**Sedative and hypnotic**

Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that seems to arise from a unknown source). Disorders involving anxiety are the most common mental disturbances. 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, the symptoms of severe, chronic, debilitating anxiety may be treated with anti-anxiety drugs (sometimes called anxiolytic or minor tranquilizers) and/or some form of behavioral therapy or psychotherapy. Sedative is anxiolytic agent that remove the anxiety, while hypnotic, is a drug that induce sleep.

**Benzodiazepine (BDZ):-** Benzodiazepines are the most widely used anxiolytic drugs. They have largely replaced barbiturates and meprobamate in the treatment of anxiety, because benzodiazepines are safer and more effective

**Mechanism of action:**

BDZ activate BDZ receptors which lead to potentiation the effect of GABA receptor, this lead to ↑ **frequency** of Cl- channel opening lead to hyperpolarization and then inhibition of brain but not lead to coma?? \*(why? → because it affect only the frequency, not the duration.).



BDZ receptor type BDZ1, BZD2 also called omega receptor, the BDZ act on both receptor, but some non – benzodiazepine agent act on BDZ1 receptor only.

**BDZ ligand receptor:-**

1. BDZ agonist →BDZ.
2. BDZ antagonist → flumazenil, block GABA effect used for BDZ poisoning.
3. Inverse agonist → β – carboline lead to anxiety and convulsion.

Therefore the GABA – Cl- – BDZ complex is a major site for action of sedatives and hypnotics, and may be affected by many drugs like gabapentin, picrotoxin, ivermectin and bicucaline.

**BDZ drugs:** Diazepam, aloprozolam,Lorazepam, clorzepate.

**Pharmacodynamic of BDZ:-**

1. **Hypnosis:-**

The BDZ affect the sleep by:-

* ↑ NREM (non – rapid eye movement) sleep.
* ↓ REM (in which recallable dream occur).
* ↓ of slow wave sleep (in which terror occurred).

So after cessation of BDZ drug, the REM sleep will ↑ lead to more dreams.

1. **Anesthesia**: - like midazolam.
2. **Anticonvulsant.**
3. **Muscle relaxation** by:-
4. Inhibition of polysynaptic transmission.
5. Neuromuscular junction inhibition.
6. **Depression of respiratory center.**
7. **Inhibition of vasomotor center, myocardial contractility, and vascular tone.**

**Biotransformation:-**

* **BDZ with long acting effect, used as sedative:-**
1. Prazepam.
2. Quezepam.
3. Flurazepam.
4. Lorazepam.
5. Temazepam.
6. Clorazepam.
7. Diazepam.
* **BDZ with short acting effect, used as hypnotic:-**
1. Triazolam.
2. Nitrazepam.

All BDZ are active drugs, except clorazepam is a prodrug which hydrolyzed in stomach to active drug.

Most BDZ give oxazepam then undergo conjugation except lorazepam, alprozolam and flurazepam, they undergo conjugation process directly.

**Indication of BDZ:-**

1. Anxiety state.
2. Insomnia.
3. Preoperative to produce sedation and amnesia.
4. Alcohol withdrawal syndrome.
5. Muscle spasticity.
6. Anesthesia.
7. Anticonvulsant.
8. Depression (alprozolam).

BDZ poising is treated by flumazenile.

**Adverse eff ects**

**1. Drowsiness and confusion:** These effects are the two 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 (decreased long-term recall and retention of new knowledge) can occur with use of benzodiazepines. Triazolam, one of the most potent oral benzodiazepines with rapid elimination, often shows a rapid development of tolerance, early morning insomnia, and daytime anxiety as well as amnesia and confusion.

**2. Precautions:** Benzodiazepines should be used cautiously in treating patients with liver disease. These drugs should be avoided in patients with acute narrow-angle glaucoma. Alcohol and other CNS depressants enhance the sedative-hypnotic eff ects 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.

* **Barbiturate: -** (phenobarbiton, Phenobarbital, primidon).
* Active GABA – Cl- – channel complex directly lead to ↑ duration of Cl‑ opening, so may lead to coma.
* Used as sedative and hypnotic and for anesthesia.
* But it enzyme inducer so can be used for jaundice because it ↑ glucoronyl activity that responsible for conjugation of bilirubin.

**Other sedative and hypnotic agents:-**

**Buspirone:** The actions of buspirone appear to be mediated by serotonin (5-HT1A) receptors, although other receptors could be involved. Because buspirone displays some affinity for DA2 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 and

causes only minimal sedation. However, it does cause hypothermia and can increase prolactin and growth hormone. The frequency of adverse effects is low, with the most common effects being headaches, dizziness, nervousness, and light-headedness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely. It does not potentiate the CNS depression of alcohol. Buspirone has the disadvantage of a slow onset of action.

**Zolpidem:** unrelated to BDZ, activate BDZ1 receptor, is rapidly metabolized to inactive metabolite, it's not a CNS depressant so can be used with ethanol, it only anxiolytic and hypnotic. NOT cause tolerance and withdrawal syndrome.

**Zaleplon:** BDZ1 receptor agonist, sedative and hypnotic, rapid onset and short duration of action, metabolized by aldehyde oxidase, so ethanol interferes with zaleplon metabolism.

**Antidepressants**

Many antidepressants have proven efficacy in managing the long-term symptoms of chronic anxiety disorders and should be seriously considered as first-line agents, especially in patients with concerns for addiction or dependence or a history of addiction or dependence to other substances. Selective serotonin reuptake inhibitors (SSRIs, such a escitalopram), or selective serotonin and norepinephrine reuptake inhibitors (SNRIs, such as venlafaxine) may be used alone, or prescribed in combination

with a low dose of a benzodiazepine during the first weeks of treatment . After four to six weeks, 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.

**Eszopiclone** is an oral nonbenzodiazepine hypnotic (also using the BZ1 receptor similar to zolpidem and zaleplon) and is also used for treating insomnia.

 **Ramelteon** is a selective agonist at the MT1 and MT2 subtypes of melatonin receptors. Normally, light stimulating the retina transmits a signal to the suprachiasmatic nucleus (SCN) of the hypothalamus

that, in turn, relays a signal via a lengthy nerve pathway to the pineal gland that inhibits the release of melatonin from the gland. As darkness falls and light ceases to strike the retina, melatonin release from the pineal gland is no longer inhibited, and the gland begins to secrete melatonin. Stimulation of MT1 and MT2 receptors by melatonin in the SCN is able to induce and promote sleep and is thought to maintain the circadian rhythm underlying the normal sleep–wake cycle. Ramelteon is indicated for the treatment of insomnia in which falling asleep (increased sleep latency) is the primary complaint. The potential for abuse of ramelteon is believed to be minimal, 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 insomnia. However, these drugs are usually ineffective for all but the milder forms of situational insomnia. Furthermore, they have numerous undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines. Some sedative antihistamines are marketed in numerous over-the-counter products.

**Ethanol** has anxiolytic and sedative effects, but its toxic potential outweighs its benefits. is a CNS depressant, producing sedation and, ultimately, hypnosis with increasing dosage. Because ethanol has a shallow dose–response curve, sedation occurs over a wide dosage range. It is readily absorbed orally and has a volume of distribution close to that of total body water. Ethanol is metabolized primarily in the liver, first to acetaldehyde by alcohol dehydrogenase and then to acetate by aldehyde dehydrogenase .

Elimination is mostly through the kidney, but a fraction is excreted through the lungs. Ethanol synergizes with many other sedative agents and can produce severe CNS depression when used in conjunction with benzodiazepines, antihistamines, or barbiturates.