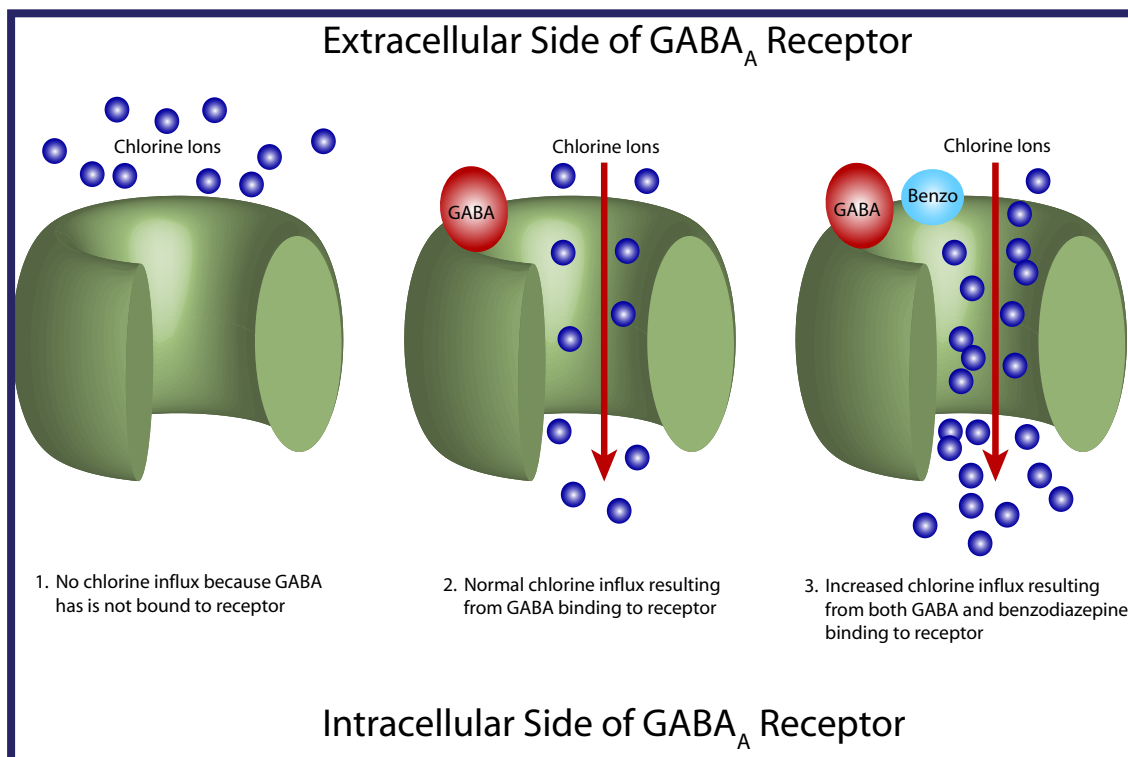
* Know name and classification for exam

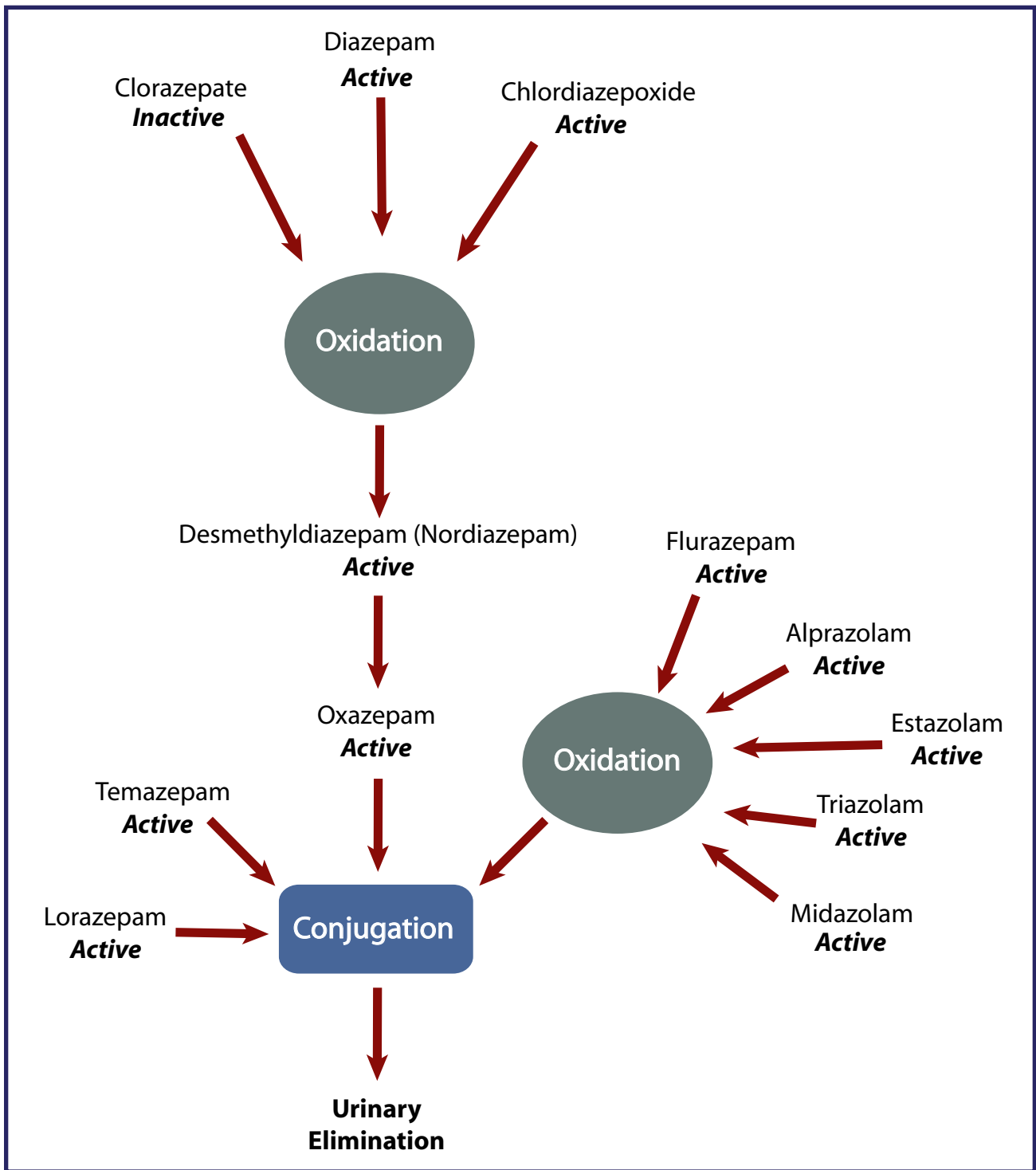
an *active metabolite*). In fact, several benzodiazepines are actually converted into other benzodiazepines that are also marketed drugs. For example, *diazepam (Valium®)* is metabolized in two steps to *oxazepam (Serax®)*.

To summarize, the *duration of action of an individual benzodiazepine is a combination of the half-life of the parent drug and the half-life of any active metabolites* generated by drug metabolism.

Most of the benzodiazepines undergo both oxidative metabolism (phase 1 metabolism) and conjugation to glucuronic acid, or glucuronidation (phase 2 metabolism). Both types of drug metabolism will be discussed in detail during Biopharmaceutics & Introductory Pharmacokinetics in the first semester of your second year of classes. For now, what is important to know is that some benzodiazepines do *not* undergo significant oxidative metabolism (*temazepam, oxazepam, lorazepam*); there may be some benefit to using these agents in patients with liver disease or compromised hepatic function, as the majority of oxidative metabolism occurs in the liver. The *diagram on the following page* outlines the general metabolic pathway of most currently marketed benzodiazepines.

The molecular site of action for the benzodiazepines is at the *GABA_A receptors* in the CNS. GABA, or *gamma-aminobutyric acid*, is an amino acid neurotransmitter that has an inhibitory effect on neurotransmission in the CNS. Therefore, an increase in the effect of GABA results in general suppression of the CNS. When GABA binds to GABA_A receptors,





the result is an influx of chlorine ions into neurons through the ion channel formed by the receptor. *It is the influx of chlorine that causes the negative effect on neurotransmission.* On the GABA_A receptors there is also a site, separate from the GABA binding site, for benzodiazepines to bind at. When both GABA and a benzodiazepine is bound to a GABA_A receptor, the result is an *increase in the influx of chlorine* through the ion channel of the receptor (*see figure on page 3*). Therefore, benzodiazepines are said to increase the effect that GABA has at GABA_A receptors when it binds.

Another way to explain this is that benzodiazepines increase the agonist effect of GABA at the GABA_A receptors. Overall, this effect is said to be *gabaergic*, because the overall effect is one of increasing the inhibitory effect of GABA in the CNS.

Finally, it should be pointed out that the benzodiazepines do not have a direct effect on the GABA_A receptor; if GABA is not bound to the GABA_A receptor, then benzodiazepine binding has no effect on chlorine ion influx.

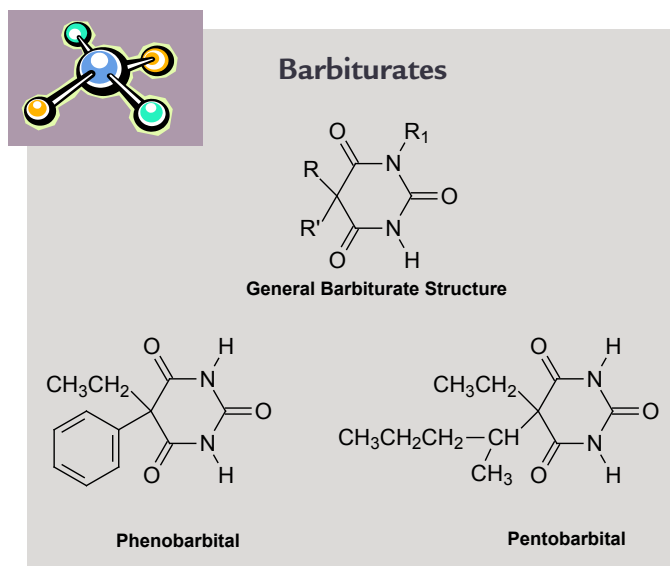
Barbiturates

Like the benzodiazepines, the *barbiturates* have a general chemical structure that gives rise to multiple therapeutic agents by chemical substitutions at various positions on that general structure. Several representative structures are shown here.

The barbiturates may also be divided into groups based on their duration of action. However, given the relative lack of use of barbiturates in modern medicine, we will not go into many details here. Basically, the barbiturates have had their day in medicine, and have largely been replaced by much safer benzodiazepines and other CNS drugs.

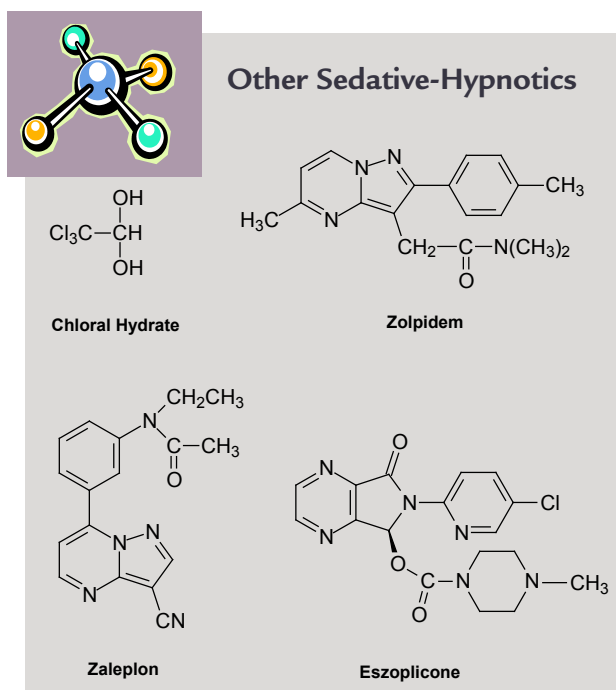
The molecular site of action for the barbiturates is nearly the same as for the benzodiazepines. Like benzodiazepines, barbiturates bind at a unique site on the GABA_A receptor. However, there is a significant difference in the effect of barbiturates at these receptors that is dependent on the dose administered.

At lower doses, barbiturates act like benzodiazepines, and simply increase the effect of GABA at the GABA_A receptor. However, *at higher doses*, barbiturates may act as direct agonists at GABA_A receptors in the place of GABA, producing profound CNS depression. This partially explains the increased risk associated with barbiturate use relative to benzodiazepine risk (*see toxicity section*).



Other Sedative-Hypnotics

The history of sedative-hypnotics is rich, and many of the older drugs have a colorful history in our society. For example, Placidyl® is an older drug that frequently shows up in fiction (an occasionally non-fiction) works of the sixties and seventies as a popular drug to commit suicide or poison someone with. Chloral hydrate has been immortalized in pop-culture as one of two ingredients in a “Mickey Finn”. However, for the most part, these older agents have been replaced by safer medications with fewer side effects.



There are three newer agents that do not fit into either the benzodiazepine or barbiturate class that are currently used often, especially for their hypnotic effects. **Zaleplon**, **zolpidem** and **zopiclone** (**eszopiclone**, the active enantiomer of zopiclone, is the marketed form of zopiclone in the U.S.) all bind to the benzodiazepine receptor at the GABA_A receptor and increase the effect of GABA at the receptor. However, none of these drugs produce effects that are identical to the benzodiazepines, and all of these drugs have chemical structures that are unrelated to the benzodiazepines. You may see these drugs abbreviated as **NBRAs** (**nonbenzodiazepine benzodiazepine-receptor agonists**).

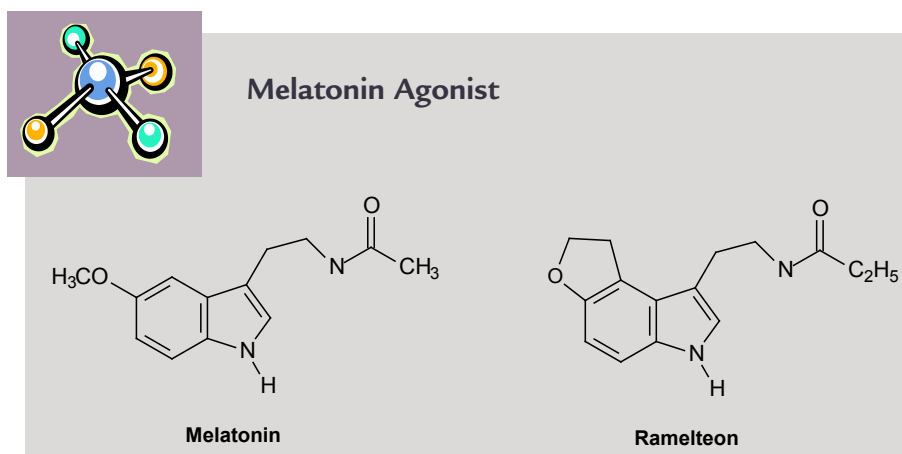
The NBRAs have shorter durations of action and shorter half-lives relative to most benzodiazepines. This is why you will often

see these drugs referred to as NBRAs - they are similar to benzodiazepines in their site of action and effect at the GABA_A receptor, but their chemistry, duration of action, and adverse effect profiles are somewhat different, and improved, relative to the benzodiazepines.

Buspirone is an anxiolytic drug in a chemical class of its own that is often classified with the sedative-hypnotics. Buspirone is a **partial agonist at 5-HT_{1A} (serotonin) receptors**.

Ramelteon is a new hypnotic agent that is in a chemical and pharmacological class of its own. Ramelteon was designed to be a chemical mimic of the endogenous hormone **melatonin**, and is an agonist with affinity for two types of melatonin receptors: (1) **melatonin type 1 (MT₁)** and (2) **melatonin type 2 (MT₂)**. Melatonin is a hormone secreted by the pineal gland (a gland in the central nervous system attached to the wall of the third ventricle) and is believed to be important in regulating the sleep-wake cycles in humans and other mammals. The production and release of melatonin varies by a circadian rhythm, and in-

creases in the evening concurrent with the onset of sleepiness. Melatonin is available as a natural product for sleep aid; however, its efficacy is questionable. Ramelteon is a more potent agonist at the MT₁ and MT₂ receptors than melatonin, and was recently approved for treatment of insomnia characterized by difficulty with sleep onset. Ramelteon has the distinction of being the only hypnotic prescription medication in the United States that is not a controlled substance.



Pharmacodynamic Effects & Uses of Sedative-Hypnotic Drugs

As their name suggest, the sedative-hypnotic drugs have a *sedative, calming, and anxiolytic* effect on patients, especially those who are acutely anxious. However, this calming effect is generally accompanied by some psychomotor and cognitive effects as well. *Lorazepam, alprazolam* and the nonbenzodiazepine *buspirone* are examples of drugs extensively used as anxiolytic drugs.

At high enough doses, all of these drugs will induce sleep (*hypnosis*). However, some are better than others for use as an aid for inducing sleep. While most of these drugs decrease the time it takes to fall asleep, they also unfortunately decrease the amount of time spent in REM sleep (*zaleplon* is an exception, as it does not change the time spent in REM sleep). The decrease in the time it takes to fall asleep makes many of these drugs useful as a sleep aid; however, the effect of the decrease in REM sleep induced by most of these drugs is currently unclear, and may explain some of the negative effects of these drugs.

Many of these benzodiazepines, as well as zolpidem and zaleplon, are indicated for short-term relief of insomnia. Zopiclone has been used in other countries for over 20 years, and was recently marketed in the U.S. as the active enantiomer (*eszopiclone*). *Eszopiclone* is

unique in that it *may be used chronically*, while nearly all other marketed hypnotics are approved for *short-term relief of insomnia (10 days or less)*.

A third major area of use for the sedative-hypnotics is *anesthesia*. Some these drugs are very useful as anesthetic agents (e.g., *barbiturates*), while others are not useful at all. The usefulness of these drugs in anesthesia is largely dependent on their onset of action and their duration of action.

Many of the sedative-hypnotics produce CNS effects that are useful for preventing and treating certain seizure disorders. Several benzodiazepines, such as *diazepam*, *clonazepam*, and *lorazepam*, are useful for treatment of generalized seizures (e.g., Grand Mal seizures). Also, phenobarbital and mephobarbital are useful for generalized and some types of partial seizure disorders. However, with the development of newer and safer anticonvulsants, the use of barbiturates in seizure disorders has significantly decreased in recent years.

Some sedative-hypnotic drugs, especially the benzodiazepines, cause *amnesia without a loss of consciousness*, which may be desirable during certain medical procedures when the patient needs to be awake and responsive, but also when memory of the event is not desired. The use of *midazolam (Versed®)* during endoscopy and colonoscopy procedures and as a precursor drug to general anesthesia is a great example of this particular effect being used in clinical practice.

With the exception of the barbiturates, most of the sedative-hypnotics have surprisingly few effects on cardiovascular and respiratory activity when used at therapeutic doses. However, in patients with heart failure or hypovolemia, sedative-hypnotics drugs may cause adverse effects in the cardiovascular and respiratory systems.

Finally, some sedative-hypnotics, such as the benzodiazepines, produce a muscle-relaxant effect. However, these agents are rarely used clinically for this purpose.



Toxicity & Pharmacodynamic Drug Interactions

A major adverse effect of nearly all sedative-hypnotic drugs is that of *tolerance and potential drug abuse*. With continual use, patients will develop tolerance to many of these drugs, especially when used at hypnotic doses. Most of the sedative-hypnotic drugs have the potential for causing both physical and psychological tolerance.

In some cases, and especially with the short-acting and intermediate-acting benzodiazepines, abrupt withdrawal of therapy after physical tolerance has developed may result in rebound effects, that are at best, manifested as mild anxiety, and at worst, manifested as *generalized seizures* (alprazolam is especially notorious for causing seizures upon withdrawal of the drug after relatively chronic use). As mentioned previously, nearly

all of these drugs are controlled substances because of these effects. Overall, the newer, nonbenzodiazepine drugs have less potential for tolerance and abuse.

One major concept to grasp with regard to the toxicity of the sedative-hypnotics is that many of these agents may be placed into two groups: (1) those that can induce coma and death with overdose, and (2) those that typically produce anesthesia, but do not induce coma and death with overdose.

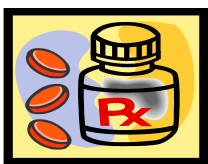
Many of the older sedative hypnotics, such as the barbiturates, *will induce coma and death* due to profound CNS depression if a patient significantly overdoses on their medication. In fact, overdosing on a sedative-hypnotic is a fairly popular method for attempting suicide.

On the other hand, at acute and high overdoses, the benzodiazepines and the newer nonbenzodiazepine sedative-hypnotics *will typically produce anesthesia that does not proceed to the point of coma and death*. This is a major reason why the benzodiazepines and the newer nonbenzodiazepines have nearly replaced the older barbiturates and other drugs for use as sedatives and hypnotics.

The benzodiazepines with an especially long duration of action may produce a “hangover” effect in which the patient remains drowsy even after 8-10 hours of sleep. The shorter-acting benzodiazepines have become more popular as sleep aids in recent years, as many avoid this hangover somnolent effect.

Most pharmacodynamic drug interactions with sedative-hypnotic drugs are easy to predict. Essentially, any other drug that has depressive effects on the CNS will potentially add to the CNS depressive effects of a sedative hypnotic. In some cases this will simply make the patient more drowsy, more lethargic, or have a significant hangover effect. However, in other cases this interaction may lead to coma and death. Of particular concern in the use of alcohol with benzodiazepines. Benzodiazepines are deceptively safe drugs - when used alone, even at high doses, they are very safe drugs. However, *when combined with alcohol, the synergistic effect on the CNS can very quickly cause profound CNS depression that can, and tragically has, led to coma and death*.





Sedative-Hypnotic Drugs

Benzodiazepines

- Alprazolam (Xanax®) ★
Oral
- Chlordiazepoxide (Librium®)
IM, IV, Oral
- Clonazepam (Klonopin®)
Oral
- Clorazepate (Tranxene®)
Oral
- Diazepam (Valium®) ★
IM, IV, Oral, Rectal
- Estazolam (Prosom®)
Oral
- Flurazepam (Dalmane®)
Oral
- Lorazepam (Ativan®) ★
Oral, IM, IV
- Midazolam (Versed®) ★
IM, IV, Oral
- Oxazepam (Serax®)
Oral
- Quazepam (Doral®)
Oral
- Temazepam (Restoril®)
Oral
- Triazolam (Halcion®) ★
Oral

Barbiturates

- Amobarbital (Amytal®)
IV
- Butobarbital (Butisol®)
Oral
- Mephobarbital (Mebaral®)
Oral
- Pentobarbital (Nembutal®) ★
IM, IV, Oral
- Phenobarbital (Luminol®) ★
IM, IV, Oral
- Secobarbital (Seconal®)
Oral

Selected Other Sedative-Hypnotics

- Buspirone (Buspar®) ★
Oral
- Chloral Hydrate (Somnote®)
Oral, Rectal
- Eszopiclone (Lunesta®) ★
Oral
- Ramelteon (Rozerem®) ★
Oral
- Zaleplon (Sonata®) ★
Oral
- Zolpidem (Ambien®) ★
Oral