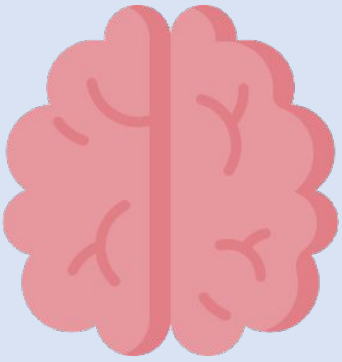

Revised & Approved

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Pharmacology 439

MED439

Neuropsychiatry Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Drugs Used in Anxiety and Panic Disorders

Objectives:

1- Define different types of anxiety disorders
2- Classify types of drugs used for treatment of anxiety
3- Recognize the pharmacokinetics & pharmacodynamics of different classes of anti-anxiety drugs.
4- Identify the specific clinical applications of each class of anti-anxiety drugs.
5- Know side effects of different classes of anti-anxiety drugs.

Editing file

What is Anxiety?

Antianxiety drugs: Drugs that can relieve anxiety without interfering with mental or physical function.
Low/moderate levels of anxiety are directly proportional with performance efficiency, but when it reaches high levels the individual will be unable to cope and will need treatment either by psychotherapy or medications.

Anxiety?

Physical and emotional distress which interferes with normal life.

Psychological Or Emotional Symptoms

- Feeling tense
- Trouble concentrating
- Irrational and excessive fear & worry
- Irritability
- Restlessness

Physical Or Somatic Symptoms

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

Types of Anxiety

Generalized Anxiety Disorder (GAD)

Patients are usually and constantly worried about health, money, work with no apparent reasons.

Obsessive-Compulsive Disorder (OCD)

anxiety disorder in which people cannot prevent themselves from unwanted thoughts or behaviours that seem impossible to stop as: Washing their hands excessively (الوسواس القهري)

Post-traumatic Stress Disorder (PTSD)

anxiety disorder that affects people who have experienced a severe emotional trauma, such as: rape or dramatic car accident, or even war.

Phobia

An intense, un--controlled fear of a specific situation such as:
open spaces & heights, animals

Panic Disorder

Sudden, intense and acute attacks of anxiety in certain situations. Panic attacks cannot be predicted.

Treatment of anxiety

- **Psychotherapy**
- **Anxiolytics**
  - Benzodiazepines (BDZ)
  - 5-HT_{1A} agonists
  - 5-HT reuptake inhibitors
  - Tricyclic Antidepressants
  - MAO inhibitors
  - Beta-adrenergic blockers
  - Pregabalin

Benzodiazepines (BDZ)

Classifications of Benzodiazepines are classified according to duration of action into:

Short acting (3-8 hours):

"TO" Tria**zolam**- Oxa**zepam**

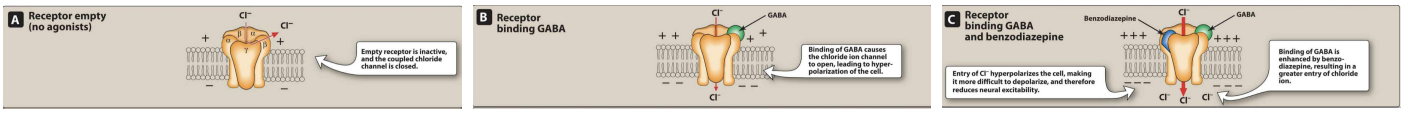
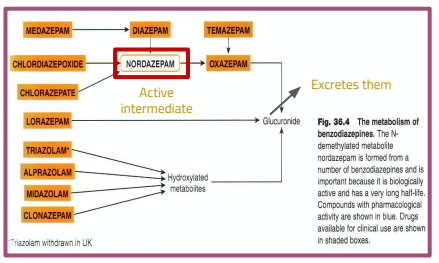
Intermediate (10-20 hours):

"LATE" Lora**zepam** (ativan) **-** Alpra**zolam** (xanax)
Tema**zepam -** Esta**zolam**

Causes issues with elderly due to its long duration

Long acting: (24-72 hours)

Chlordiazepoxide - Dia**zepam** (valium) -
Flura**zepam** - Clora**zepate** -
Qua**zepam**

Drug	**Benzodiazepines (BDZ)** Nomenclature of Benzodiazepines : Have the suffix "zolam" or "zepam"
M.O.A Most drugs in this block act as CNS depressants	Benzodiazepines act by binding to BZ receptors in the brain → enhance **GABA (γ-aminobutyric acid): an inhibitory neurotransmitter** action on the brain → chloride channels opening → ↑ chloride influx to the cell → hyperpolarization → more difficult to depolarize → reduction of neural excitability. 
P.k	• Lipid soluble (crosses BBB and has anesthetic effect) • Well absorbed orally, can be given parenterally • Chlordiazepoxide - Diazepam (IV only NOT IM) I.M. absorption is slow and erratic because it's not water soluble → might precipitate • Widely distributed. • Cross placental barrier (Fetal respiratory depression). • Excreted in milk (neonatal depression). • Metabolized in the liver to active metabolites (long D.O.A- cumulative effect) and excreted in urine. (Adjust dose in liver disease patients) 
Action	• CNS depressants • Sedation • Anxiolytic action (Dose is ⅓ of hypnotic) • Hypnotic action (induce sleep) • Anterograde amnesia ↓ ability to retain new info (useful in surgery) • Depression of cognitive and psychomotor function e.g. typing and driving توافق ذهني-عضلي • Some have skeletal muscle relaxing effect (diazepam) • Some have anticonvulsant effect (e.g. clonazepam, diazepam, lorazepam) • Therapeutic doses have minimal depressant effects on: ❖ Cardiovascular system ❖ Respiratory system Only group in this lecture used for several disorders. N.B. That the effect is stronger as the dose increases

Uses

- **Anxiety disorders:**

Benzodiazepines are fast acting, typically bringing relief within thirty minutes to an hour.

  - Short term relief of severe anxiety **Not** for long term because it leads to dependence
  - General anxiety disorder (GAD)
  - Obsessive compulsive disorder (OCD)
  - **Panic disorder with depression: Alprazolam (antidepressant effect)**
- **Sleep disorders (Insomnia):** Triazolam, Lorazepam, Flurazepam
- **Treatment of epilepsy:** Lorazepam, Diazepam (IV in status epilepticus)
- **In anesthesia:**
  - Pre-anesthetic medication (diazepam).
  - Induction of anesthesia (Midazolam, IV) Moments not remembered

Alcohol withdrawal syndrome: (diazepam) Both are CNS depressants

ADRs

- Cognitive impairment.
- Ataxia (motor incoordination) leading to Impairment of driving ability
- Anterograde amnesia (Date rape drug used in drug-facilitated sexual assaults to make the victim forget events occuring after taking it)
- Hangover: (excess sedation, drowsiness, confusion) usually with long acting drugs or elderly
- **Tolerance**
- **Psychological & physical dependence with continuous use**
- **Risk of withdrawal symptoms:** Especially with **Triazolam**, the shortest acting with the most severe withdrawal symptoms e.g. irritation and seizures. Therefore it has been withdrawn in many countries
  - (Rebound insomnia, anorexia, anxiety, agitation, tremors & convulsion).

benzodiazepines used to be the 1st choice in treatment of anxiety due to its very fast onset of action but due to its tolerance & dependence it is now avoided for long term use.

- Respiratory & cardiovascular depression in large doses only (toxic effects).
- Coma
- **Potentially death if used with alcohol**

Drug Int.

CNS depressants	**Cytochrome P450 inhibitors**	**CYT P450 inducers**
Alcohol & Antihistaminics (1st Gen)	Cimetidine & Erythromycin	Phenytoin & Rifampicin
↑ effect of benzodiazepines (Additive effect)	↑ t ½ of benzodiazepine	↓ t ½ of benzodiazepines

Precaut-ions

- Pregnant women or breast feeding.
- Dose reduction is recommended in: 1-Liver disease 2-Old people

Drug

Benzodiazepine Antagonist: Flumazenil

M.O.A

Selective benzodiazepine (BZ) receptor antagonist, bind competitively to GABA receptors displacing BDZ.

P.k

- I.V Only
- Short half life so repeated dosing is required

Uses

Benzodiazepines overdose (antidote) as in severe respiratory depression seen in alcoholics who've ingested a high dose of benzodiazepine

ADRs

Can precipitate withdrawal symptoms in benzodiazepine addicts.

Drug	**5-HT$_{1A}$ Agonist: Buspirone**
M.O.A	• Acts as a **partial agonist** at brain **5-HT$_{1A}$ receptors** Remember SARi M.O.A? • Adaptive changes after chronic treatment, reduction 5-HT$_2$ receptors in cortex • Weak dopamine D2 action, but not antipsychotic
P.k	• Rapidly absorbed orally • **Slow onset of action (delayed effect)** **if pt. complains of no effect after a few days, tell them to continue use** • T ½: (2–4 hr) • Undergoes extensive hepatic metabolism, its clearance is reduced by liver dysfunction
Action	• Only anxiolytic all drugs here other than BDZ • Minimal psychomotor & cognitive dysfunction • No hypnotic effect • No muscle relaxant effect. • No anticonvulsant action • No potentiation of other CNS depressants. • No alcohol additive effect. (advantage) • Doesn't impair memory and coordination • Doesn't affect **driving** skills **least sedative effect** • Minimal risk of dependence • No withdrawal symptoms Bus driver uses Buspirone
Uses	• Anxiolytic in generalized anxiety disorders and in mild anxiety. NOT used in **panic attacks** due to slow onset
ADRs	• GIT upset, dizziness, drowsiness • **Not effective in severe anxiety/panic disorders** • **Increasing blood pressure in people taking MAOI** (both Increase serotonin, may cause serotonin syndrome)
Drug Int.	**CYP450 3A4 Inhibitors**: (verapamil, diltiazem) → ↑ buspirone level. / **CYP450 3A4 Inducers**: (Rifampin) → ↓ buspirone level.
Preca-utions	• Pregnant women or breast-feeding. • People over 65. • Dose reduction is recommended in liver disease and old people.
Drug	**Selective Serotonin Reuptake Inhibitors (SSRIs):** **⋆DOC: Fluoxetine (brand name: Prozac)**
M.O.A	acts by **blocking** uptake of 5-HT thus increase serotonin in the brain
P.k	• Given orally. • Long half life • Delayed onset of action (weeks) **co-administration** with BDZ until SSRIs effect is established
Uses	Considered the **first line of treatment** **for most anxiety disorders** (panic disorder, OCD, GAD, PTSD, phobia) because they are well tolerated, have low risk for dependency and abuse and low potential for overdose. Unlike BDZ
ADRs	• Increase in anxiety symptoms, insomnia or headache in the first days or weeks of treatment may ↓ compliance "delayed action → trust issues (patient become less compliant to doctor's orders)" • Nausea, diarrhea • Weight gain • Sexual dysfunction • Dry mouth • Sleep disturbance or insomnia • Seizures (rare)

Tricyclic Antidepressants (TCAs)			
Drug	**Imipramine**	**Desipramine**	**Doxepin**
M.O.A	act by **reducing** uptake of 5-HT & NA (Non selective, ↑ serotonin & noradrenaline conc.)		
P.k	Delayed onset of action (weeks).		
Uses	• Used for anxiety especially associated with **depression**. • Effective for panic attacks.		
ADRs	• Atropine like actions (muscarinic blocking actions) (dry mouth-blurred vision, tachycardia, urinary retention). • α-blocking activity (Postural hypotension). • Sexual dysfunction. • Weight gain. • Because of the high frequency of ADRs compared to SSRIs, SSRIs should be tried first		

Drug	**MonoAmine Oxidase Inhibitors (MAOIs): Phenelzine**
M.O.A	act by blocking the action of MAO enzymes (MAO: breaks down catecholamines)
P.k For more details check antidepressants Lecture	Require dietary restriction: Avoid wine, beer, **fermented foods** as: old(aged) cheese, banana, that contain **Tyramine:** ↑NA release, if administered with MAOIs → severe sympathetic stimulation → severe vasocon. → **Hypertensive crisis**
Uses	• Panic attacks and phobia. • **Reserved** for patients who have not responded to, or proved intolerant of, other treatments.
ADRs	Dry mouth & constipation (Atropine like) diarrhea, restlessness, dizziness.

Beta Blockers		
Drug	**Propranolol**	**atenolol**
M.O.A	• Act by blocking peripheral sympathetic system. • Reduce **somatic symptoms** of anxiety. Physical NOT mental • Decrease BP & slow heart rate.	
Uses	• **Used in performance or social anxiety.** • Are less effective for other forms of anxiety	
ADRs	Should be used with caution in asthma, cardiac failure, peripheral vascular disorders	

Drug	Pregabalin
M.O.A	• **Modulates calcium channels in CNS, ↓Ca^{++} influx** (proven effect) • Modulates release of neurotransmitters. (thought to ↑ GABA release by ↑ action of the enzyme involved in GABA synthesis, although it is yet to be proven)
P.k	• Onset occurs in the first days of treatment. Unlike SSRIs delayed onset • Excreted unchanged in the urine.
Uses	• Effective in treatment & prevention of relapse of GAD **(1st line as SSRIS)**. • Used in epilepsy & neuropathic pain
ADRs	• Dizziness and somnolence. • Withdrawal symptoms may occur but **less** severe than benzodiazepines • Hypoglycemia

Females Slides Summary

Classes of Anxiolytics	Uses	ADRs
Benzodiazepines	• Generalized anxiety disorders • OCD • Phobia • Panic attack	• Ataxia • confusion • dependence • tolerance • withdrawal symptoms
SSRIs (Fluoxetine)	• Generalized anxiety disorders • OCD • Phobia • Panic attack	• Sexual dysfunction • atropine like actions
TCAs (doxepin, imipramine)	• Anxiety with depression panic attacks	• weight gain • arrhythmia • sexual dysfunction • atropine like actions
5-HT_{1A} agonists (Buspirone)	• Mild anxiety Not effective in panic attack	• Minimal adverse effects
Beta blockers (propranolol, atenolol)	• Phobia (social Phobia)	• Hypotension

Extra Summary

Drug	MOA	Uses	ADRS
Benzodiazepines (Triazolam- Oxazepam, Alprazolam -Lorazepam- Estazolam - Temazepam, Chlordiazepoxide-Diazepam - Flurazepam)	Bind to BZ receptors in the brain, enhance **GABA**	**-Anxiety disorders** **-Insomnia:** Triazolam, Lorazepam, Flurazepam **-Epilepsy**: Lorazepam, Diazepam **-Anesthesia:** diazepam (preanesthetic), midazolam(induction) **-Alcohol withdrawal syndrome:** diazepam	Cognitive impairment, Ataxia, Impairment of driving ability, Anterograde amnesia, Hangover, Tolerance, dependance, withdrawal symptoms, Respiratory & cardiovascular depression in large doses only (toxic effects)
Flumazenil	Selective benzodiazepine receptor antagonist, bind competitively to GABA receptors, displacing BDZ	**Benzodiazepine overdose** (antidote)	Can precipitate withdrawal symptoms in benzodiazepine addicts
Buspirone	Partial agonist at brain 5-HT_{1A} receptors	**GAD and mild anxiety**	GIT upset, dizziness, drowsiness, Not effective in severe anxiety/panic disorders
SSRI (Fluoxetine)	**SSRI**: acts by blocking uptake of 5-HT	**Anxiety disorders** (first line)	Increase in anxiety symptoms, insomnia or headache in the first days or weeks of treatment may ↓compliance, Nausea, diarrhea, Weight gain, Sexual dysfunction, Dry mouth, Sleep disturbance or insomnia, Seizures
TCAs (Doxepin,Imipramine, Desipramine)	Tricyclic AD (non-selective): Reduces uptake of 5-HT & NA	**Anxiety** (especially associated with depression) **Panic attacks** (Because of the high frequency of ADRS compared to SSRIs, **SSRIs should be tried first**)	Atropine like actions (muscarinic blocking actions; dry mouth-blurred vision, tachycardia, urinary retention), α-blocking activity (Postural hypotension), Sexual dysfunction. Weight gain.
MAOIs (Phenelzine)	**MAOIs**: block action of MAO	**-Panic attacks** **-Phobia** **(Non-responsive/intolerant of other medications)**	Dry mouth, constipation, diarrhea, restlessness, dizziness.
Beta-Blockers (propranolol, atenolol)	-Block peripheral sympathetic system -Reduce somatic symptoms of anxiety -Decrease BP & slow HR	**-Performance/social anxiety** (less effective for other forms of anxiety)	used with caution in asthma, cardiac failure, peripheral vascular disorders
Pregabalin	-Modulates calcium channels in CNS, ↓Ca++ influx -Modulates release of neurotransmitters	**-Treatment of GAD** **-Prevention of relapse of GAD** (1st line as SSRIS) **-Epilepsy & neuropathic pain**	dizziness and somnolence. Withdrawal symptoms may occur but **less** severe than benzodiazepines

MCQs

Check out **these flashcards** made by Nouf AlSubaie!

Q1: Hussam a 36 year-old patient came to ER with trouble breathing and depressed cardiac function, PMH revealed that he is on diazepam. History taking showed that he drinks alcohol frequently. Which one of the following drugs would help him in this case			
A- Flumazenil	B- Buspirone	C- Propranolol	D- Pregabalin
Q2: Nawaf is a 25 year-old lawyer, he recently moved to a new firm which requires a lot of work and later on he started doubting himself since he's not as productive as before. Which of the following drugs is the drug of choice for Nawaf?			
A- Chlordiazepoxide	B- Propranolol	C- Triazolam	D- Buspirone
Q3: A limitation of buspirone is:			
A- A low therapeutic index	B- An extremely slow onset of action	C- A high potential of development of physical dependance	D-Impairment of mentation or motor functions during working hours
Q4: A patient was diagnosed with GAD and the doctor prescribed him fluoxetine but she knew that it would take time for the drug to start showing effect, which drug should she add on to the patient's prescription?			
A- Propranolol	B- Doxepin	C- Diazepam	D- Buspirone
Q5: Which of the following has α-blocking activity which causing postural hypotension			
A- Buspirone	B- Fluoxetine	C- Pregabalin	D- Doxepin
Q6: Muneerah is a 32 years old teacher who came into the clinic complaining of stress that is disruptive but not affecting her daily tasks. The psychiatrist told her that she has mild anxiety. Which of the following drugs should the psychiatrist prescribe for Muneerah?			
A- Flumazenil	B- Buspirone	C- Phenelzine	D- Imipramine
Q7: Which drugs works by modulating calcium channels in CNS?			
A- Atenolol	B- Nordazepam	C- Doxepin	D- Pregabalin
Q8: Which of the following drugs considered as the first line of treatment for most of anxiety disorders			
A- Fluoxetine	B- Doxepin	C- Buspirone	D- Nordazepam

1	2	3	4	5	6	7	8
A	B	B	C	D	B	D	A

SAQ

Q1) Explain the importance of Nordazepam.

Q2) Therapeutic doses of benzodiazepines have minimal depressant effects on?

Q3) Enumerate types of anxiety.

Q4) How do benzodiazepines reduce neural excitability?

Q5) A 26 years old patient visited a psychiatrist and he prescribed him a drug for panic attacks and he asked him to avoid wine and old cheese, what is the drug and what is the M.O.A

Q6) A 54-year-old man was sent by his physician to a psychiatrist because of the onset of a distressing and embarrassing behavior. For the past 3 months, the man had been experiencing an irresistible urge to disinfect any object in his room and to wash his hands again and again. He was disturbed by the unreasonable amount of time he spent on such activities, and he acknowledges that his behavior was totally inappropriate, but he felt he could not stop it. He denied any substance abuse or use of medications. Which drug would be most appropriate for this patient? What is its MOA? Enumerate 3 side effects of the selected drug.

Q7) CASE FROM MALES' SLIDES: A 22-year-old woman is brought in the emergency department via ambulance because of a suicide attempt. Soon after a "night on the town," she called her boyfriend saying that she took a handful of sleeping tablets. On examination, she appears lethargic, but groans and moves all her extremities to painful stimuli. Her blood pressure is 110/70 mm Hg, heart rate is 80 bp/m, and oxygen saturation is 99 percent. Her pupils are of normal size and reactive to light. Her deep tendon reflexes are normal bilaterally. In the field, she was given an intravenous bolus of dextrose and an ampoule of naloxone without response. Her boyfriend, with whom she had an argument, brings in the bottle of sleeping medication which reads "lorazepam."

a) What is the danger of an overdose with this class of medication?
b) What is the cellular mechanism of action of this class of medication?
c) What pharmacologic agent can be used to treat this patient, and what is its mechanism of action?

Answers

A1) Its biologically active and has a very long half life.

A2) Cardiovascular and respiratory systems.

A3) Generalized Anxiety Disorder, obsessive-compulsive Disorder, Post Traumatic Stress Disorder, Phobia, Panic Disorder.

A4) Act by binding to BZ receptors and enhancing GABA's action on the brain and opening chloride channels for chloride influx hyperpolarizing the cell, reducing its neural excitability.

A5) Phenelzine, acts by blocking the action of MAO enzymes

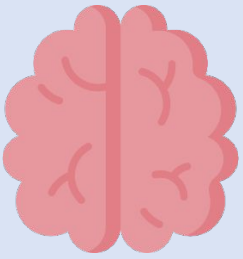
A6) Fluoxetine. MOA: acts by blocking uptake of 5-HT. ADRs: Increase anxiety symptoms, sexual dysfunction, seizures

A7) a- Respiratory & cardiovascular depression.

b- Benzodiazepines act by binding to BZ receptors in the brain → enhance GABA action on the brain.

c- Flumazenil, Selective benzodiazepine (BZ) receptor antagonist

Feedback Form



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