PHARMACOLOGICAL MANAGEMENT OF ANXIETY DISORDERS

OUTLINE

- Overview of anxiety disorders
- Benzodiazepines
- Azapirones (buspirone)
- Antidepressants
- Beta- adrenoceptor antagonists
- Pregabalin
- Hypnotics
- Advice on management of anxiety disorders

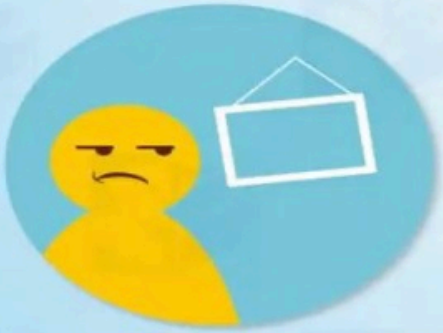
ANXIETY DISORDERS

VILLA MEDICA
CLINIC FOR REGENERATIVE MEDICINE
GERMANY-SINCE 1978

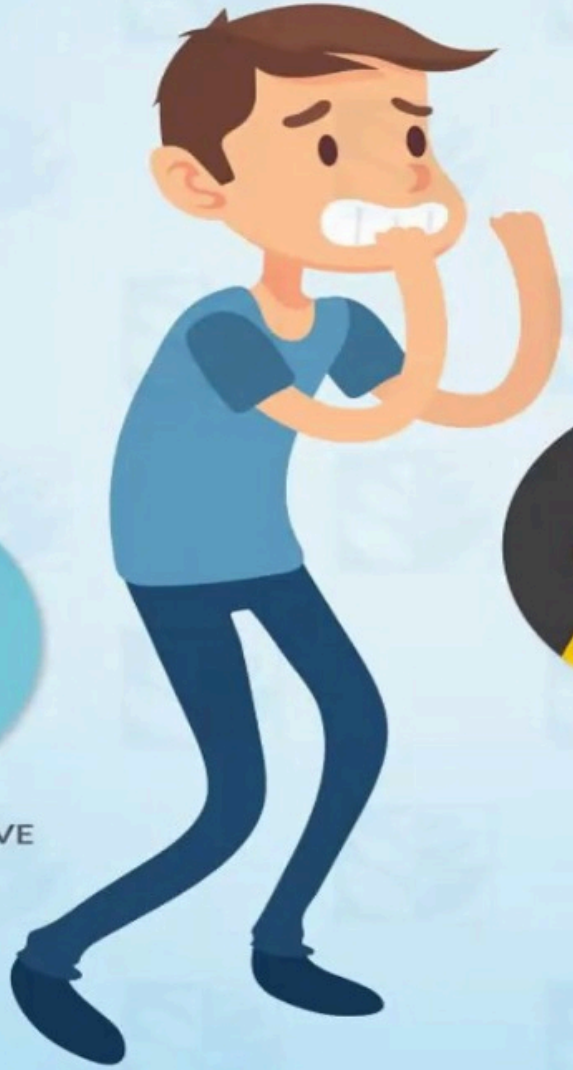
An anxiety disorder is a debilitating mental illness that shows signs of fear, worry, and uneasiness.

TYPES OF ANXIETY

POSTTRAUMATIC STRESS DISORDER PTSD



OBSESSIVE-COMPULSIVE DISORDER - OCD



SPECIFIC PHOBIA (FEAR)

GENERALIZED ANXIETY DISORDER

PANIC DISORDER

Psychological theory

1. Psychoanalytic theory

Sigmund Freud defined anxiety as a signal of the presence of danger in our unconscious.

Anxiety occurs when instinctual drives are thwarted so if you do not let the instinct get through then one get anxiety.

2. Behavioural theory

Anxiety is a conditioned response to a specific environmental stimulus.

3. **Existential theory**

The concept is that persons experience feelings of anxiety living in a purposeless universe perceived void in existence and meaning.

Biological theory

. **Genetic evidence** – Studies have shown that about 15-20 % of first degree relatives of patients with anxiety disorders exhibits anxiety disorders themselves. Monozygotic twins have 80 % chance of getting anxiety .

2. **Neurotransmitters** - The three major neurotransmitters associated with anxiety: increased level of serotonin , increased norepinephrine functions and low levels of GABA.

3. Autonomic nervous system – Stimulation of the autonomic nervous system cause the symptoms that are found in anxiety disorders e.g tachycardia, tachypnoea, diarrhoea etc.

Biological theory

4. **Brain imaging studies-** Structural studies show cerebral asymmetries associated with symptoms of anxiety disorders.

   - EEG of patients with anxiety disorders reported abnormalities in various parts of the brain e.g frontal cortex occipital and temporal lobes etc.

5. **Chemically induced**- Infusions of chemicals such as caffeine ,sodium lactate ,ingestion of yohimbine , inhalation of 5% CO can cause anxiety in predisposed individuals .

6. **Organic anxiety disorders -** Anxiety which is secondary to various medical conditions e.g hyperthyroidism, pheochromocytoma.

SIGNS AND SYMPTOMS OF ANXIETY

1. **PSYCHOLOGICAL SYMPTOMS**

Cognitive Symptoms - Poor concentration ,distractibility ,negative autonomic thoughts.

2. PERCEPTUAL SYMPTOMS

Derealisation ,depersonalisation

3. AFFECTIVE SYMPTOMS

Diffuse unpleasant and vague sense of apprehension ,fearfulness ,irritability, inability to relax, increased sensitivity to noise ,exaggerated startle responses.

4.PHYSICAL SYMPTOMS

1. Motor symptoms - Tremors, restlessness, muscle twitches fearful facial expressions
2. Autonomic Symptoms - Palpitations ,tachycardia, sweating dyspnoea, hyperventilation, diarrhea

Benzodiazepines

Pharmacology

- Benzodiazepines have several actions:
  - anxiolytic
  - sedative and hypnotic
  - muscle relaxant
  - anticonvulsant

Benzodiazepines

- Their pharmacological actions are mediated through specific receptor sites located in a supramolecular complex with gamma-aminobutyric acid ($GABA_A$) receptors.
- Benzodiazepines enhance GABA neurotransmission, thereby indirectly altering the activity of other neurotransmitter systems, such as those involving noradrenaline and 5-HT.

Benzodiazepines

- **Differ** both **in the potency** with which they **interact** with **benzodiazepine receptors** and in their **plasma half- life**.
- In general, **high- potency benzodiazepines** and those with short half- lives are more likely to be associated with dependence and withdrawal.
- Benzodiazepines with short half- lives (less than 12 hours) include **lorazepam, temazepam, and lormetazepam.**

Benzodiazepines

- Because of problems with dependence, **long-acting benzodiazepines** are preferable for the management of anxiety, even if such treatment is to be given intermittently on an 'as- required' basis.
- Long- acting benzodiazepines include drugs such as **diazepam, Chlodiazepoxide, alprazolam, and clonazepam**.

Half- lives of some drugs that act at the GABA–benzodiazepine- receptor complex

Diazepam	20–100 h*
Chlordiazepoxide	5–30 h*
Lorazepam	8–24 h
Temazepam	5–11 h
Zopiclone	4–6 h
Zolpidem	1.5–2 h
Chlormethiazole	4–6 h
	(4–12 h in the elderly)
Chloral	6–8 h

* Active metabolite increases half-life further.

Benzodiazepines

Pharmacokinetics

- Benzodiazepines are **rapidly absorbed**.
- They are strongly bound to plasma proteins but, because they are lipophilic, pass readily into the brain.
- They are metabolized to a large number of compounds, many of which have therapeutic effects of their own; **temazepam and oxazepam are among the metabolic products of diazepam**.

Benzodiazepines

- **Excretion** is mainly as conjugates in the urine.
- Benzodiazepines with short half- lives, such as temazepam and lorazepam, have a 3- hydroxyl grouping, which allows a one- step metabolism to inactive glucuronides.
- Other benzodiazepines, such as diazepam and clorazepate, are metabolized to long- acting derivatives, such as desmethyldiazepam, which are themselves therapeutically active.

Benzodiazepines

- Benzodiazepines are well tolerated.
- Main side effects are due to the sedative properties of large doses, which can lead to ataxia and drowsiness and falls (especially in the elderly), and occasionally to confused thinking and amnesia.
- Minor degrees of impaired coordination and judgement.

Benzodiazepines

- **Toxic effects**
- Benzodiazepines have few toxic effects.
- Patients usually recover from large overdoses because these drugs do not depress respiration and blood pressure as barbiturates.
- Fatal overdoses of benzodiazepines have occasionally been reported

Benzodiazepines

- **Drug interactions**
- Potentiate the effects of alcohol and of drugs that depress the central nervous system.
- Significant respiratory depression has been reported in some patients receiving combined treatment with benzodiazepines and clozapine.

Benzodiazepines

- Dependence and tolerance develops after prolonged use.
- The withdrawal syndrome associated with benzodiazepines is characterized by several different kinds of symptoms:
  - Apprehension
  - Anxiety and Insomnia
  - Tremor
  - Nausea
  - Heightened sensitivity to perceptual stimuli and perceptual disturbances
  - Depression and suicidal thinking
  - Epileptic seizures (rarely).

Benzodiazepines

- Withdrawal symptoms generally begin within;
  - 2 to 3 days of stopping a short- acting benzodiazepine.
  - 7 days of stopping a long- acting one.
- The symptoms generally last for 3– 10 days.
- Withdrawal symptoms seem to be more frequent after taking drugs with a short half- life than after taking those with a long one.
- Best to withdraw them gradually over a period of several weeks, if taken over a long duration.

Benzodiazepines

- Benzodiazepine should be administered on a short- term basis only (not more than 4 weeks) to help a patient to cope with functionally disabling anxiety while other treatment measures are instituted.

Buspirone

Indications

- Effective in the treatment of generalized anxiety disorder.

Pharmacology

- No affinity for benzodiazepine receptors
- Stimulates a subtype of 5- HT receptor called the 5- HT1A receptor. This receptor is found in high concentration in the raphe nuclei in the brainstem, where it regulates the firing of 5- HT cell bodies.
- Buspirone lowers the firing rate of 5- HT neurons and thereby decreases 5- HT neurotransmission in certain brain regions. This action may be the basis of its anxiolytic effect.

Buspirone

Pharmacokinetics and adverse effect

- Buspirone has poor systemic availability because it has an extensive first- pass metabolism.
- Buspirone is often associated with lightheadedness, nervousness, and headache early in treatment.
- There is little evidence that tolerance and dependence occur during buspirone use.

Buspirone

Drug interactions

- It is relatively free from significant drug interactions, but combination with MAOIs has been reported to cause raised blood pressure.

Antidepressant drugs used for anxiety

- **Tricyclic antidepressants** effective, whether or not significant depressive symptoms are present in the management of;
  - generalized anxiety disorder
  - panic disorder
  - post- traumatic stress disorder
- **Selective Serotonin Reuptake Inhibitors (SSRIs)** are effective in a broad range of anxiety disorders, including obsessive– compulsive disorder (Baldwin et al., 2014).

Antidepressant drugs used for anxiety

- **Selective serotonin and noradrenaline reuptake inhibitors (SNRIs),** are licensed for the treatment of generalized anxiety disorder as well as depression E.g. Venlafaxine and Duloxetine.
- The time of onset of effect is much slower with antidepressants and, particularly in panic disorder.

Antidepressant drugs used for anxiety

- There may be an exacerbation of symptoms early in treatment.
- The ultimate therapeutic effect of antidepressants is as least as great as that of benzodiazepines, and they are less likely to produce cognitive impairment (Baldwin et al., 2014).
- The use of antidepressants is not associated with tolerance and dependence although, as noted above, sudden cessation of treatment can cause abstinence symptoms.

Antipsychotic drugs used for anxiety

- Conventional and atypical antipsychotic drugs have sometimes been prescribed in low doses for their anxiolytic effects, particularly in patients with;
  - persistent anxiety who have become dependent on other drugs.
  - Patients with aggressive personalities who respond badly to the disinhibiting effects of benzodiazepines.

Beta- adrenoceptor antagonists

- These drugs relieve some of the autonomic symptoms of anxiety, such as tachycardia, almost certainly by a peripheral effect.
- They are best reserved for anxious patients whose main symptom is palpitation or tremor, particularly in social situations.
- An appropriate drug is propranolol in a dose of 20– 40 mg three times a day.

Beta- adrenoceptor antagonists

- Contraindications are heart block, systolic blood pressure below 90 mmHg, or a pulse rate of less than 60 beats/ minute, and a history of bronchospasm.
- Beta- adrenoceptor antagonists precipitate heart failure in a few patients, and should not be given to those with atrioventricular node block.
- They can exacerbate Raynaud's phenomenon and hypoglycemia in diabetics.

Pregabalin

- Pregabalin is a derivative of the anticonvulsant drug, gabapentin.
- Like gabapentin, pregabalin has anticonvulsant and analgesic properties.
- It is licensed for the treatment of generalized anxiety disorder but not other anxiety disorders.

Pregabalin

- Both gabapentin and pregabalin are analogues of GABA; however, neither compound is active at GABA or benzodiazepine receptors.
- Therapeutic effects are mediated through interaction with the α2- δ subunit of voltage-gated calcium channels with a consequent modification of neurotransmitter release.
- Doses of 150– 600 mg, are effective in the treatment of generalized anxiety disorder.

Pregabalin

Pharmacokinetics and adverse effect

- Rapidly absorbed, with peak plasma concentrations occurring within about 1 hour.
- Its half- life is about 6 hours .
- It is eliminated unchanged primarily through renal excretion.
- Dose adjustment is therefore required in patients with impaired renal function.

Pregabalin

- Because of its pattern of elimination, it does not cause pharmacokinetic interactions with other drugs, but the effects of central sedatives (e.g. benzodiazepines and alcohol) may be potentiated.
- The most common adverse effects are somnolence and dizziness.
- Other common unwanted effects include increased appetite, mood changes, confusion, ataxia, tremor, and memory impairment.

Pregabalin

- The most potentially serious reactions are visual disturbances, including vision loss, blurred vision, and other changes of visual acuity. These symptoms mostly improve when pregabalin is discontinued.
- Associated with discontinuation symptoms, such as insomnia, headache, nausea, diarrhoea, anxiety, sweating, and dizziness.

Hypnotics

- Hypnotics are drugs that are used to improve sleep.
- Many anxiolytic drugs also act as hypnotics.
- Most prescribed hypnotics enhance the action of GABA through interaction with either the benzodiazepine receptor or other adjacent sites located on the GABA macromolecular complex.

Hypnotics

- The most commonly used hypnotics are benzodiazepines or non- benzodiazepine ligands.
- The latter include **zopiclone** and **zolpidem** (**'the Z drugs').**
- The actions of these drugs can be reversed by the benzodiazepine- receptor antagonist, flumazenil.
- Other available hypnotic agents include chloral hydrate (or its derivatives), chlormethiazole, and sedating antihistamines

Hypnotics

Unwanted effects

- Residual effects; Feelings of being slow and drowsy.
- Tolerance
- 'Rebound' insomnia on withdrawal, which makes preparations difficult to stop.
- Tolerance is less of a problem with sedating antidepressants, but such drugs have long half-lives accompanied by residual psychomotor effects the next day.

Advice on management of anxiety disorders

- Before an anxiolytic drug is prescribed, the cause of the anxiety should always be sought.
- It is helpful to classify the nature of the anxiety disorder, as this can have implications for drug treatment.
- Although medication is helpful, psychological treatments are as effective and are often preferred by patients.
- Medication tends to be used when psychological treatments are not readily available or have not been successful..

Advice on management of anxiety disorders

- If an anxiolytic is needed, a benzodiazepine should be given for a short time— not more than 3 weeks— and withdrawn gradually.
- It is important to remember that dependency is particularly likely to develop among people with alcohol- related problems.
- If the drug has been taken for several weeks, the patient should be warned that they may feel tense for a few days when it is stopped

Advice on management of anxiety disorders

- For longer- term treatment of severe generalized anxiety disorder, antidepressant medication is more appropriate.
- Antidepressants are often helpful in the treatment of panic disorder, although the risk of early symptomatic worsening must be remembered and explained to the patient.
- The use of small doses early in treatment (e.g. 10 mg imipramine, 5 mg citalopram) can be helpful.

Reference

- Shorter Oxford textbook of Psychiatry-Oxford University Press(2017).