MED437
KING SAUD UNIVERSITY

Pharmacology
Team 437

Drugs used in anxiety and panic disorders

Objectives:

- 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:

- Drugs names
- Doctors notes
- Important
- Extra

Introduction

Anxiety

Physical and emotional distress which interferes with normal life.

Emotional or psychological symptom

- Feeling tense
- Trouble concentrating
-Irrational (without reason) and excessive fear and worry
- Irritability
-Restlessness

Physical or somatic symptoms

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

Types of anxiety

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.

Generalized anxiety disorder (GAD)

Patients are usually and constantly worried about **everything**, health, money, work with **no** apparent reason.

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**

Phobias

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

Panic disorder

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

Overview of anxiety treatment

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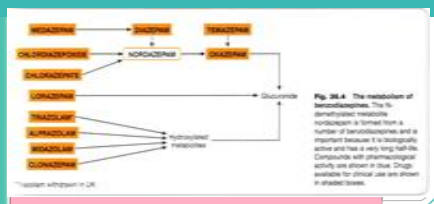
- Treatment of anxiety
  - Psychotherapy (cognitive behavioral therapy)
  - anxiolytic
    - Benzodiazepine (BDZ)
    - 5HT reuptake inhibitors
    - 5HT1A agonist
    - antidepressant
    - B-adrenergic blockers

Benzodiazepines

suffix "zolam ' or "zepam"



Classification according to duration of action

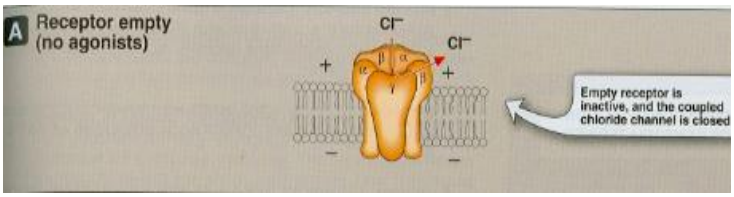
- Short 3-8 H (TO)
  - Triazolam
  - oxazepam
- Intermediate 10-20 H (late)
  - Lorazepam
  - Alprazolam
  - Temazepam
  - Estizolam
- Long 24-72 H
  - Diazepam
  - Chlordiazepoxide
  - Flurazepam

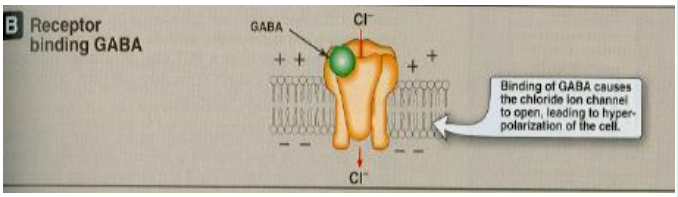
MOA

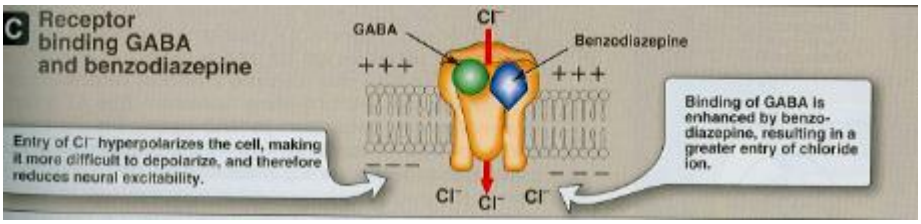
1-binding to **BZ receptors** in the brain **enhance GABA** action on the brain
GABA (γ-aminobutyric acid):is an inhibitory neurotransmitter

2- chloride channels opening → chloride **influx** to the cell

3-hyperpolarization → more difficult to depolarize →reduction of neural excitability.







P.K

- are lipid soluble , widely distributed.
- cross placental barrier (Fetal depression).
- excreted in milk (neonatal depression).
- well absorbed orally , Chlordiazepoxide- Diazepam(IV only NOT IM)
- metabolized in the liver to active metabolites (long duration of action-cumulative effect) and excreted in urine.

Benzodiazepines

actions

- Depression of cognitive and psychomotor function
- skeletal muscle relaxing effect (*diazepam*) → by increasing presynaptic inhibition in the spinal cord
- anticonvulsant effect e.g. *clonazepam*, *diazepam*, *lorazepam*.
- Therapeutic doses have minimal depressant effects on: cardiovascular & respiratory systems

CNS depressants:
- Anxiolytic action.
- Sedation , **Hypnotic action**. = sleeping pills
-Anterograde amnesia.→ temporary impairment of memory

Therapeutic uses

- **Anxiety disorders:**

Short term relief of severe anxiety, General anxiety disorder, OCD,
Panic disorder with depression **Alprazolam** (antidepressant effect)

- Benzodiazepines are **fast acting** typically bringing relief within (30mins – hour).
- **Sleep disorders (Insomnia): Triazolam**, **Lorazepam**, **Flurazepam**.

→ They tend to decrease the latency to sleep onset and increase Stage II of NREM sleep.

- **Treatment of epilepsy: Diazepam – Lorazepam**.
- **In anesthesia:**

Pre-anesthetic medication (**diazepam**). Induction of anesthesia (**Midazolam**, IV)

- **Alcohol withdrawal syndrome:** (**diazepam**)

ADRs

- Psychological & physical dependence with continuous use.
- withdrawal symptoms:(insomnia, anorexia, anxiety, agitation,tremors,convulsion).
- Respiratory & cardiovascular depression in large doses only (toxic effects).
- cognitive impairment
- ataxia (motor incoordination) → impairment of driving ability
- anterograde amnesia
- hangover:(excess sedation , drowsiness , confusion)
- tolerance

Precautions

- Pregnant women or breast-feeding.
- Dose reduction is recommended in **Liver disease** & **old people**

Drug-Drug interaction

CNS depressants e.g. *alcohol* & *antihistamine* (1st generation)	increase effect of benzodiazepines **(Additive effect)**
Cytochrome P450 inhibitors e.g. *cimetidine* & *erythromycin*	**increase** $t_{1/2}$ of benzodiazepines
CYT P450 inducers *phenytoin* & *rifampicin*	**decreased** $t_{1/2}$ of benzodiazepines (all epileptic drugs are inducers)

flumazenil

M.O.A	- Selective, benzodiazepine receptor antagonist. bind compatitivly to GABA recptors replacing BDZ
P.K	- Injection (IV only) - **Short plasma** half life so **repeated dosing is required**.

- Benzodiazepines overdose (**antidote**)
- Can precipitate **withdrawal symptoms** in benzodiazepines **addicts**

5HT-1A agonist
Buspirone

M.O.A	acts as a partial agonist at 5HT-1A receptors pre-synapticaly inhibiting 5HT release -Adaptive changes after chronic treatment , reduction in 5HT2 receptors in cortex -Weak dopapamineD2 action , but not antipsychotic
P.K	• rapidly absorbed orally • slow onset of action (delayed effect) - T1/2 :(2-4)H • undergoes extensive hepatic metabolism , it's clearance is reduced by liver dysfunction
actions	**Only** anxiolytic **No hypnotic effect**. No muscle relaxant effect. **No anticonvulsant action**. **No alcohol additive effect**. it **doesn't impair memory and coordination**. -**Does not affect driving skills**. **-Minimal risk of dependence**. -No withdrawal symptoms -No potentiation of other CNS depressants -Minimal psychomotor & cognitive dysfunctions
indications	- As anxiolytic in generalized anxiety disorders.
disadvan-tage / ADRs	Slow onset of action (delayed effect) GIT upset, **dizziness, drowsiness** Not effective in severe anxiety/panic disorders Drug interactions with CYT P450 inducers and inhibitors
drug interactions	- **CYP450 3A4 Inhibitors** (**verapamil**, **diltiazem**) → ↑ buspirone level - **CYP450 3A4 Inducers** (**Rifampin**) → 10 folds ↓ **buspirone** level. - MAOIs → increase BP.
precautions	- **Pregnant** women or **breast-feeding**. - Old people (>65) - Dose reduction is recommended in **liver disease**, old

selective sertonin reuptake inhiptors (SSRIs)
Fluoxetine

M.O.A	acts by blocking uptake of 5-HT
P.K	-given orally -long half life
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	1- Delayed onset of action (weeks). 2- Nausea, diarrhea → GIT upset 3- SSRIs may cause **weight gain or loss.** 4- Sexual dysfunction 5- Dry mouth 6- Sleep disturbance or insomnia 7- Seizures

tricyclic antidepressant
Doxepin - Imipramine - Desipramine

M.O.A	Act by **reducing uptake of 5HT & NA**
O.O.A	**Delayed** onset of action (weeks).
uses	1- Used for **anxiety** especially associated with **depression** 2- Effective for **panic** attacks.
ADRs	• Atropine like actions (dry mouth-blurred vision, tachycardia, urinary retention). • α-blocking activity (**Postural hypotension**). • Sexual dysfunction. • **Weight gain**.

beta blockers
Propranolol – atenolol

M.O.A	Act by **blocking peripheral sympathetic system**. → Reduce **somatic** symptoms of anxiety. 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. → because of beta2 effect

Monoamine oxidase inhibitors (MAOIs)
Phenelzine

M.O.A	Acts by blocking the action of MAO enzymes
P.K	Require dietary restriction avoid wine, beer, fermented foods and old cheese that contain tyramine.
uses	Used for panic attacks and phobia
ADRs	Dry mouth, constipation, diarrhea, restlessness, dizziness.

summary & Q

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

MCQs

1)Which one of the following drug cause muscle relaxant ?
A-Triazolam
B-Lorazepam
C-Diazepam
D-Alprazolam

2)Which one of the following drugs is used in performance and social anxiety?
A-lorazepam
B-fluoxetine
C-imipramine
D-propranolol

3)Which one of the following is considered the 1st line of treatment in most anxiety disorders ?
A-triazolam
B-atenolol
C-fluoxetine
D-buspirone

4)Which one of the following is used as an antidote to benzodiazepines overdose ?
A-flumazenil
B-atenolol
C-fluoxetine
D-buspirone

4-A
3-C
2-D
1-C

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References:

- Doctors' slides and notes.
- pharmacology Team 435.

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