Anxiolytic and Hypnotic Drugs

Anxiety: Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that arises from either a known or an unknown source). The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation.

An effective **anxiolytic** agent should reduce anxiety and exert a calming effect. Because many antianxiety drugs also cause some sedation, they may be used clinically as both anxiolytic and hypnotic (sleep-inducing) agents. A **hypnotic** drug should produce drowsiness and encourage the onset and maintenance of a state of sleep.

Benzodiazepines:

They 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.

Though benzodiazepines are commonly used, they are not necessarily the best choice for anxiety or insomnia. Certain antidepressants with anxiolytic action, such as the selective serotonin reuptake inhibitors (SSRIs), are preferred in many cases, and nonbenzodiazepine hypnotics and antihistamines may be preferable for insomnia.

Mechanism of action

The targets for benzodiazepine actions are the γ-aminobutyric acid (GABAA) receptors. [Note: GABA is the major inhibitory neurotransmitter in the central nervous system (CNS).]

Binding of GABA to its receptor triggers an opening of the central ion channel, allowing chloride through the pore. The influx of chloride ions causes hyperpolarization of the neuron and decreases neurotransmission by inhibiting the formation of action potentials.

Benzodiazepines modulate GABA effects by binding to a specific, high-affinity site (distinct from the GABAbinding site) located at the interface of the α subunit and the γ subunit on the GABAA receptor.

Benzodiazepines increase the frequency of channel openings produced by GABA.

The clinical effects of individual benzodiazepines correlate well with the binding affinity of each drug for the GABA receptor–chloride ion channel complex.

Actions:

1. Reduction of anxiety. At low doses, the benzodiazepines are anxiolytic.
2. Sedative/hypnotic. All benzodiazepines have sedative and calming properties, and some can produce hypnosis (artificially produced sleep) at higher doses.
3. Anterograde amnesia :Temporary impairment of memory & the ability to learn and form new memories is also impaired.

4. Anticonvulsant.
5. Muscle relaxant. At high doses, the benzodiazepines relax the spasticity of skeletal muscle. [Note: Baclofen is a muscle relaxant that is believed to affect GABA receptors at the level of the spinal cord.]

Therapeutic Uses:

1. Anxiety disorders: These drugs should be reserved for severe anxiety and should not be used to manage the stress of everyday life. Because of their addictive 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 patients with anxiety that require prolonged treatment. The antianxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects. [Note: Tolerance is decreased responsiveness to repeated doses of the drug that occurs when used for more than 1 to 2 weeks.] For panic disorders, ***alprazolam*** is effective for short- and long-term treatment, although it may cause withdrawal reactions in approximately 30% of patients.

2. Sleep disorders: Benzodiazepine hypnotics decrease the latency to sleep onset. In the treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation ("hangover") upon awakening. Short-acting ***triazolam*** is effective in treating individuals who have problems falling asleep. The risk of withdrawal and rebound insomnia is higher with triazolam than with other agents. Intermediate-acting ***temazepam*** is useful for patients who experience frequent awakenings and have difficulty staying asleep. Temazepam should be administered 1 to 2 hours before the desired bedtime. Long-acting ***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. ***Estazolam*** and ***quazepam*** are considered intermediate- and long-acting agents, respectively. In general, hypnotics should be used for only a limited time, usually 1 to 3 weeks.

3. Amnesia: 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 patient to be receptive to instructions during these procedures. ***Midazolam*** is a benzodiazepine used to facilitate anterograde amnesia while providing sedation prior to anesthesia.

4. Seizures ***Clonazepam*** is occasionally used as an adjunctive therapy for certain types of seizures, whereas ***lorazepam*** and ***diazepam*** are the drugs of choice in terminating status epilepticus.Due to cross-tolerance, ***chlordiazepoxide***, ***clorazepate***, ***diazepam***, ***lorazepam***, and ***oxazepam*** are useful in the acute treatment of alcohol withdrawal and reduce the risk of withdrawal-related seizures.

5. Muscular disorders: Diazepam is useful in the treatment of skeletal muscle spasms and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

Pharmacokinetics:

The benzodiazepines are lipophilic. 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.

Most benzodiazepines, including chlordiazepoxide and diazepam, are metabolized by the hepatic microsomal system to compounds that are also active.

The benzodiazepines are excreted in the urine.

All benzodiazepines cross the placenta and may depress the CNS of the newborn if given before birth. The benzodiazepines are not recommended for use during pregnancy. Nursing infants may also be exposed to the drugs in breast milk.

Dependence:

Psychological and physical dependence can develop if high doses of benzodiazepines are given for a prolonged period.

All benzodiazepines are controlled substances. Abrupt discontinuation of these agents 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.

Adverse effects:

Drowsiness and confusion are the most common adverse effects of the benzodiazepines.

Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile. Cognitive impairment (decreased recall and retention of new knowledge) can occur with use of benzodiazepines. Benzodiazepines should be used cautiously in patients with liver disease.

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 or opioids, are taken concurrently.

Benzodiazepine Antagonist:

Flumazenil is a GABA receptor antagonist that rapidly reverses 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. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine. 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 adverse effects.

Barbiturates:

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. They have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance and physical dependence, are lethal in overdose, and are associated with severe withdrawal symptoms. All barbiturates are controlled substances.

The sedative–hypnotic action of the barbiturates is due to their interaction with GABAA 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. These molecular actions lead to decreased neuronal activity.

Other Anxiolytic Agents:

A. Antidepressants: 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. SSRIs (such as ***escitalopram*** or ***paroxetine***) or (SNRIs, such as ***venlafaxine*** or ***duloxetine***) may be used alone or prescribed in combination with a benzodiazepine during the first week of treatment.

B. *Buspirone:* is useful for the chronic treatment of generalized anxiety disorder (GAD) and has an efficacy comparable to that of benzodiazepines. It has a slow onset of action and is not effective for short-term or "as-needed" treatment of acute anxiety.

The actions of buspirone appear to be mediated by serotonin receptors, although it also displays some affinity for D2 dopamine receptors . Thus, its mode of action differs from that of the benzodiazepines. In addition, buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines.

The frequency of adverse effects is low, with the most common effects being headache, dizziness, nervousness, nausea, and light-headedness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely. Buspirone does not potentiate the CNS depression of alcohol.

Other Hypnotic Agents:

A. ***Zolpidem:*** is not structurally related to benzodiazepines, but it binds to GABAA receptors with relative selectivity for those with the α1 subunit. Zolpidem has no anticonvulsant or muscle-relaxing properties at hypnotic doses. It shows few withdrawal effects, exhibits minimal rebound insomnia, and little tolerance occurs with prolonged use. Zolpidem is rapidly absorbed after oral administration. It has a rapid onset of action and short elimination half-life (about 2 to 3 hours). The drug provides a hypnotic effect for approximately 5 hours.

[Note: A lingual spray and an extended-release formulation are also available. A sublingual tablet formulation may be used for middle-of-the-night awakening.]

Zolpidem undergoes hepatic oxidation by the CYP450 system to inactive products. Thus, drugs such as rifampin, which induce this enzyme system, shorten the half-life of zolpidem, and drugs that inhibit the CYP3A4 isoenzyme may increase the half-life.

Adverse effects of zolpidem include headache, dizziness, anterograde amnesia, and next-morning impairment (especially with extended-release formulations). Sleep-walking, sleep-driving, and performing other activities while not fully awake have been reported. Unlike the benzodiazepines, at usual hypnotic doses, the nonbenzodiazepine drugs, zolpidem, zaleplon, and eszopiclone, do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics. All three agents are controlled substances.

B. ***Zaleplon***: is an oral nonbenzodiazepine hypnotic similar to zolpidem; however, zaleplon causes fewer residual effects on psychomotor and cognitive function compared to zolpidem or the benzodiazepines. This may be due to its rapid elimination, with a half-life of approximatelya 1 hour. The drug is metabolized by CYP3A4.

C. ***Eszopiclone***: is an oral nonbenzodiazepine hypnotic that has been shown to be effective for insomnia for up to 6 months. Eszopiclone is rapidly absorbed (time to peak, 1 hour), extensively metabolized by CYP450 system, and mainly excreted in urine. Elimination half-life is approximately 6 hours. Adverse events with eszopiclone include anxiety, dry mouth, headache, peripheral edema, somnolence, and unpleasant taste.

D. Antidepressants:
The use of sedating antidepressants with strong antihistamine profiles has been ongoing for decades. ***Doxepin***, an older tricyclic agent with SNRI mechanisms of antidepressant and anxiolytic action, is approved at low doses for the management of insomnia.

E. Antihistamines
Antihistamines with sedating properties, such as ***diphenhydramine***, ***hydroxyzine***, and ***doxylamine***, are effective in treating mild situational insomnia. However, they have undesirable adverse effects (such as anticholinergic effects) that make them less useful than the benzodiazepines and the nonbenzodiazepines. Sedative antihistamines are marketed in numerous over-the-counter products.

F. Melatonin receptor agonists:
Ramelteon and ***tasimelteon*** are selective agonists 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 and tasimelteon is thought to induce and promote sleep. They have minimal potential for abuse, and no evidence of dependence or withdrawal has been observed. Therefore, ramelteon and tasimelteon can be administered long-term.
Ramelteon is indicated for the treatment of insomnia characterized by difficulty falling asleep (increased sleep latency). Common adverse effects of ramelteon include dizziness, fatigue, and somnolence. Ramelteon may also increase prolactin levels.
Tasimelteon is indicated for non–24-hour sleep–wake disorder, often experienced by blind patients . The most common adverse effects of tasimelteon are headache, abnormal dreams, increase in liver function tests, and possible upper respiratory tract infections.

CYP450 1A2 and 3A4 are the principle isoenzymes required for metabolism of ramelteon and tasimelteon, and, thus, drug–drug interactions are possible with inducers or inhibitors of these enzymes.