Other anxiolytic agents

A. **Buspirone**
   Useful in the treatment of generalized anxiety disorder, it's efficacy comparable to that of the BZDs. It is not effective for short-term or “as-needed” treatment of acute anxiety states.
   - **Buspirone's** actions appear to be mediated by 5-HT1A receptors, although other receptors could be involved, such DA2 dopamine receptors & 5-HT2A receptors. Thus, its mode of action differs from that of BZDs.
   - Unlike BZDs, **buspirone** lacks the anticonvulsant & muscle-relaxant properties & causes only minimal sedation.
   - Most common adverse effects are headaches, dizziness, nervousness & light-headedness. Sedation & psychomotor & cognitive dysfunction are minimal & dependence is unlikely.
   - It does not potentiate the CNS depression of alcohol.
   - **Buspirone** has the disadvantage of a slow onset of action.

B. **Hydroxyzine**
   - Antihistamine with antiemetic activity.
   - Has a low tendency for habituation, thus, is useful for patients with anxiety who have a history of drug abuse.
   - Used for sedation prior to dental procedures or surgery.

C. **Antidepressants**
   - Many antidepressants should be seriously considered as first-line agents in patients with concerns for addiction or dependence or a history of addiction or dependence to other substances.
   - SSRIs, TCAs, (eg. **escitalopram**), SNRIs (**Venlafaxine** & **Duloxetine**) & MAOIs all have potential usefulness in treating anxiety.

**Barbiturates**
   - They were the mainstay to sedate patients or to induce & maintain sleep. But today they have been largely replaced by BZDs because they induce tolerance, drug-metabolizing enzymes & physical dependence & are associated with very severe withdrawal symptoms.
   - Foremost is their ability to cause coma in toxic doses.
   - Very short-acting barbiturates, such as the **thiopental**, are still used to induce anesthesia.

**Mechanism of action**
   - Interact with GABA\(\alpha\) receptors, enhancing GABAergic transmission (note: the binding site is distinct from that of the BZDs).
   - Prolong chloride-channel openings.
   - Block excitatory glutamate receptors.
   - **pentobarbital** in anesthetic concentrations also block high-frequency sodium channels.
   - All of these molecular actions lead to decreased neuronal activity.

**Actions**
Barbiturates are classified according to their duration of action. For example:
   - **Thiopental**, acts within seconds & has a duration of action of about 30 minutes, it is used in the IV induction of anesthesia.
   - **Phenobarbital** duration of action is greater than a day, it is useful in the treatment of seizures.
   - **Pentobarbital, secobarbital & amobarbital** are short-acting barbiturates, which are effective as sedative & hypnotic (but not anti-anxiety) agents.
1. Depression of CNS:
- At low doses, the barbiturates produce sedation (have a calming effect & reduce excitement).
- At higher doses, they cause hypnosis, followed by anesthesia and finally coma & death.
- Barbiturates do not raise the pain threshold & have no analgesic properties. They may even exacerbate pain.
- Chronic use leads to tolerance.

2. Respiratory depression:
They suppress the hypoxic & chemoreceptor response to CO₂ & overdosage is followed by respiratory depression & death.

3. Enzyme induction:
They induce CYP450 microsomal enzymes in the liver. Therefore, chronic barbiturate use diminishes the action of many drugs that are dependent on CYP450 metabolism.

Therapeutic uses
1. Anesthesia:
Selection of a barbiturate is strongly influenced by the desired duration of action. The ultrashort-acting barbiturates, such as thiopental, are used IV to induce anesthesia.

2. Anticonvulsant:
- Phenobarbital is used in long-term management of tonic-clonic seizures, status epilepticus & eclampsia.
- Phenobarbital is the drug of choice for treatment of young children with recurrent febrile seizures, however, it can depress cognitive performance in children thus, it should be used cautiously.
- Phenobarbital has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.

3. Anxiety:
- Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension & insomnia (when used as hypnotics, they suppress REM sleep more than other stages).

Pharmacokinetics
- They redistribute, from the brain to the splanchnic areas, skeletal muscle, and, finally, adipose tissue. This movement is important in causing the short duration of action of thiopental & similar short-acting derivatives.
- They readily cross the placenta & can depress the fetus.

Adverse effects
1. CNS:
- Drowsiness, impaired concentration & mental & physical sluggishness.
- The CNS depressant effects of barbiturates synergize with those of ethanol.

2. Drug hangover:
Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient wakes. This drug hangover may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea & dizziness can occur.

3. Precautions:
- They may decrease the duration of action of drugs that are metabolized by CYP450 hepatic enzymes.
- Barbiturates increase porphyrin synthesis & are contraindicated in patients with acute intermittent porphyria.

4. Physical dependence:
- Barbiturates abrupt withdrawal may cause tremors, anxiety, weakness, restlessness, nausea & vomiting, seizures, delirium & cardiac arrest.
• Withdrawal is much more severe than that associated with opiates & can result in death.

5. Poisoning:
• Barbiturate poisoning has been a leading cause of death resulting from drug overdoses.
• Severe depression of respiration is coupled with central CV depression & result in a shock-like condition with shallow, infrequent breathing.
• Treatment includes artificial respiration & purging the stomach of its contents if the drug has been recently taken.

Note: No specific barbiturate antagonist is available.
• Hemodialysis may be necessary if large quantities have been taken.
• Alkalization of the urine often aids in the elimination of Phenobarbital.

Other hypnotic agents

A. Zolpidem
• It is not a BZD in structure, but it acts on BZD1 receptor.
• Has no anticonvulsant or muscle-relaxing properties.
• Shows few withdrawal effects & exhibits minimal rebound insomnia & little or no tolerance occurs with prolonged use.
• Has rapid onset of action & short elimination half-life (2-3 hours). An extended-release formulation is now available
• Metabolized into inactive products, thus Zolpidem half-life is shortened by some drugs eg. Rifampin, while increased by others that inhibit CYP 3A4 isoenzyme.
• Nightmares, agitation, headache, GI upset, dizziness & daytime drowsiness may occur.

B. Zaleplon
• Very similar to Zolpidem in its hypnotic actions, but compared to Zolpidem or BZDs it causes fewer residual effects on psychomotor & cognitive functions. This may be due to its rapid elimination.

C. Eszopiclone
• An oral non BZD hypnotic (like Zolpidem & Zaleplon it also utilizes the BZD1).
• Effective for up to 6 months compared to a placebo.
• Elimination half-life is 6 hours.
• It may cause anxiety, dry moth, headache, peripheral edema, somnolence & unpleasant taste.

D. Ramelteon
• Selective agonist at the MT1 & MT2 subtypes of melatonin receptors found in the suprachiasmatic nucleus (SCN) of the hypothalamus.
Note: normally melatonin is able to induce & promote sleep.
• Ramelteon is indicated for falling asleep insomnia (increased sleep latency).
• Potential for abuse is minimal with no evidence of dependence or withdrawal effects. Therefore, ramelteon can be administered long term.

E. Chlora hydrate
• Trichlorinated derivative of acetaldehyde, in the body it is converted into trichloroethanol an active metabolite.
• Effective sedative & hypnotic that induce sleep in about 30 minutes & the duration of sleep is about 6 hours.
• It is irritating to the GIT & causes epigastric distress; also it produces an unusual, unpleasant taste sensation.

E. Antihistamines
• Some antihistamines with sedating properties, eg. diphenhydramine, hydroxyzine & doxylamine are effective in treating mild types of insomnia.
• Have numerous undesirable side effects (eg. anticholinergic effects).
F. Ethanol
- Ethanol (ethyl alcohol) has anxiolytic & sedative effects, but its toxic potential outweighs its benefits.
- Produce sedation & ultimately, hypnosis with increasing dosage.
- Metabolized primarily in the liver, first to acetaldehyde by alcohol dehydrogenase & then to acetate by aldehyde dehydrogenase.
- Chronic consumption can lead to severe liver disease, gastritis & nutritional deficiencies.
- Heavy drinking cause cardiomyopathy.
- BZDs are the treatment of choice for alcohol withdrawal, carbamazepine is effective in treating convulsive episodes during withdrawal.

G. Drugs to treat alcohol dependence

1. Disulfiram:
   - It blocks the oxidation of acetaldehyde to acetic acid by inhibiting aldehyde dehydrogenase, results in the accumulation of acetaldehyde in the blood, causing flushing, tachycardia, hyperventilation & nausea.
   - So that the patient abstains from alcohol to prevent the unpleasant effects of disulfiram-induced acetaldehyde accumulation.

2. Naltrexone:
   - Long-acting opiate antagonist that should be used in conjunction with supportive psychotherapy.
   - It is better tolerated than disulfiram & does not produce the aversive reaction that disulfiram does.

3. Acamprosate:
   - Used in alcohol dependence treatment programs.
   - Its mechanism of action is understood.
   - It should also be used in conjunction with supportive psychotherapy.