The Islamic University
College of Pharmacy
Pharmacology & Toxicology Dep.

Applied Therapeutics–II

Generalized Anxiety Disorder

Level: 5th
Semester: 2nd

Lecture-4

الموضوعات المقررة
Clinical presentation and diagnosis
Treatment
Evaluation of therapeutic outcomes

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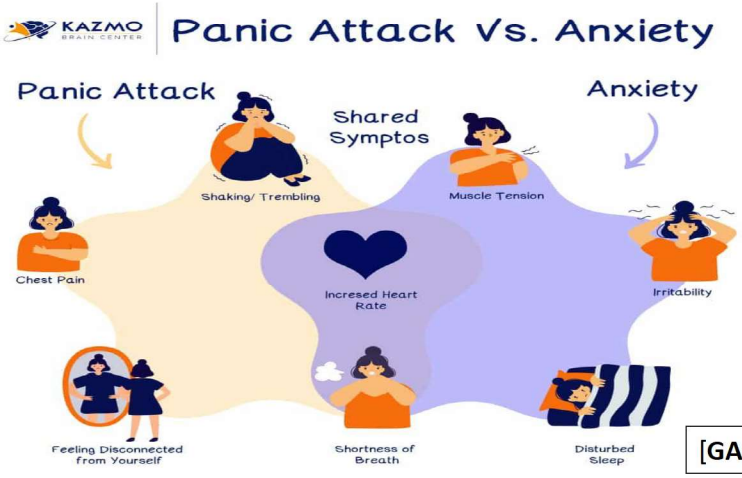
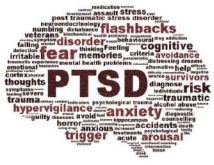
Anxiety Disorders

- ***Anxiety disorders*** (eg, **generalized anxiety** disorder [**GAD**] and **panic** disorder [**PD**]) have **prominent features of anxiety** and that are irrational or that **impair functioning**.

In **post-traumatic stress disorder** (**PTSD**), there is *previous exposure to trauma* and intrusive, avoidant, and hyperarousal symptoms.
مابعد الصدمة : أعراض تطفلية-وتجنبية (فى نفس الوقت)-(بمعنى التردد نتيجة صديمة سابقة) + ومفرطة الإثارة.





[**GAD**] and [**PD**]) have **prominent features of anxiety**

PATHOPHYSIOLOGY

- **Noradrenergic model**. The autonomic nervous system (**ANS**) of anxious patients is hypersensitive and overreacts to various stimuli.
- The **locus ceruleus** (**LC**) may have a role in ***regulating anxiety***, because it activates **norepinephrine release** and **stimulates the sympathetic** and **parasympathetic** nervous systems. (ANS)
- Drugs with anxiolytic or antipanic effects (eg, **benzodiazepines & antidepressants**) inhibit **LC firing**, decrease noradrenergic activity, and block the effects of anxiogenic drugs. لو السبب
- ***Y-Aminobutyric acid (GABA) receptor model***. **GABA** is the major inhibitory neurotransmitter in the central nervous system (CNS). **Benzodiazepines** enhance the inhibitory effects of GABA, which regulates or inhibits serotonin (5-hydroxytryptamine; 5-HT), norepinephrine, and dopamine activity.
- The number of GABAA receptors can change with alterations in the environment, and GABA receptor subunit expression can be altered by hormonal changes.
- **Abnormal functioning** of several neurotransmitter systems, including norepinephrine, GABA, glutamate, dopamine, and **5-HT**, may **affect manifestations** of anxiety disorders.

- ***5-HT model*: Abnormalities in serotonergic functioning** may play a role.

Preclinical models suggest that **greater 5-HT function** facilitates avoidance behavior; but primate studies show that **reducing 5-HT** increases aggression.

زيادة وظيفة سيريتونين ← سلوك التجنب ؛ لكن التقليل ← يزيد من العدوانية او العنفوانية.

- **GAD** symptoms may reflect **excessive 5-HT transmission** or **over-activity of the stimulatory 5-HT** pathways.

أعراض GAD تعكس وجود (تدل على) فرط فى الانتقال العصبى من خلال 5- HTأو نشاطا مفرطا لمسارات 5- HTالتحفيزية.

- The selective serotonin reuptake **inhibitors (SSRIs) increase 5-HT levels at the synapse** and are effective in **blocking manifestations** of **panic** and **anxiety**.

SSRIs يقلل من بعض الاعراض الناتجة عن قلة السريتونين - مثل العنفوانية والاكتئاب

choice for long-term management of chronic anxiety, especially in the presence of depressive symptoms

• CLINICAL PRESENTATION & DIAGNOSIS: من أول هنا منهج العام الحالى

(1) Psychological and cognitive symptoms of GAD include excessive anxiety, worries that are difficult to control, feeling keyed up or on edge, and trouble concentrating or mind going blank.

(2) Physical symptoms of GAD include restlessness, fatigue, muscle tension, sleep disturbance, and irritability=Agitation.

- **Women are twice as likely as men to have GAD**. The illness has a **gradual onset** at an average age of **21 years**. The course is chronic, with multiple exacerbations and remissions.

The **diagnosis** of GAD requires excessive anxiety and worry most days **for at least 6 months** with **at least three physical symptoms** present. Significant distress or impairment in functioning is present, and the **disturbance is not caused by a substance or another medical** condition.

الاعراض النفسية والمعرفية للقلق العام:
القلق المفرط ، والمخاوف التي يصعب السيطرة عليها ، والشعور بالضغط أو على حافة الهاوية ، وصعوبة التركيز أو احساس أن العقل أصبح فارغا.
الأعراض الجسدية للتوتر والقلق العام: الأرق والتعب وتوتر العضلات واضطراب النوم والهياج (التهيج والانفعالات).

النساء أكثر عرضة مرتين من الرجال للإصابة ب GAD. المرض له بداية تدريجية في متوسط عمر 21 سنة. دورات متعددة ومزمنة، (تفاقم الاعراض تارة والهدوء تارة اخري).

يتطلب تشخيص GADالقلق المفرط والقلق في معظم الأيام **لمدة 6 على الأقل أشهر** مع **وجود ثلاثة أعراض جسدية على الأقل.+ ضعف كبير في الأداء**، علي ان يكون هذه الاضطراب ليس ناتجا عن مادة أو مشكلة صحية أخرى.

TREATMENT

- **Goals of Treatment**: The goals are to **reduce** severity, duration, and frequency of symptoms and **improve** functioning.

• NON-PHARMACOLOGIC THERAPY

1. **Psychotherapy**, stress management, meditation, and exercise.
2. **Ideally**, patients with GAD should have **psychological therapy**, alone or in combination with antianxiety drugs.
3. **Cognitive behavioral therapy (CBT)**, though not widely available, is the **most effective** psychological therapy.
4. Patients should **avoid** caffeine, nicotine, stimulants, excessive alcohol, and diet pills.

Psychotherapy → alone or/combin. w' drugs
Cognitive behavioral therapy (CBT) →most effective
وينصح بعدم تناول المنبهات العصبية والكحول وادوية التخسيس التى قد تسبب قلق او أرق

PHARMACOLOGIC THERAPY

Drug **choices** for GAD and PD

Drug Choices for Anxiety Disorders			
Anxiety Disorder	First-Line Drugs	Second-Line Drugs	Alternatives
Generalized anxiety disorder (GAD)	Duloxetine Escitalopram Paroxetine Sertraline Venlafaxine XR SSRIs	Benzodiazepines Buspirone Imipramine Pregabalin Alprazolam	Hydroxyzine Quetiapine
Panic disorder (PD)	Venlafaxine XR	Citalopram Clomipramine Clonazepam Imipramine	Phenelzine

SSRI, selective serotonin reuptake inhibitor; XR. extended-release.

Antidepressants: مضادات الإكتئاب

- Antidepressants are **effective** for **acute and long-term** management of GAD.
- They are the treatment of **choice** for **long-term** management of ***chronic*** anxiety, *especially in the presence* of **depressive symptoms**.
  - ❑ **Venlafaxine** extended-release, **Duloxetine**, **Paroxetine**, and **Escitalopram** are **FDA-approved for GAD**.
  - ❑ **Imipramine** is considered a **second-line agent**.
- Anti-anxiety response requires 2-4 weeks or longer.
- Selective serotonin reuptake inhibitors (**SSRIs**), extended-release **Venlafaxine**, and **Duloxetine** are effective in **acute** therapy (**response rates of 60%-68%**).
- In a **meta-analysis**, **Fluoxetine** was **most** likely to **achieve remission** of **GAD** symptoms; **Sertraline** was **best tolerated**.

Antidepressants, Continue .....

Common side effects and monitoring parameters for patients taking medications used for anxiety disorders are shown in ***Table 66-5.***

- Some patients require **small initial doses** of **antidepressants** for the first week to limit the development of **transient** increased anxiety, also known as **jitteriness syndrome**.

- All antidepressants carry a **black box warning** regarding **suicidality** (suicidal thinking and behaviors) in children, adolescents, and young adults < 25 years and recommends specific **monitoring** parameters.
- **Clinical practice guidelines** recommend use of **Fluoxetine**, **Sertraline**, or **citalopram** for **pregnant women**; however, jitteriness, myoclonus, and irritability **in the neonate** and **premature infant** have been reported and **Paroxetine** should be avoided due to *cardiovascular* malformation risk. اثناء الحمل

Antidepressant-induced jitteriness/Transient anxiety syndrome, cluster of symptoms appearing immediately after an initiation of antidepressant treatment or after an increase of antidepressant dosage.

Benzodiazepines

- Benzodiazepines are the **most effective** and **frequently prescribed** drugs for the treatment of **acute** anxiety.
- About **65%-75% of patients with GAD** have a moderate response, and **most** of the **improvement** occurs in the **first 2 weeks** of therapy.
- They are **more effective** for **somatic and autonomic symptoms** of GAD (panic, chest pain, insomnia, tachycardia, muscle tension), whereas **antidepressants** are more effective for the **psychic symptoms** (eg, apprehension and worry الخوف والقلق).

Benzodiazepines أشهر الادوية التى توصف وأكثرها فاعلية لعلاج **acute** anxiety.

Benzodiazepines → **most** effective in **acute** anxiety **65%-75% of patients with GAD**
Antidepressants (**SSRIs**), **Venlafaxine**, and **Duloxetine**) are effective in **acute** therapy (**60%-68%**).

Benzodiazepines **more effective** for **somatic and autonomic symptoms** of GAD
الذعر ، ألم في الصدر ، الأرق ، عدم انتظام دقات القلب ، توتر/اجهاد العضلات
Antidepressants are more effective for the **psychic symptoms** (eg, apprehension and worry)
الخوف والقلق

- **Older patients** are more **sensitive** to benzodiazepines and may experience *falls when taking them*. السقوط أثناء السير
- The most common **side effect** of benzodiazepines is **CNS depression**. **Tolerance** usually develops to this effect. Other side effects are disorientation, confusion, aggression, excitement, and anterograde amnesia.
- Benzodiazepines **should** be used with a **regular dosing regimen** and **not** on an **as-needed** basis **when** used for the **treatment** of an **anxiety disorder**.
- **Long half-life** benzodiazepines may be dosed **once** daily at bedtime, providing nighttime hypnotic and next day anxiolytic effects. منومة ليلا مزيل القلق في اليوم التالي

- **Diazepam** and **Clorazepate** have **high lipophilicity** and are *rapidly absorbed and distributed into the CNS*. They have **rapid antianxiety effects**, but a *shorter duration* of effect *after a single dose*, as they are rapidly distributed to the periphery.

- **Lorazepam and oxazepam** are **less lipophilic, have a slower onset, but a longer duration of action. They are not** recommended for **immediate** relief of anxiety**.**

- **Avoid intramuscular (IM) diazepam** and **chlordiazepoxide** because of *variability in rate and extent of absorption*. **IM lorazepam** provides **rapid and complete** absorption.

❑ **Several** benzodiazepines are converted to **desmethyldiazepam**, which has a **long** half-life & can **accumulate**.

❑ **Intermediate- or short-acting** benzodiazepines are **preferred for chronic use** in **older** patients & those with **liver disorders because of** minimal accumulation and achievement of steady state within 1–3 days.

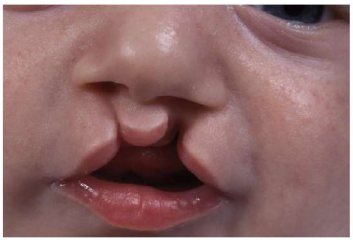
• Interactions:

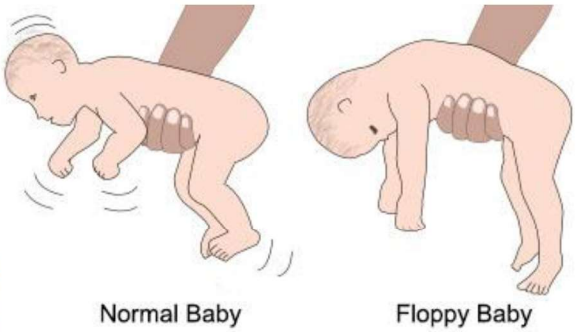
1. Combining **benzodiazepines** with alcohol or other CNS depressants may be **fatal**.
2. Addition of **nefazodone, ritonavir, or ketoconazole** (CYP3A4 **inhibitors**) can **increase the blood** levels of **alprazolam** and **diazepam**.
3. Drugs that **induce** cytochrome CYP3A4 (eg, **carbamazepine, St. John's wort**) can **reduce benzodiazepine** levels.
4. Drugs that inhibit or induce CYP2C19 (eg, fluoxetine, fluvoxamine, omeprazole) or N-acetyltransferase 2 activity can **alter** diazepam and clonazepam metabolism, respectively.

• Pregnancy

- **Benzodiazepine** use in **pregnant women** has been associated with **teratogenic effects** (ie, **cleft** lip and palate + **floppy baby syndrome** + neonatal **withdrawal**. شق بالشفة والحلق +متلازمة الطفل المرن + أعراض انسحابية لحديثي الولادة
- **Antidepressants are preferred**.

➢ If a **benzodiazepine must be used**, **diazepam** and **chlordiazepoxide** may be **preferred but** may cause sedation, lethargy, and weight loss *in breastfed infants*.





Benzodiazepine in **pregnant women** → **teratogenic effects**

diazepam and **chlordiazepoxide** may be **preferred**

- ***Benzodiazepine Discontinuation***

➢ After benzodiazepines are **abruptly discontinued**, **three events** can occur: توقف فجأة

(1) **rebound** symptoms :return of original symptoms with an increased;
(2) **recurrence** or **relapse**: is the return of original symptoms at the same intensity; or
(3) **withdrawal** is the emergence of new symptoms and a worsening of preexisting symptoms.

- **The onset of withdrawal symptoms is within 1-2 days (24-48 hours) after discontinuation of short elimination half-life benzodiazepines and 3-8 days after discontinuation of long-elimination half-life drugs.**

- **Discontinuation strategies include:** الاستراتيجيات الصحيحة لوقف تناول الدواء BDZ

❑ A **25%** per week **reduction** in dosage until 50% of the dose is reached, and then **reduce** by **1/8** every 4-7 days.
❑ If therapy **duration exceeds 8 weeks**, a taper over 2-3 weeks is recommended, but if **duration of treatment is 6 months**, a taper over 4-8 weeks is reasonable. **Longer durations of treatment** may require a 2- to 4-month taper.
❑ Adjunctive use of **pregabalin** can help to **reduce withdrawal symptoms during the benzodiazepine taper**.

- ***Abuse, Dependence, Withdrawal, and Tolerance***

○ Benzodiazepine **dependence** is defined by appearance of a withdrawal syndrome (ie, anxiety, insomnia, agitation, muscle tension, irritability, nausea, diaphoresis, nightmares, depression, hyperreflexia, tinnitus, delusions, hallucinations, and seizures) **upon abrupt discontinuation**.
○ **Those** with a history of **drug abuse** should **not** receive **benzodiazepines**. Those with **GAD** and PD **are at high risk for dependence** because of the **chronicity** of the illnesses.

Buspirone:

- **Buspirone** is a **5-HT1A partial agonist**, that **lacks** anticonvulsant, muscle relaxant, sedative hypnotic, motor impairment, and dependence-producing properties.
- **It is a second-line agent for GAD** because of
  1. *inconsistent reports of long-term efficacy*, and
  2. *delayed onset* of effect.

❖ **It is an option for patients who fail other anxiolytic therapies or patients with a history of alcohol or substance abuse.**

- The **onset** of anxiolytic effects requires **2 weeks or more**; maximum benefit may require **4-6 weeks.**
- It may be **less effective** in patients who have previously taken ***benzodiazepines***.

Interactions

- Buspirone may **elevate blood pressure** in patients taking a **monoamine oxidase inhibitor** (MAOI).
- **Verapamil, itraconazole, and fluvoxamine** can **increase buspirone levels** through CYP3A4 inhibition, and **rifampin reduces buspirone** blood levels 10-fold.

Rifampin → inducer CYP

• Alternative Pharmacotherapy:

- **Hydroxyzine**, is considered **a second-line** agent.
- **Pregabalin** produced **anxiolytic** effects ***similar*** *to* **lorazepam, alprazolam, and venlafaxine** in acute trials. Sedation and dizziness were the **most common adverse effects**.
- **Quetiapine** extended release, **150** mg/day, was *superior to placebo* and ***as effective as*** **paroxetine 20** mg/day and **escitalopram 10** mg/day, **but** with **earlier onset of action**.

➢ Quetiapine is not FDA-approved for GAD and the long-term risks are unknown.

Hydroxyzine is **an antihistamine**

Pregabalin, is **an anticonvulsant, analgesic and anxiolytic medication**

Quetiapine is **an atypical antipsychotic used to treat schizophrenia, bipolar disorder and depression.**

• EVALUATION OF THERAPEUTIC OUTCOMES

❖ Initially, **monitor anxious patients every 2 weeks** for reduction in anxiety symptoms, improvement in functioning, and side effects.

❖ **Treatment resistance** "may be diagnosed after poor, partial, or lack of response is seen" **with** at least **two antidepressants** from **different classes**.

• **For those who do not achieve an appropriate response with a first-line agent:**

1. the dose may be increased,
2. changed to a different agent in the same class or different class, or
3. augmented.

• **If treatment fails, the clinician should assess for:**

(a) symptoms (eg, *psychotic* symptoms) that need **additional medications** or
(b) treatment **non adherence**.

➢ Patients should also be assessed for **concurrent substance** use disorder, concurrent **illnesses**, and **suicidal thoughts**.

All benzodiazepines possess **anxiolytic properties**, although **only 7 marketed agents** have **FDA approval** for the treatment of **GAD**, as the other agents have different FDA approved indications

7 BDZ → TTT of GAD

- **Alprazolam**
- **Chlordiazepoxide**
- **Clonazepam**
- **Clorazepate**
- **Diazepam**
- **Lorazepam**
- **Oxazepam**

TABLE 66-6 Benzodiazepine Antianxiety Agents

Drug	Brand Name	Approved Dosage Range (mg/day)	Maximum Dosage for Older Patients (mg/day)	Approximate Equivalent Dose (mg)	Comments
Alprazolam[a]	Niravam[b], Xanax	0.75–4	2	0.5	Associated with interdose rebound anxiety
	Xanax XR	1–10[c]			
Chlordiazepoxide[a]	Librium	25–400	40	10	
Clonazepam[a]	Klonopin	1–4[c]	3	0.25–0.5	
	Klonopin Wafer[b]				
Clorazepate[a]	Tranxene	7.5–60	30	7.5	
Diazepam[a]	Valium	2–40	20	5	
Lorazepam[a]	Ativan	0.5–10	3	1	Preferred in elderly
Oxazepam[a]	Serax	30–120	60	30	Preferred in elderly

[a]Available generically.
[b]Orally disintegrating formulation.
[c]Panic disorder dose.
XR, extended-release.

Thank You !