**Central Nervous System Depressants**

**(CNS Depressants)**

**CNS Depressants:- they are the drugs that depress the CNS function and they include:-**

1. **General anesthetics. (G.A.)**
2. **Anxiolytics.**
3. **Sedative/hypnotics. (S/H)**
4. **Anticonvulsants.**
5. **Antipsychotics.**

***Anxiolytics and Sedative –hypnotics agent***

**Anxiolytic, sedative, and hypnotic drugs are:-**

1. **Benzodiazepines.**
2. **Barbiturates.**
3. **Miscellaneous.**

***Benzodiazepines and Related Compounds***

Are group of CNS epressants which induce feelings of calm(anxiolysis) they act by facilitating the binding of the inhibitory neurotransmitter CABA at various GABA receptors through the CNS.

Benzodiazepines and benzodiazepine like drugs bind to recognition site, one of several allosteric sites that modulate the effect of GABA binding to GABAA1 receptors. The GABAA1 receptors is a ligand-gated Cl̅ion channel.

**Benzodiazepine is a two ring system; one of them is heterocyclic containing nitrogen.**



***SAR of benzodiazepines***

1. **Aromatic or heteroaromatic ring A is required for the activity that may participate in π-π stacking with aromatic amino acid residues of the receptor.**
2. **An electronegative substituent at position 7 is required for activity, and the more electronegative it is, the higher the activity.**
3. **Positions 6, 8, and 9 should not be substituted.**
4. **A phenyl ring C at position 5 promotes activity.**
5. **If this phenyl group is ortho (2') or diortho (2',6') substituted with electron withdrawing groups, activity is increased.**
6. **On the other hand, para substitution decreases activity greatly.**
7. **In diazepine ring B, saturation of the 4,5-double bond or a shift of it to the 3,4-position decreases activity.**
8. **Alkyl substitution at the 3-position decreases activity; substitution with a 3-hydroxyl does not. The presence or absence of the 3-hydroxyl group is important pharmacokinetically.**
9. **Compounds without the 3-hydroxyl group are nonpolar, have long half-lives, and undergo hepatic oxidation to 3-hydroxyl metabolites.**
10. **Compounds with the hydroxyl are much more polar and are readily converted to the inactive 3-glucuronide, which are excreted in urine and thus are short-lived.**
11. **The 2-carbonyl function is optimal for activity, as is the nitrogen atom at position l.**
12. **The N-substituent should be small.**
13. **Compounds with a fused triazolo ring, represented by triazolam and alprazolam, Midazolam, with a fused imidazolo ring, also followed. These compounds are short acting because they are metabolized rapidly by α-hydroxylation of the methyl substituent on the triazolo or imidazolo ring (analogs to benzylic oxidation). The resulting active α-hydroxylated metabolite is quickly inactivated by glucuronidation. The compounds are also metabolized by 3-hydroxylation of the benzodiazepine ring. Interestingly, an electron-attracting group at position 7 is not required for activity in some of these compounds.**



***Properties of benzodiazepines***

1. **The benzodiazepines generally are well absorbed from the gastrointestinal (Gl) tract, although the more polar compounds (e.g.. those with a hydroxyl at the 3-position) tendto be absorbed more slowly than the more nonpolar compounds.**
2. **The drugs tend to be highly bound to plasma proteins: in general, the more nonpolar the drug, the greater the binding.**
3. **They are also very effectively distributed to the brain. Generally, the more nonpolar the compound, the greater the distribution to the brain, at least initially. When diazepam is used as an anesthetic, it initially distributes to the brain and then redistributes to sites outside the brain.**
4. **Compounds without the 3-hydroxyl group usually have long half-lives and undergo conversion to the 3-hydroxy compounds by hepatic oxidation. Compounds with the 3-hydroxyl group have short half-lives because of rapid conjugation to the 3- glucuronide. which undergoes urinary excretion.**
5. **In addition to lower abuse potential, and a much greater margin of safety than the barbiturates, the drugs have fewer drug interactions. Especially noteworthy is that they do not promote the metabolism of other drugs.**