pharmacology
Team 438

MED438
KING SAUD UNIVERSITY

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Neuropsychiatry Block

Pharmacology Team 438

Drugs Used in Anxiety And Panic Disorders

Objectives

By the end of the lecture , you should know:

- Define different types of anxiety disorders
- Classify types of drugs used for treatment of anxiety
- Recognize the pharmacokinetics & pharmacodynamics of different classes of anti-anxiety drugs.
- Identify the specific clinical applications of each class of anti-anxiety drugs.
- Know side effects of different classes of anti-anxiety drugs.
- Discuss the different characteristics of antianxiety drugs

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Pink : Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

Anxiety

Physical and emotional distress which interferes with normal life.

1 Emotional or psychological symptom

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

2 Physical or somatic symptoms

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

Types of Anxiety:

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

02 Phobias
An intense, uncontrolled fear of a specific situation such as open spaces & heights

03 Generalized anxiety disorder (GAD)
Patients are usually and constantly worried about health, money, work with **no** apparent reason.

04 Panic disorder[1]
Sudden, intense and acute attacks of anxiety in certain situations. Panic attacks **cannot** be predicted.

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

Treatment of Anxiety:

Treatment of anxiety contains: **Psychotherapy & Anxiolytics**

Anxiolytics

- **MAOI**
- **Pregabalin**
- **Benzodiazepines (BDZ)**
- **5HT reuptake inhibitors**
- **B-adrenergic[2] blockers**
- **Tricyclic Antidepressant**
- **5HT1A agonist**

1- involve autonomic disturbance may urinate or defecate.
2- used to treat the somatic symptoms of anxiety eg. heart palpitations (weak on emotional symptoms)

Benzodiazepines (BDZ)

Drugs	• Triazolam • Oxazepam	• Lorazepam • Alprazolam • Temazepam • Estazolam	• Diazepam • Chlordiazepoxide • Flurazepam
Duration	Short[1] 3-8 h	Intermediate 10-20 h	Long[2] 24-72 h
MOA	binding to **BZ receptors** in the brain⟶ **enhance GABA** action on the brain ⟶ chloride channels opening ⟶ ↑chloride **influx** to the cell ⟶ hyperpolarization ⟶ more difficult to depolarize ⟶reduction of neural excitability.		
P.K	• are lipid soluble , widely distributed. • well absorbed orally , **Chlordiazepoxide, Diazepam(IV[3] only NOT IM)** • cross placental barrier **(Fetal depression).** • excreted in milk **(neonatal depression).** • metabolized in the liver to active metabolites **(long duration of action-cumulative effect)** and excreted in urine		
Actions	**Anxiolytic action** • Depression of cognitive and psychomotor function • Some have skeletal muscle relaxing effect (*diazepam*) • Some have anticonvulsant effect e.g. *clonazepam*,*diazepam*, *lorazepam.* • Therapeutic doses have minimal depressant effects on: cardiovascular & respiratory systems **CNS depressants:** • Anxiolytic action. • Sedation , **Hypnotic action**.[4] • Anterograde[5] amnesia.		
clinical uses	**1- Anxiety disorders:** • Benzodiazepines are **fast acting** typically bringing relief within (30mins – hour). • **Short term** relief of severe anxiety, General anxiety disorder, OCD,Panic attack with depression: **Alprazolam** (antidepressant effect) **2- Sleep disorders (Insomnia): Triazolam**, **Lorazepam**, **Flurazepam**. **3-Treatment of epilepsy: Diazepam, Lorazepam**. **4- In anesthesia:** • Pre-anesthetic medication (**diazepam**) • Induction of anesthesia (**Midazolam**, IV) **5- Alcohol withdrawal syndrome: (diazepam)**		

1- no longer used due to short duration and withdrawal symptoms.
2- long because after their metabolism they turn into another benzo drug. Eg. diazepam is metabolized first into nordiazepam then into oxazepam and all are active.
3- Administration via IM causes erratic absorption (inconsistent absorption).
4- relatively low dose-> anxiolytic. Higher dose> hypnotic. higher> anesthesia. higher> coma
5- can not form new memory. Helpful in induction of anesthesia.

Benzodiazepines (BDZ) cont..

ADRs	• Psychological & physical dependence with **continuous** use. • Risk of withdrawal symptoms:(rebound insomnia, anorexia, anxiety, agitation, tremors, convulsion). • Respiratory & cardiovascular depression in large doses only (toxic effects).[1] • cognitive impairment • ataxia (motor incoordination) → impairment of driving ability • anterograde amnesia • Hangover: (excess sedation , drowsiness , confusion) • Tolerance & dependance[2]
Precaution	• Pregnant women or breast-feeding. • Dose reduction is recommended in **Liver disease** & **old people**[3]
Drug interaction	**CNS depressants** e.g. alcohol & antihistamine → increase effect of benzodiazepines **(Additive effect)** **CYT P450 inhibitors** e.g. cimetidine & erythromycin → **increase** t1/2 of benzodiazepines **CYT P450 inducers** e.g phenytoin & rifampicin → **decreased** t1/2 of benzodiazepines

Drug	**Flumazenil**
MOA	• Selective benzodiazepine receptor antagonist, bind competitively to GABA receptors replacing BDZ
P.K	• Given I.V only • Has **Short** half life so **repeated dosing is required**.
Clinical uses	• Benzodiazepines overdose (**antidote**)
ADRS	• Can **precipitate withdrawal symptoms** in benzodiazepines **addicts**

1- in large doses and if combined with alcohol.
2-benzodiazepines used to be the 1st option in treatment of anxiety due to its very fast onset of action but because it causes dependence & tolerance it is now avoided for long term use.
3- because it is metabolized in the liver & elderly patients have hypersensitivity to most CNS drugs, especially with long acting benzodiazepines.

5HT-1A agonist

Drug	Buspirone
MOA	• Acts as a partial agonist at brain $5HT_{1A}$ receptors pre-synapticaly inhibiting 5HT release. • Adaptive changes after chronic treatment , reduction in 5HT2 receptors in cortex • Weak dopapamine D2 action , but not antipsychotic
P.K	• rapidly absorbed orally • slow onset of action (delayed effect) "disadvantage" • T1/2 :(2-4) • undergoes extensive hepatic metabolism, some of the metabolites are active • it's clearance is reduced by liver dysfunction
Actions	**Only anxiolytic**[1] -No hypotonic effect -No muscle relaxant effect -No anticonvulsant action -No alcohol additive effect -Minimal risk of dependance -No withdrawal symptoms -Minimal psychomotor & congestive dysfunction→Does not affect driving skills. -No potentiation of other CNS depressants
uses	• As anxiolytic in mild anxiety & generalized anxiety disorders.
ADRs	• GIT upset, dizziness, drowsiness • Not effective in severe anxiety/panic disorders
Drug interaction	**CYT P450 3A4 inhibitors** e.g. **verapamil**, **diltiazem** → **increase** buspirone level **CYT P450 3A4 inducers** e.g. **Rifampin** → **decreased** 10 folds of **buspirone** level. **In people taking MAOIs** → increase BP.
Precaution	• **Pregnant** women or **breast-feeding &** Old people (>65) • Dose reduction is recommended in **liver disease, old people**

Monoamine oxidase inhibitors (MAOIs)

Drug	Phenelzine[2]
MOA	• Acts by blocking the action of MAO enzymes[3]
P.K	• Require dietary restriction avoid wine, beer, fermented foods and old cheese that contain tyramine[4] **(hypertensive crisis)**
uses	• Used for panic attacks and phobia • **Reserved** for patients who have not responded to,or proved intolerant of, other treatments.
ADRs	• Dry mouth, constipation, diarrhea, restlessness, dizziness.

1- selective , better than beta-2 drugs.
2- little use, only given when others fail! LAST OPTION.
3- recall that catecholamines(NE, N, DA, 5HT, etc) are degraded by MAO & COMT.
4- it will displace NE in nerve endings and release of high amounts causing hypertensive crisis.

selective serotonin reuptake inhibitors (SSRIs)

Drug	Fluoxetine[1]
MOA	• Acts by **blocking uptake of 5-HT**
P.K	• given orally • long half life • **Delayed** onset of action (weeks)
clinical 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**.
ADRs	• Nausea, diarrhea • weight gain • Dry mouth • Sexual dysfunction • Sleep disturbance or insomnia • Seizures • Increase in anxiety symptoms, insomnia or headache in the first days of treatment may ↓ compliance

Tricyclic Antidepressant

Drug	• Doxepin • Imipramine • Desipramine
MOA	• Act by **reducing uptake of 5HT & NA**
P.K	• **Delayed** onset of action (weeks).
clinical uses	• Used for **anxiety** especially associated with **depression** • Effective for **panic** attacks.
ADRs	• Atropine like actions **(dry mouth-blurred vision, tachycardia, urinary retention)** • Sexual dysfunction. • Weight gain. • α-blocking activity (**Postural hypotension**). • Because of the high frequency of ADRS compared to SSRIs, SSRIs should be tried first

Beta blockers

Drug	• Propranolol • Atenolol
MOA	• Act by **blocking peripheral sympathetic system** →Reduce **somatic symptoms of anxiety** • Decrease BP & slow heart rate.
clinical 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.

1- it is recommended to prescribe benzodiazepines with it to (1) decrease initial increases in anxiety(so that patients would remain compliant to treatment). (2) & because SSRIs have delayed onset of action.

Drug	Pregabalin
MOA	• Modulates calcium channels in **CNS**, ↓Ca++ influx modulates release of neurotransmitters
P.K	• Onset occurs in the first days of treatment[1] • Excreted unchanged in the urine
Clinical uses	• Effective in 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.

Case from Doctor 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."

Q1. What is the danger of an overdose with this class of medication?
Ans: respiratory and cardiac depression.

Q2. What is the cellular mechanism of action of this class of medication?
Ans:
binding to **BZ receptors** in the brain→ **enhance GABA** action on the brain → chloride channels opening → ↑chloride **influx** to the cell → hyperpolarization → more difficult to depolarize →reduction of neural excitability.

Q3.What pharmacologic agent can be used to treat this patient, and what is its mechanism of action?
Ans: **Flumazenil.**
It is Selective, benzodiazepine receptor antagonist. bind competitively to GABA receptors replacing BDZ

1- isn't as slow as the rest, but it also isnt as fast as benzodiazepines.

Quiz

MCQ

1- Which one of the following is a short-acting hypnotic?

A- Diazepam B- Chlordiazepoxide C- Triazolam D- Flurazepam

2- A 45-year-old man who has been injured in a car accident is brought into the emergency room. His blood alcohol level on admission is 275 mg/dL. Hospital records show a prior hospitalization for alcohol-related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal?

A- None B- Diazepam C- Phenytoin D- Buspirone

3- Which one of the following agents has a rapid anxiolytic effect and would be best for the acute management of anxiety?

A- Buspirone B- Fluoxetine C- Lorazepam D- Doxepin

4- Which agent is best used in the Emergency Room setting for patients who are believed to have received too much of a benzodiazepine drug or taken an overdose of benzodiazepines?

A- Diazepam B- Doxepin C- Flumazenil D- Ramelteon

SAQ

1-Which anxiolytic drug considered as the first line of treatment for most anxiety disorders?

-Lulu is a 15-years-old female came to see a psychologist with her parents, her parents explain to the doctor that she has no friends and always set alone in her room which seemed normal until they force her to attend a family gathering where they noticed that she started sweating and breathing fast then she locked herself in the bathroom.

2-Which drug would be the most helpful to this patient ?
3-What is the mechanism of action of this drug ?

4-A 40-years-old male with history of anxiety associated with depression, in the last visit to his psychologist he told him that he noticed that since he started taking the medication he gain a lot of weight and feels dizzy when he stand up. Which anxiolytic drug he most likely taking that cause that symptoms ?

Answers:

MCQ

Q1	C
Q2	B
Q3	C
Q4	C

SAQ

Q1	Fluoxetine
Q2	Propranolol or atenolol
Q3	beta blockers-blocking peripheral sympathetic system.
Q4	Doxepin - Imipramine - Desipramine

pharmacology

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Good Luck , Future Doctors!

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Share with us your ideas !