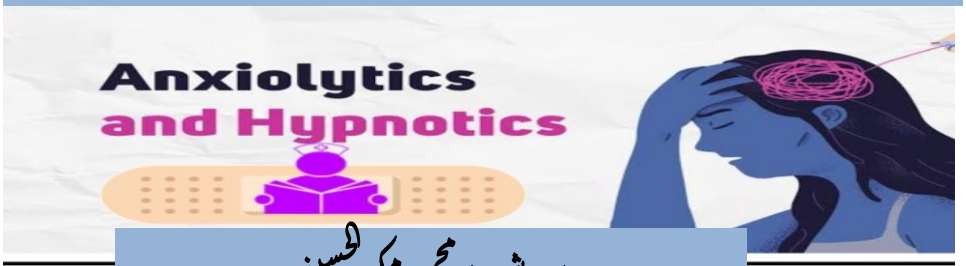
Pharmacology II, 4th Stage

Lippincott's Illustrated Reviews, 6th ed.

Unit III: Drugs Affecting the Central Nervous System

9- Anxiolytics and Hypnotics

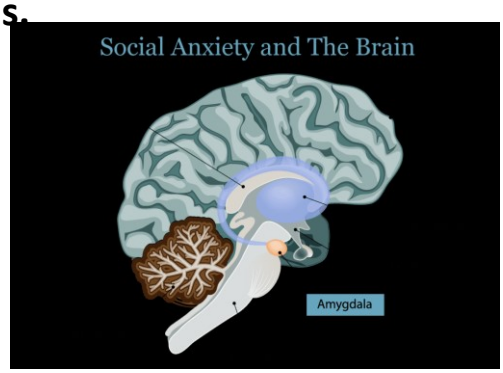


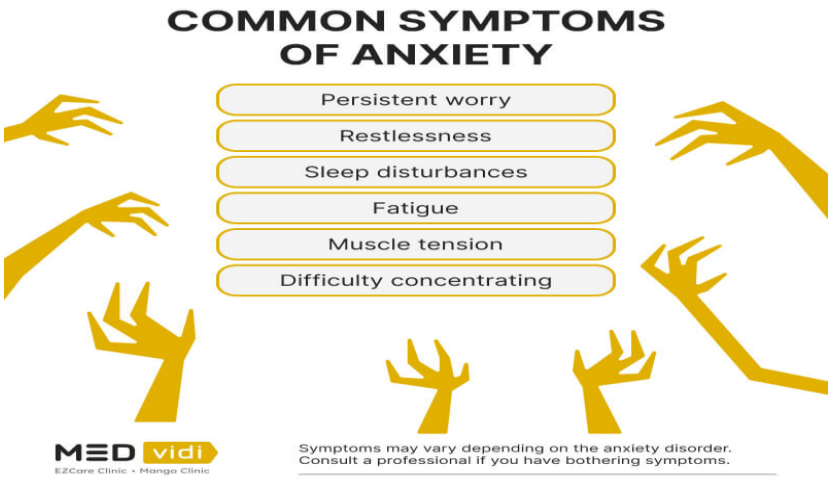
م.د شيرين محمد مكي الحسيني

Anxiety and Anxiolytics

- 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.
- Episodes of mild anxiety are common life experiences and do not warrant treatment. However, severe, chronic, debilitating anxiety may be treated with 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 (sleep inducing) agents. Some antidepressants are also indicated for certain anxiety disorders.

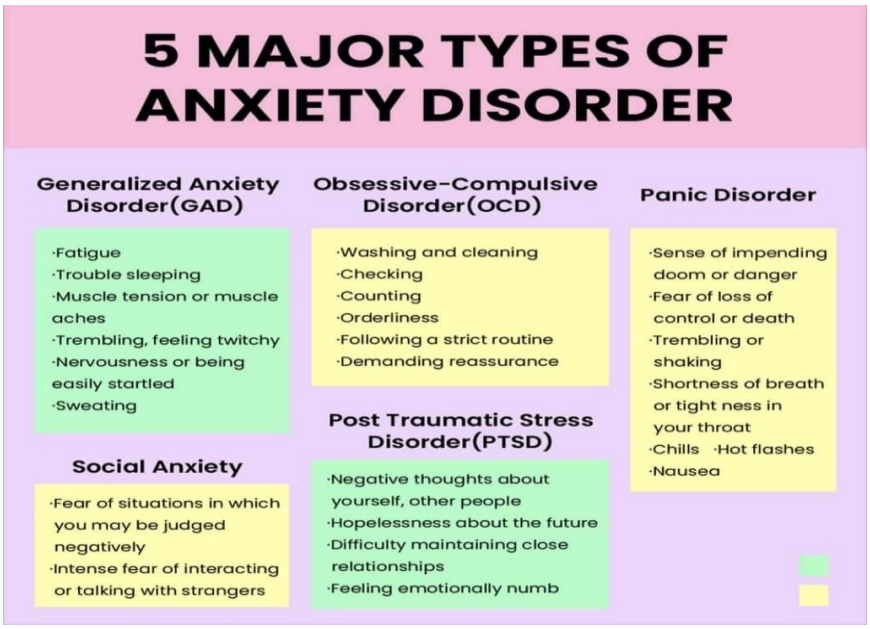
- **The brain's limbic system, comprised of the hippocampus, amygdala, hypothalamus and thalamus, is responsible for the majority of emotional processing. Individuals with an anxiety disorder may have heightened activity in these areas.**



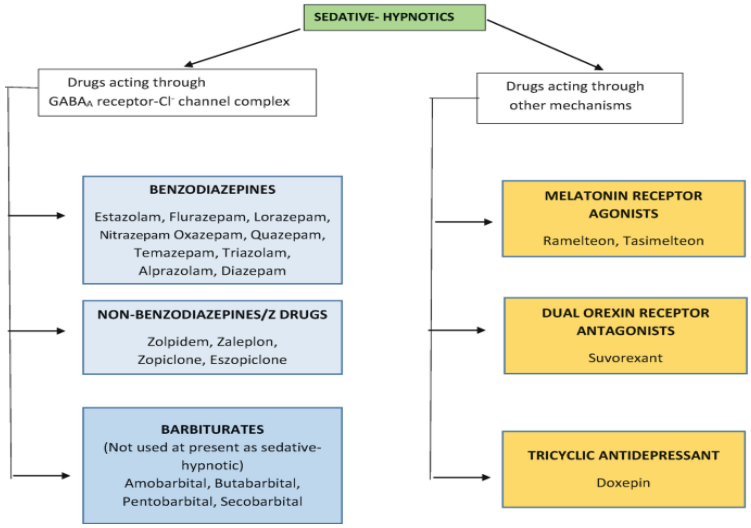


Some Definitions

Term	Definition
Anxiolytic	A drug that reduces anxiety
Sedative	A drug that reduces a person's response to most external stimuli and causes drowsiness
Hypnotic	A drug that induces sleep
General anesthetic	A drug that causes loss of consciousness associated with absence of response to painful stimuli



Classification of sedative- Hypnotic- Anxiolytic Drugs



Benzodiazepines

- **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.**
- **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, nonbenzodiazepine hypnotics and antihistamines may be preferable for insomna.**

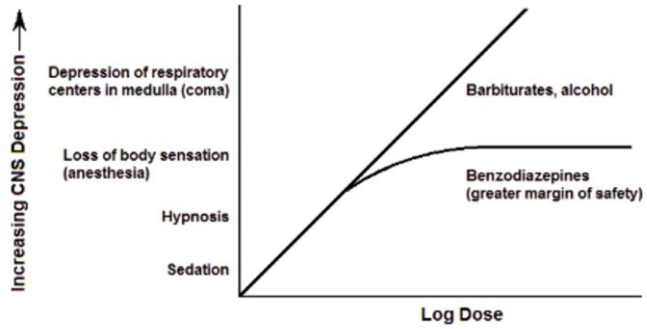
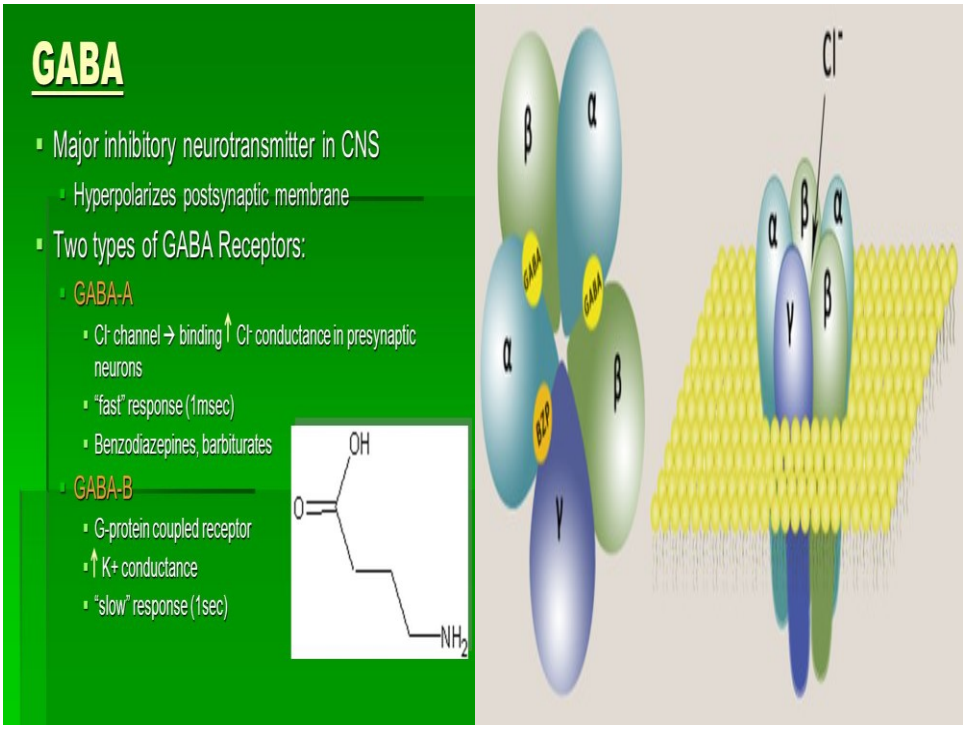


Figure 17.6. Comparison of Barbiturate- and Benzodiazepine-Induced CNS Depression

Original drawing by Raymond M. Quock



A. Mechanism of action

- **The targets for benzodiazepine actions are the γ-aminobutyric acid (GABAA) receptors.**
- **The GABAA receptors are composed of a combination of five α, β, and γ subunits that span the postsynaptic membrane (Figure 9.3).**
- **For each subunit, many subtypes exist (for example, there are six subtypes of the α subunit).**
- **Binding of GABA to its receptor triggers an opening of the central ion channel, allowing chloride through the pore (Figure 9.3). 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 GABA-binding site) located at the interface of the α subunit and the γ subunit on the GABAA receptor (Figure 9.3).**
- **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 increase the frequency of channel openings produced by GABA. Binding of a benzodiazepine to its receptor site increases the affinity of GABA for the GABA-binding site (and vice versa).] The clinical effects of the various benzodiazepines correlate well with the binding affinity of each drug for the GABA receptor–chloride ion channel complex.**

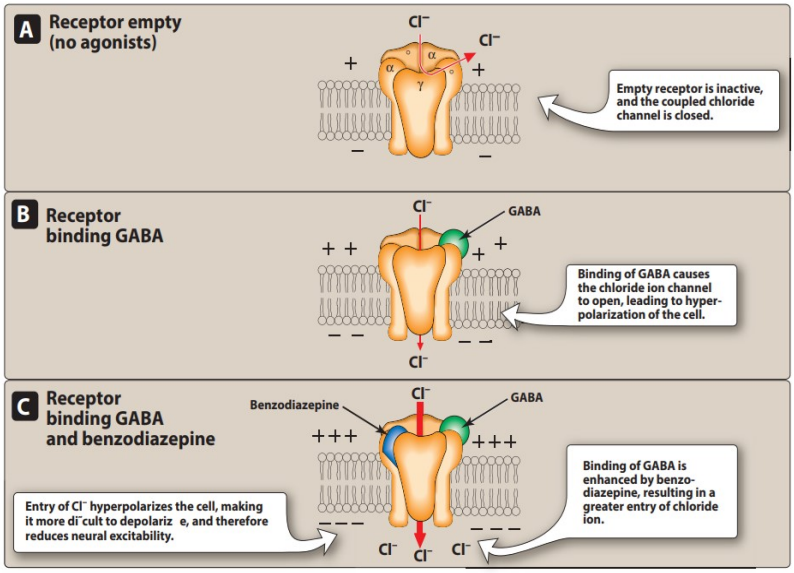


Figure 9.3
Schematic diagram of benzodiazepine–GABA–chloride ion channel complex. GABA = γ-aminobutyric acid.

Actions of BZD

1. **Reduction of anxiety: by selectively enhancing GABAergic transmission in neurons having the α2 subunit in their GABA- A (limbic system).**
2. **Muscle relaxant: At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition (in the spinal cord), where the α2 -GABAA receptors are largely located.**
3. **Sedative/hypnotic: these effects are mediated by the α1 -GABAA receptors.**
4. **Anterograde amnesia: Temporary impairment of memory with use of the benzodiazepines is also mediated by the α1 -GABAA receptors. The ability to learn and form new memories is also impaired.**
5. **Anticonvulsant: Several benzodiazepines have anticonvulsant activity. This effect is partially, although not completely, mediated by α1 -GABAA receptors.**

CLASSIFICATIONS OF BENZODIAZEPINES

are classified according to duration of action into:

1.Short acting (3-8 hours): triazolam, Oxazepam

2.Intermediate (10-20 hours):

Alprazolam, Lorazepam, Estazolam, Temazepam

3. Long acting: (1-3 days):

Diazepam, Chlordiazepoxide, Flurazepam, Quazepam, Clorazepate

Therapeutic Uses of BZD

- **1. Anxiety disorders:**
- **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.**
- **The antianxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects. Tolerance occurs when used for more than 1 to 2 weeks and is associated with a decrease in GABA receptor density.**
- **Cross-tolerance exists between the benzodiazepines and ethanol.**
- **For panic disorders, alprazolam is effective for short- and long-term treatment, although it may cause withdrawal reactions in about 30% of patients.**

2. Sleep disorders: 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 temazepam** (useful in patients who experience frequent wakening) and **short-acting triazolam** (effective in treating individuals who have difficulty in going to sleep but tolerance frequently develops within a few days, and withdrawal of the drug often results in rebound insomnia), long-acting flurazepam is rarely used.

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 **(Midazolam).**

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.

- **5. Muscular disorders: (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.
- **Dependence**

Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given for a prolonged period. Abrupt discontinuation of the BZD results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures. BZD 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 side effects of the benzodiazepines. Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile, Cognitive impairment also occurs.

These drugs should be avoided in patients with acute angle closure glaucoma. Alcohol and other CNS depressants may increase CNS depression effect.

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.

Flumazenil is a GABA receptor 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. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine.

Other Anxiolytic Agents

A. **Antidepressants:** they 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) or serotonin/norepinephrine reuptake inhibitors (SNRIs), may be used alone or prescribed in combination with a low dose of a benzodiazepine during the first weeks of treatment.

Long-term use of antidepressants and benzodiazepines for anxiety disorders is often required to maintain ongoing benefit and prevent relapse.

B. Buspirone: is useful for the chronic treatment of generalized anxiety disorder (GAD) and has an efficacy comparable to that of the BZD.

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 to be mediated by serotonin (5-HT1A) receptors, although it also displays some affinity for D2 dopamine receptors and 5-HT2A serotonin 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.

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.**
- **A. Mechanism of action**
- **The sedative–hypnotic action of the barbiturates is due to their interacation 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. Anesthetic concentrations of pentobarbital also block high-frequency sodium channels. All of these molecular actions lead to decreased neuronal activity.**
- **B. Actions**

1. Depression of CNS: At low doses, the barbiturates 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. Thus, any degree of depression of the CNS is possible, depending on the dose.

2. Respiratory depression: Barbiturates suppress the hypoxic and chemoreceptor response to CO_2 , and overdosage is followed by respiratory depression and death.

Classification and Uses of Barbiturates According to Their Duration of Action

Classification	Compounds	Clinical applications
Ultra short acting	Thiopental, thiamylal, thialbarbital, hexobarbital, methohexital.	As general anesthetic
Short acting	Pentobarbital, secobarbital.	As hypnotic, pre-anesthetic & emergency management of seizures.
Intermediate acting	Amobarbital, aprobarbital, mephobarbital.	As hypnotic, pre-anesthetic & emergency management of seizures.
Long acting	Barbital, phenobarbital.	As anticonvulsant & sedatives.

- **Adverse effects Barbiturates cause drowsiness, impaired concentration, and mental and physical slowness. 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 induce cytochrome P450 (CYP450) microsomal enzymes in the liver.**

Other Hypnotic Agents

A. **Zolpidem** This drug is not structurally related to BZD but it selectively binds to the benzodiazepine receptor subtype BZ1. **Zolpidem has no anticonvulsant or muscle-relaxing properties. It shows few withdrawal effects, exhibits minimal rebound insomnia, and little tolerance occurs with prolonged use.**

Unlike the BZD, 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. This may be due to their relative selectivity for the BZ1 receptor.

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.

- **C. Eszopiclone is an oral nonbenzodiazepine hypnotic that also acts on the BZ1 receptor. It has been shown to be effective for insomnia for up to 6 months.**
- **D. Ramelteon 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 (increased 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. Ramelteon may also increase prolactin levels.**

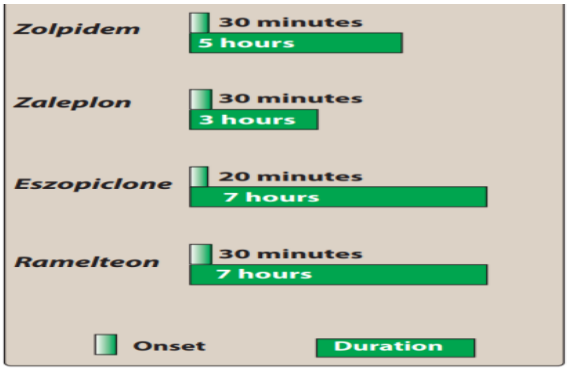


Figure 9.10
Onset and duration of action of the commonly used nonbenzodiazepine hypnotic agents.

E. Antihistamines **Some antihistamines with sedating properties, such as diphenhydramine, hydroxyzine, and doxylamine, are effective in treating mild types of situational insomnia.**

F. Antidepressants **The use of sedating antidepressants with strong antihistamine profiles has been ongoing for decades. Doxepin an older tricyclic agent with SNRI (selective serotonin inhibitor) mechanisms of antidepressant and anxiolytic action, was recently approved at low doses for the management of insomnia. Other antidepressants, such as trazodone, and mirtazapine are used off-label for the treatment of insomnia.**


scared
chest
headache
phobia
tense
panic
attacks
trembling
ANXIETY
stress
fear
sweating
feelings
worry
emotional
disorder
tension
angst
jumpy

THANK U