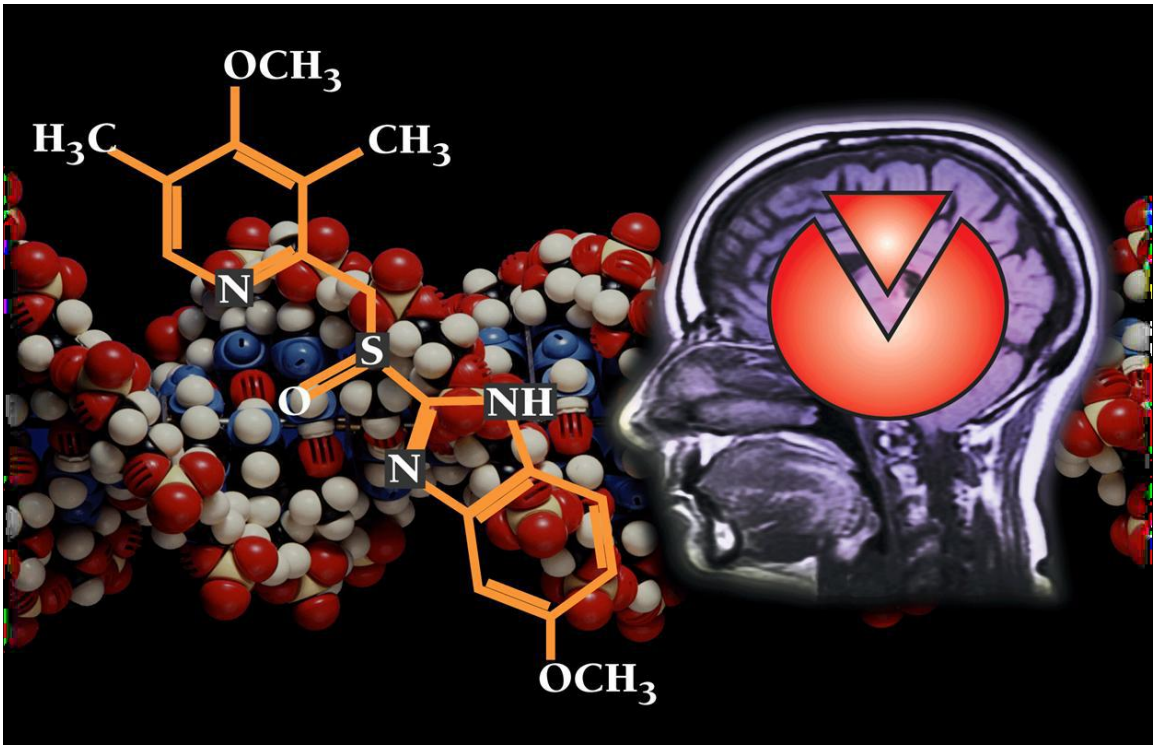
King Saud University
College Of Medicine
Pharmacology Team 430
CNS Block

Drugs used in Anxiety & Panic Disorders



Done By:

Hussam Alrazqan

Mohammed Aldohan

Anfal Alshaya

Arwa Abudawood

Introduction:

Anxiety: a physical and emotional distress which interfere with normal life.

Anxiety

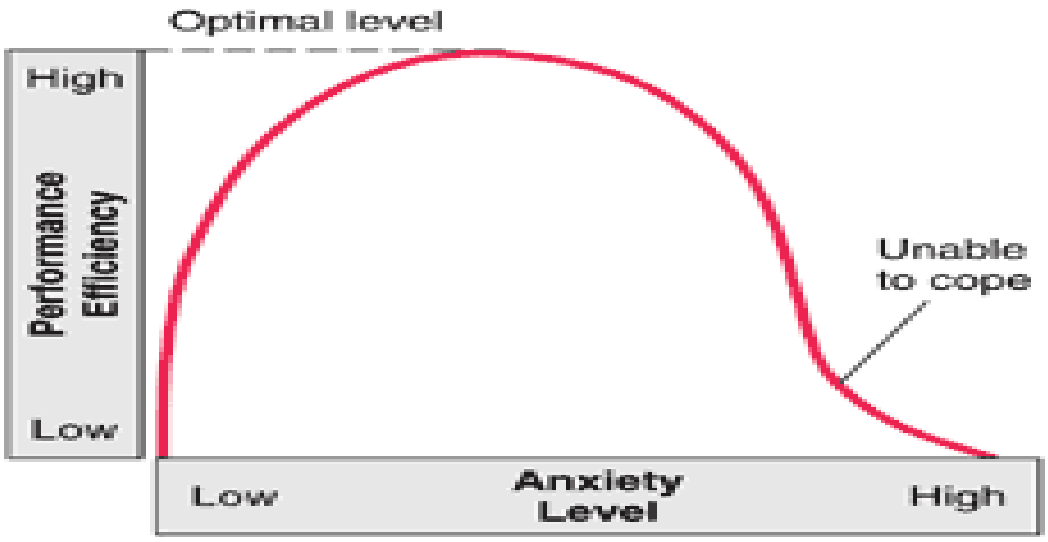
Emotional Symptoms

- irrational and excessive fear and worry
- Irritability
- Restlessness
- Trouble concentrating
- Feeling tense

Physical Symptoms

- Sweating
- Tachycardia
- Stomach upset
- Frequent urination or diarrhea
- Sleep disturbances (Insomnia)
- Fatigue

Note: Physical symptoms are induced by excessive sympathetic activation. (Which can be controlled by beta-blockers)



Note: The effects of anxiety on performance can be shown on a curve. As the level of anxiety increases, performance efficiency increases proportionately, but only up to a point. As anxiety increases further, performance efficiency decreases. Before the peak of the curve, anxiety is considered adaptive, because it helps people prepare for a crisis and improve their functioning. Beyond the peak of the curve, anxiety is considered maladaptive, because it produces distress and impairs their functioning.

Types of anxiety disorders

1- **Generalized anxiety disorder :** Patients are usually and constantly worried about health, money, work with no apparent reasons.

2- **Panic disorder :** An disorder in which people have sudden and intense attacks of anxiety in certain situations.

3- **Phobia :** An intense, uncontrolled fear of a specific situation such as open spaces & heights

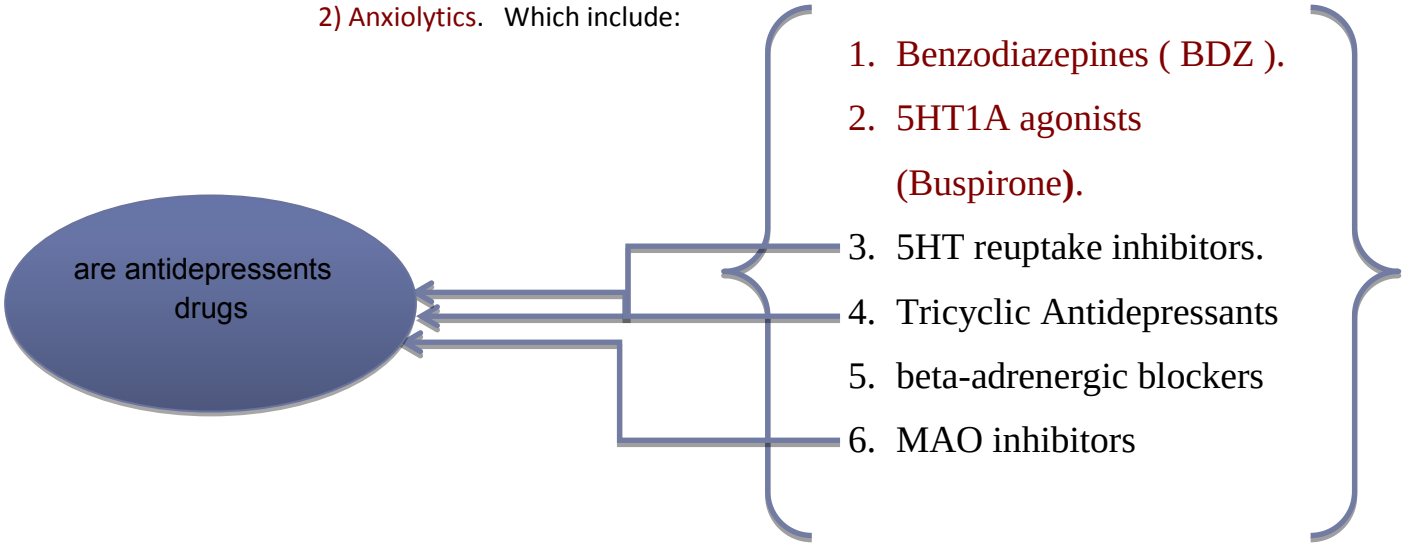
4- **Post-traumatic stress disorder :** An anxiety disorder that affects people who have experienced a severe emotional trauma, such as rape or dramatic car accident, or even war**.**

5- **Obsessive compulsive disorder (OCD) :** An anxiety disorder in which people cannot prevent themselves from unwanted thoughts or behaviors that seem impossible to stop as washing their hands

Note: In anxiety the neurotransmission is hyper-excited, so the goal of treatment is to reduce this excitement.

Treatment of anxiety

Treatment of anxiety: 1) psychotherapy.
2) Anxiolytics. Which include:



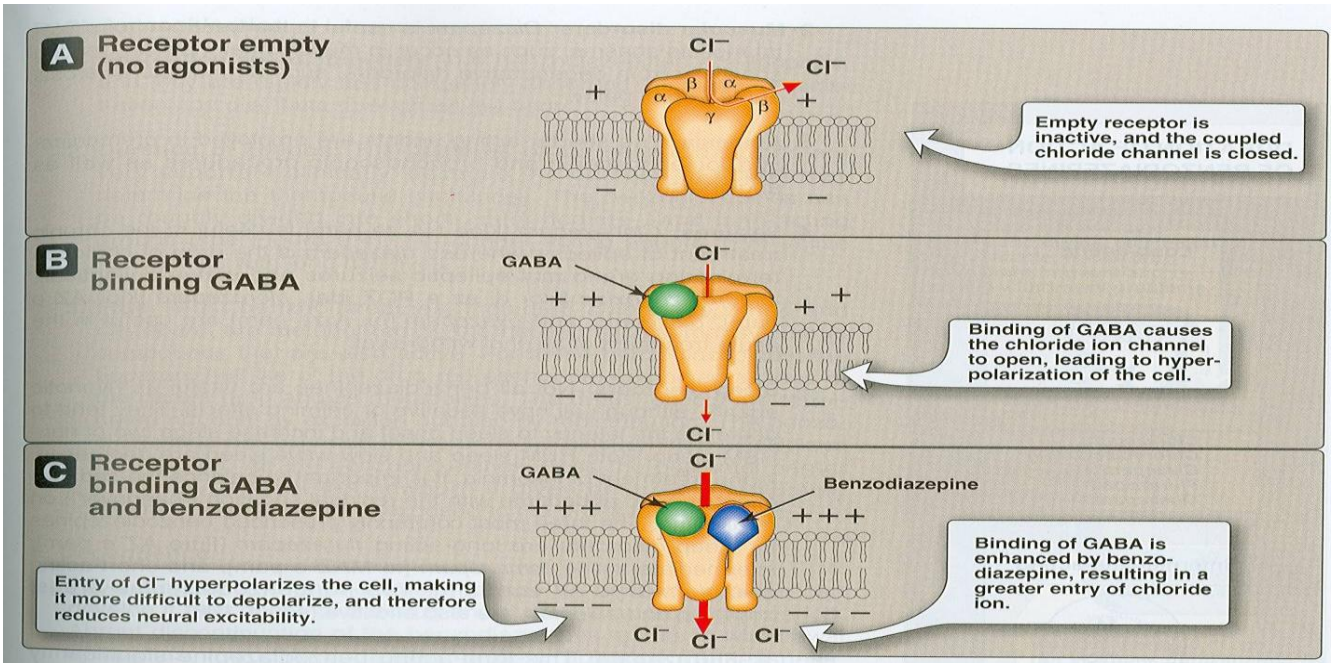
1) Benzodiazepines: Can be classified according to the duration of action into:

- **Short action (3-8 h): triazolam, oxazepam**
- **Intermediate action (10-20 h): alprazolam, , estazolam, lorazepam, temazepam (LATE)**
- **Long action (1-3 days): clorazepate, chlordiazepoxide, diazepam, flurazepam, Quazepam**

Mechanism of Action

- **Benzodiazepines act by binding to BZ receptors in the brain → enhance GABA action on brain chloride channels opening → ↑ chloride influx to the cell → hyper- polarization → inhibition of brain.**

Note: GABA (γ-aminobutyric acid): is an inhibitory neurotransmitter



PHARMACOKINETICS

- **Are lipid soluble**
- **Well absorbed orally,**
- **Can be given parenterally**
- **Chlordiazepoxide- Diazepam (IV only NOT IM)**
- **Widely distributed.**
- **Cross-placental barrier (Fetal depression).**
- **Excreted in milk (neonatal depression).**

Avoided In pregnant and nursing mothers

- **metabolized in the liver to active metabolites (long duration of action- cumulative effect).**
- **Redistribution from CNS to skeletal muscles and adipose tissue (termination of action).**

Redistribution of drug means that drug is withdrawn from its site of action to other site, redistribution results in termination of the drug action.

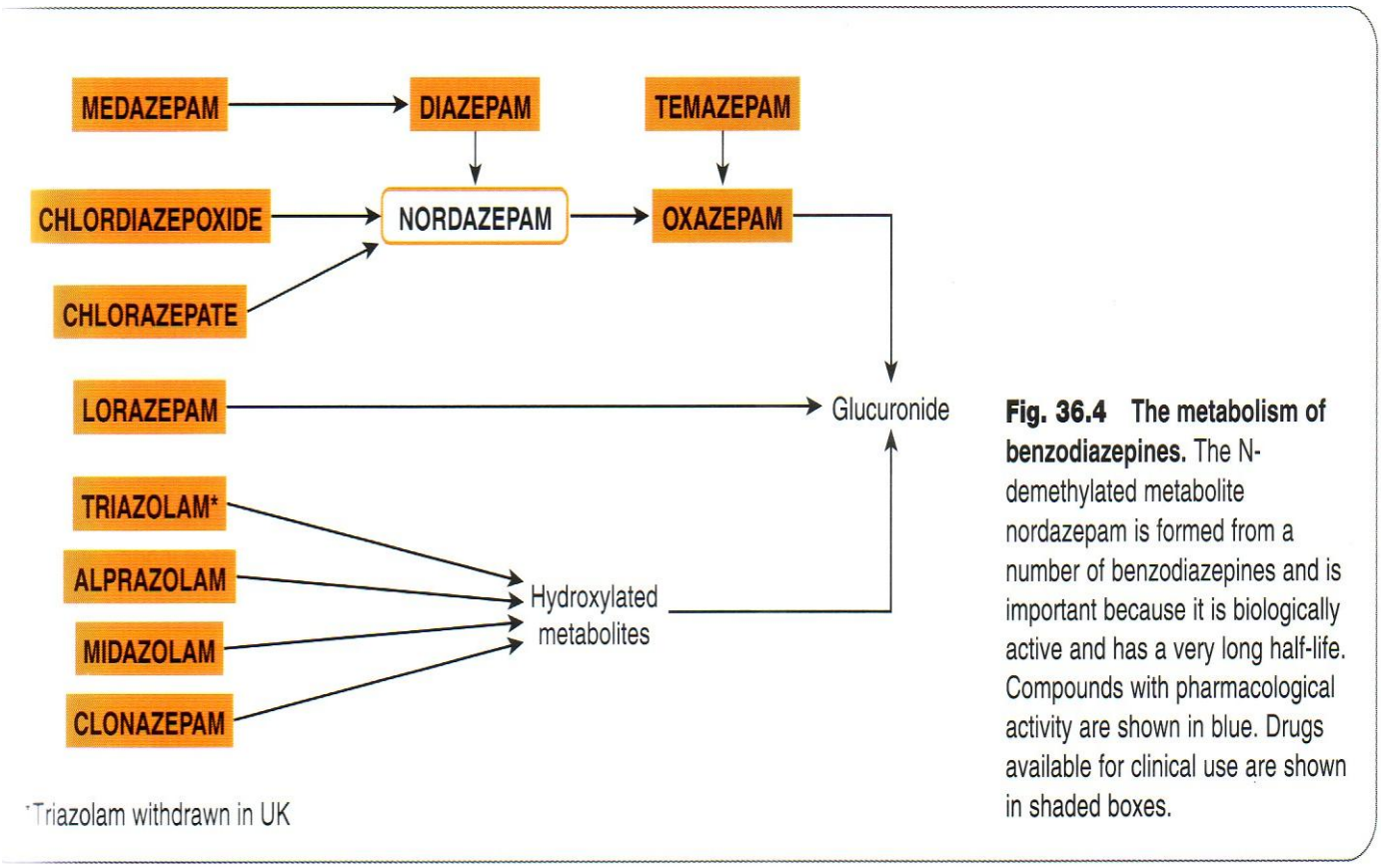


Fig. 36.4 The metabolism of benzodiazepines. The N-demethylated metabolite nordazepam is formed from a number of benzodiazepines and is important because it is biologically active and has a very long half-life. Compounds with pharmacological activity are shown in blue. Drugs available for clinical use are shown in shaded boxes.

Benzodiazepines drugs metabolize by three ways:

1- Hydroxylase metabolites then conjugates to the Glucuronide
2- Direct conjugated to Glucuronide. **Ex: lorazepam (so has fastest onset of action)**
3- by oxidise metabolites into nordazepam (which has long plasma half-life) then into oxazepam and finally conjugate to Glucuronide.

Note: Now after we know drugs that oxidise into **nordazepam** will have long half-life, you should avoid giving drugs metabolized by oxidation to elderly patient, why??

Oxidative metabolism deteriorates with age; Therefore, if it's given will lead to accumulation of the drug and may cause confusion and drowsiness.

-

Pharmacological Actions

Can relief all types of anxiety:

1. Depression of cognitive and psychomotor function >>> (patients should not drive)
2. Sedative & hypnotic actions (treat insomnia)
3. Anterograde amnesia
4. Minimal depressant effects on
    a. Cardiovascular system
    b. Respiratory system
5. Some have anticonvulsant effect:
    EX: clonazepam, diazepam.

Is the temporary impairment of memory with use of the benzodiazepines is also mediated by the α1-GABAA receptors. This also impairs a person's ability to learn and form new memories.

Therapeutic Uses

1. Anxiety disorders:
    - **short term relief of severe anxiety**
    - **General anxiety disorder**
    - **Obsessive compulsive disorder**
    - **Panic attack with depression Alprazolam (antidepressant effect)**

2. Sleep disorders (Insomnia)
    - **Triazolam, Lorazepam, Flurazepam**

3. Treatment of epilepsy
    - **Diazepam – Lorazepam**

4. In anesthesia
    - **Preanesthetic medication (diazepam).**
    - **Induction of anesthesia (Midazolam, IV)**

It used prior to the administration of an anesthetic agent, with the important object of making anesthesia safe and more agreeable to the patient. Also , because the patient will be anxious.

Note: there two important factors in anesthesia: Induction & maintenance. **Midazolam** does the induction effect.

Adverse Effects

- **Ataxia (motor incoordination)**
- **Cognitive impairment.**
- **Hangover: (drowsiness, confusion)**
- **Tolerance & dependence**
- **Risk of withdrawal symptoms** (symptoms arise when the patient stop the drug) **: Rebound Insomnia, anorexia, anxiety, agitation, tremors and convulsion.**
- **Toxic effects: respiratory & cardiovascular depression in large doses.**

(If it was taken with alcohol can cause respiratory & cardiovascular depression)

Tolerance: the reduction or loss of the normal response to a drug or other substance that usually provokes a reaction in the body. Drug tolerance may develop after taking a particular drug over a long period of time. In such cases increased doses are necessary to produce the desired effect. Some drugs that cause tolerance also cause dependence.

Note: Dependence is of two types. **In physical dependence** withdrawal of the drug causes specific symptoms (withdrawal symptoms), such as sweating, vomiting, or tremors that are reversed by further doses. Treatment is difficult and requires specialist skills. Much more common is **psychological dependence**, in which repeated use of a drug induces reliance on it for a state of wellbeing and contentment, but there are no physical withdrawal symptoms if use of the drug is stopped.

Note: Psychological and physical dependence on benzodiazepines can develop if **high doses** of the drugs are given over a **prolonged period**. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms. Because of the long half-lives of some benzodiazepines, withdrawal symptoms may occur slowly and last a number of days after discontinuation of therapy. 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 *diazepam.*

❖ **Drug interactions**

	Examples
CNS depressants	Alcohol & Antihistaminics of ↑ effect of benzodiazepines
Cytochrome P450 (CYT P450) inhibitors	Cimetidine & Erythromycin ↑ $t_{½}$ of benzodiazepines
CYT P450 inducers	Phenytoin & Rifampicin ↓ $t_{1/2}$ of benzodiazepines

Dose should be reduced in:

- **Liver disease** because it is metabolize in the liver
- **Old people :** because the liver and kidney functions reduced by age

Precaution: Should not be used in

- **pregnant women or breast-feeding.**
- **People over 65.** : Because they are very sensitive to the central acting drugs. e.g : benzodiazepam → convulsion

2) $5HT_{1A}$ agonists (Buspirone)

5HT
(5-hydroxytryptamine
Or Serotonin)

Pharmacokinetics

- ☐ **acts as agonist at brain $5HT_{1A}$ receptors (has an inhibitory effect)**
- ☐ **rapidly absorbed orally.**
- ☐ **T½ : (2 – 4 h).**
- ☐ **liver dysfunction → ↓ its clearance.**

Pharmacological Actions

Only anxiolytic (specific to anxiety)

- **No hypnotic effect.**
- **Not muscle relaxant.**
- **Not anticonvulsant.**
- **No potentiation of other CNS depressants.** (alcohol doesn't increase its effect)
- **Minimal psychomotor and cognitive dysfunctions.** (Because of that it's preferred for old people instead of benzodiazepine)

- **Does not affect driving skills.**
- **Minimal risk of dependence.**
- **No withdrawal signs.**

Uses of buspirone

- **As anxiolytic in mild anxiety & generalized anxiety disorders.**
- **They are not very effective in panic disorder & severe anxiety.**

Disadvantages of buspirone

- ☐ **Slow onset of action (delayed effect)** **(the antidepressant effect occur after 2 weeks of using drug)**
- ☐ **Not effective in severe anxiety/panic disorder.**
- ☐ **GIT upset, dizziness, drowsiness**
- ☐ **Drug Interactions with CYT P450 inducers and inhibitors**

3. Beta Blockers (Propranolol – atenolol)

- ☐ **act by blocking peripheral sympathetic system.**
- ☐ **Reduce somatic symptoms of anxiety.**
- ☐ **Decrease BP & slow HR.**
- ☐ **Used in performance anxiety**
- ☐ **are less effective for other forms of anxiety**

Is the anxiety, fear, or persistent phobia which may be aroused in an individual by the requirement to perform in front of an audience

4. Antidepressant drugs

In case of anxiety disorder (dopamine, noradrenaline, and serotonin) are found in the brain in a small amount, so in order to treat we need to increase their level by either inhibit their re-uptake (ex: tricyclic antidepressants) or inhibit Monoamine oxidase enzymes (MAOIs).

1-Tricyclic Antidepressants: (Doxepin- imipramine – desipramine)

- ☐ **Act by reducing uptake of 5HT & NA.** **(Serotonin & noradrenaline)**
- ☐ **Used for anxiety especially associated with depression.**
- ☐ **Effective for panic attacks.**
- ☐ **Delayed onset of action (weeks).**

Side effects:

- ☐ Atropine like actions (dry mouth-blurred vision-tachycardia).
- ☐ α-blocking activity (Postural hypotension).
- ☐ Sexual dysfunction.
- ☐ Weight gain.

2-Selective serotonin reuptake inhibitors (SSRIs): Fluoxetine

- acts by blocking uptake of 5HT
- Orally
- Delayed onset of action (weeks).
- Long half life
- Used for panic disorder – OCD depression-Generalized anxiety disorders - phobia.

Side effects

- Nausea, diarrhea
- Weight gain or loss
- Sexual dysfunction
- Dry mouth
- Seizures
- Sleep disturbance

3-Monoamine oxidase inhibitors (MAOIs): Phenelzine

- Act by blocking the action of MAO enzymes.
- Used for panic attacks and phobia.
- Require dietary restriction
- Avoid wine, beer, fermented foods as old cheese that contain tyramine.

Side effects:

- Dry mouth, constipation, diarrhea, restlessness, dizziness.

CLASSES OF ANXIOLYTICS	USES	Adverse effects
Benzodiazepines	**Generalized anxiety disorders, OCD, phobia, panic attack**	**Ataxia, confusion, dependence, tolerance, withdrawal symptoms,**
SSRIs (**Fluoxetine**)	**Generalized anxiety disorders, OCD, phobia, panic attack**	**weight gain, sexual dysfunction Dry mouth**
Tricyclic antidepressants (**doxepin, imipramine)**	**Anxiety with depression. panic attacks**	**weight gain, sexual dysfunction, atropine like actions**
5HT1A agonists **(Buspirone)**	**Mild anxiety Not effective in panic attack**	**Minimal adverse effects**
Beta blockers **(propranolol, atenolol)**	**Phobia (social Phobia)**	**Hypotension**

Summary:

- All **Benzodiazepines have sedative effects.**
- It is better to avoid using benzodiazepined for more than 2 weeks because of its dependence effect
- Short action (3-8 h): **oxazepam, triazolam**
- Intermediate action (10-20 h): alprazolam, estazolam, lorazepam, temazepam
- Long action (1-3 days): clorazepate, chlordiazepoxide, diazepam, flurazepam, Quazepam
- **Triazolam, Lorazepam, Flurazepam** are used to treat sleep disorders.
- **Benzodiazepines** act by enhancing **GABA** action on brain
- **B blockers** are used in stage fright anxiety.
- 5Ht1A agonists **(Buspirone)** are more specific to treat only mild anxiety.
- Both **Benzodiazepines** and **buspirone** have Drug Interactions with CYT P450 inducers and inhibitors
- Tricyclic Antidepressants**: (Doxepin- imipramine – desipramine**) Increase levels of serotonin and norepinephrine .
- Tricyclic Antidepressant used in anxiety with depression, and panic attack.
- Selective serotonin reuptake inhibitors (SSRIs): **Fluoxetine** increase the level of serotonin.
- Monoamine oxidase inhibitors (MAOIs): **Phenelzine** increase the level of norepinephrine.

Review questions

1-Which of the following is a Short-acting benzodiazepine?

A.diazepam (Valium)
B.flurazepam (Dalmane)
C. triazolam (Halcion)
D.buspirone (BuSpar)

2- **Anxiolytic drug acting through serotonin receptors:**

A. diazepam (Valium)
B. buspirone (BuSpar)
C. triazolam (Halcion)
D. phenobarbital

3- which of the following bennzodiazpines used for induction of anesthesia ?

A. Midazolam
B. diazapam
C. Flurazepam.
D. buspirone

Answers:
C
B
A