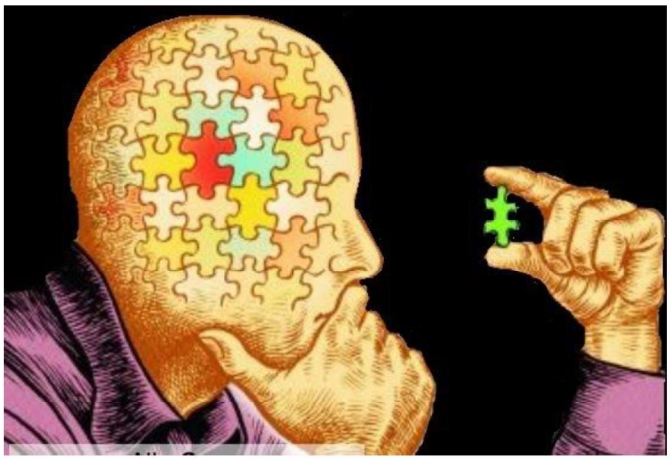
The Islamic University
College of Pharmacy
Pharmacology & Toxicology Dep.

Applied Therapeutics–II

Alzheimer Disease



Level: 5th
Semester: 2nd

Lecture-3

By
Dr. Mohamed Elnagar

Alzheimer Disease

Alzheimer disease (AD) is a progressive illness of **unknown** cause characterized by **loss of *cognitive and physical functioning***, commonly *with* ***behavior*** *symptoms*.

- **AD risk factors** include:

1- Age,
2- Head injury,
3- Down syndrome,
4- Depression,
5- Mild cognitive impairment
6- Risk factors for **vascular disease**, including hypertension, elevated homocysteine, elevated LDL-cholesterol, low HDL-cholesterol, obesity, metabolic syndrome, and diabetes.

PATHOPHYSIOLOGY

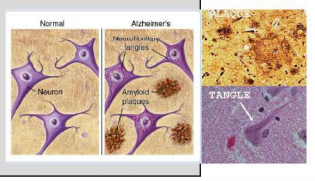
- ❑ **Dominantly Inherited form of AD** cases (***< 1% of cases***) are attributed to **chromosomal alterations** that affect processing of the **amyloid precursor** protein.
- ❑ Genetic susceptibility to **late-onset AD** is primarily linked to the **apolipoprotein E** ***(APOE)*** genotype,
- ❑ But an interaction of multiple genes with the environment may be at play.
  - **Amyloid precursor protein**: a protein that is important to regulate several cellular functions especially in the nervous system
  - Apolipoprotein E ***(APOE)*** genotype: a protien that represent a future risk for Alzheimer's disease

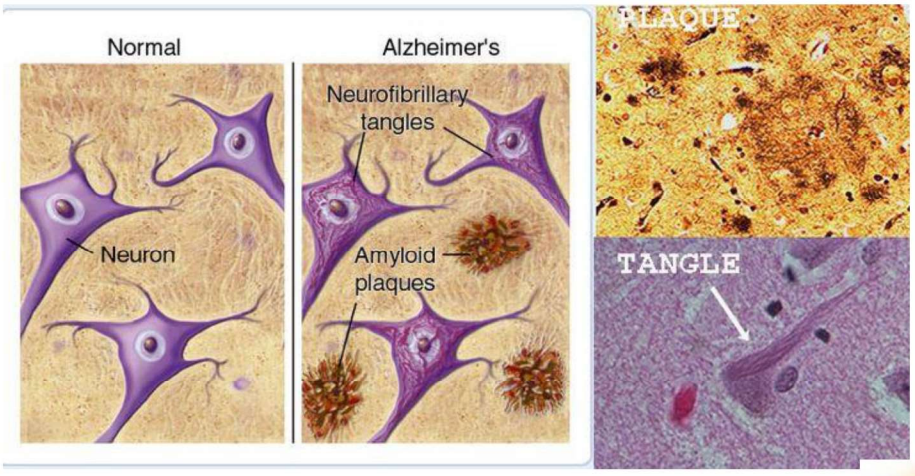
APP + APOE

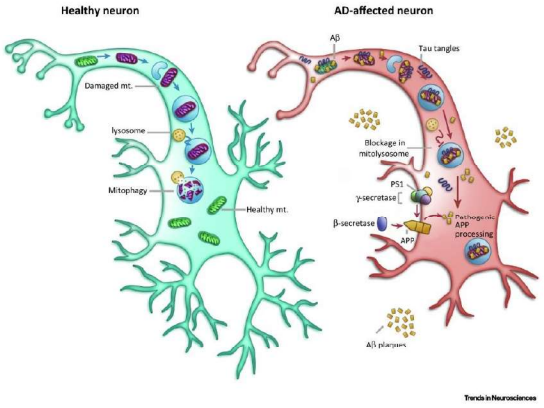
Signature findings include:

a) **intra**cellular **neurofibrillary tangles** (NFTs),
b) **extra**cellular **amyloid plaques** in the **cortex** and **medial temporal** lobe,
c) **degeneration** of neurons and synapses, and
d) **cortical atrophy**.

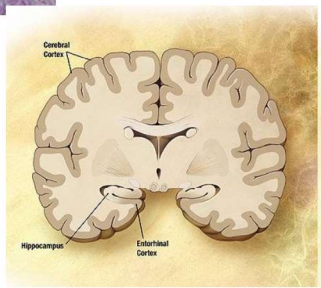
**** Density of NFTs correlates with severity of dementia.***

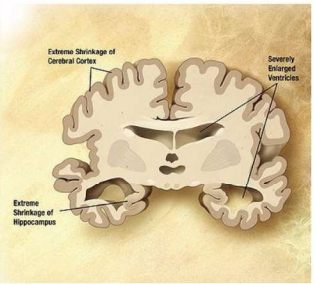






a) intracellular **neurofibrillary tangles** (NFTs),
b) extracellular **amyloid plaques**





c) degeneration of neurons and synapses, and
d) **cortical atrophy**.

* Proposed mechanisms hypothesis for Alzheimer's changes include:

(1) β-*amyloid protein aggregation*, leading to formation of **plaques**;
(2) *Hyperphosphorylation* of **tau protein**; leading to **NFTs**
(3) Synaptic *failure* and *depletion* of neurotransmitters;
(4) *Mitochondrial* dysfunction; and
(5) *Oxidative* stress.

A- The amyloid cascade hypothesis states that there is an **imbalance** ***between production & clearance of β-amyloid***, with aggregation and accumulation of β-amyloid leading to AD. Whether **this is the primary pathology in most forms of AD** remains to be shown.

B- Neurotransmitter deficits, **loss of cholinergic activity** is most prominent, and it correlates with AD severity. Cholinergic cell loss seems to be a **consequence of AD pathology**, not the cause of it.

C- Other neurotransmitter considerations include:

(1) ***serotonergic*** neurons are lost;
(2) monoamine oxidase type B activity is increased;
(3) glutamate pathways of the cortex and limbic structures are abnormal; and
(4) excitatory neurotransmitters, including **glutamate**, may be neurotoxic.

loss of cholinergic activity is most prominent and correlates with AD severity.

β-amyloid
Ach
Glutamate
MAO-B
serotonergic

CLINICAL PRESENTATION

- **Cognitive decline is gradual and includes**: التدهور المعرفي يحدث تدريجا
  - **Memory loss,**
  - **Aphasia** (inability to speak or communicate),
  - **Apraxia** (inability to perform movements on commands)
  - **Agnosia** (inability to identify objects, persons, sounds..)
  - **Disorientation**/confusion , **and**
  - **impaired executive function**

الاعراض المعرفية/ الادراكية

- فقدان الذاكرة ،
- - فقدان القدرة على الكلام (عدم القدرة على الكلام أو التواصل) ،
- - تعذر الأداء (عدم القدرة على أداء الحركات بناء على الأوامر)
- - غشاوة (عدم القدرة على تحديد الأشياء والأشخاص والأصوات ..)
- توهان
- ضعف الوظيفة التنفيذية

- **Other non-cognitive symptoms include:** depression, psychotic symptoms, aggression, motor hyperactivity, uncooperativeness, wandering, and combativeness. Patients become increasingly unable to care for themselves.

الاكتئاب ، والأعراض النفسية، عنفوانية/عدوانية، وفرط النشاط الحركي ، وعدم التعاون، والتجول ، الميل الى الشجار. يصبح المرضى غير قادرين بشكل متزايد على رعاية أنفسهم.

الاعراض الغير ادراكية

Stages of Alzheimer Disease

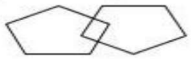
Mild (MMSE score **26-21**)	Patient has **difficulty remembering recent events**. Ability to manage finances, prepare food, and carry out other household activities declines. May get lost while driving. Begins to withdraw from difficult tasks and to give up hobbies. May deny memory problems.
Moderate (MMSE score **20-10**)	Patient **requires** **assistance with activities of daily living**. Frequently **disoriented** with regard to time (date, year, and season). **Recall of recent** events is severely impaired. May forget some details of past life events and names of family and friends. Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tearful. Loses ability to drive safely. **Agitation, paranoia, and delusions are** common.
Severe (MMSE score **9-0**)	Patient loses ability to speak, walk, and feed self. Incontinent of urine and feces. **Requires** **care 24/7** **i.e** →24 hours a day, 7 days a week.

MMSE, Mini-Mental State Examination.

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: ***Ask the questions in the order listed. Score one point for each correct response within each question or activity.***

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

DIAGNOSIS:

- The **National Institute on Aging and the Alzheimer's Association** view **AD as a spectrum** *beginning with* an asymptomatic preclinical phase *progressing to* the symptomatic preclinical phase *and then to* the dementia phase.
  - AD is a **clinical diagnosis**, based largely on identified **symptoms** and **difficulty with activities** of daily living revealed by patient and **caregiver interviews**.مقابلات مقدمي الرعاية
- Patients with **suspected AD** should have a **history** and **physical examination** with appropriate **laboratory tests (serum B12, Folate, Thyroid panel, blood cell counts, serum electrolytes, and liver function tests),** and **computed tomography (CT) or magnetic resonance imaging (MRI)** may aid diagnosis.
- **International guidelines** recommend **structural imaging** (ie, **non contrast enhanced CT** or **MRI**) be performed **when** evaluating people with **suspected dementia** ***to identify***
  1- *structural abnormalities consistent with AD*, *or*
  2- *other pathology, such as brain atrophy, vascular damage, or tumors.*
  - ✓ To exclude other diagnoses, **cerebrospinal fluid analysis** or an **electroencephalogram** can occasionally be justified.

DIAGNOSIS;Continue ……

Patients History:

1. Obtain information on **medication** use; alcohol or other substance use;
2. **Family** medical history;
3. History of **trauma**,
4. **Depression**, or
5. **Head injury**.
6. Rule out medication **use** (eg, **anticholinergics, sedatives, hypnotics, opioids, antipsychotics**, and **anticonvulsants**) as contributors to dementia symptoms.
7. **Rule out medications** that could contribute to **delirium** (eg, **digoxin**, nonsteroidal anti-inflammatory drugs [**NSAIDs**], histamine-2 receptor **[H2] antagonists, amiodarone, antihypertensives**, and **corticosteroids**).

- The Folstein Mini-Mental State Examination (**MMSE**) can help establish a history of deficits in two or more areas of cognition at baseline against which to **evaluate change in severity over time. The average expected decline in an untreated patient is 2–4 points per year** (**Table** السابق). Other scales for assessment are also available.
- **In the future**, **improved brain imaging** and validated **biomarkers** of disease will enable a more sophisticated diagnosis with identified **cognitive strengths and weaknesses** and **neuro-anatomic localization** of deficits.

TREATMENT

- **Goals of Treatment:** The goal of treatment in AD is to
  1. maintain cognitive functioning and **activities** of daily living as long as possible,
  2. with a secondary goal to treat the psychiatric and behavioral symptoms.

- **NON-PHARMACOLOGIC THERAPY**

1) The general **approach** to non-pharmacologic **strategies** for cognitive and noncognitive symptoms of AD is to Identify the **symptom** and **causative factors**, and adapt the **caregiving** environment to remedy the situation. تحديد الأعراض والعوامل المسببة ، وتكييف بيئة تقديم الرعاية لعلاج الوضع/الحالة.
2) On initial diagnosis, the **patient** and **caregiver** should be educated on the course of illness, and available treatments.
3) Sleep disturbances, wandering, urinary incontinence, agitation, and aggression should be managed with **behavioral and environmental interventions** whenever possible.
4) **Primary prevention of AD** may include **smoking cessation**, increasing **physical activity**, and reducing midlife **obesity, hypertension, and diabetes**. Also adherence to the Mediterranean Diet or **Dietary Approaches to Stop Hypertension (DASH)** Diet may reduce the risk of cognitive impairment or decline.

- **PHARMACOLOGIC THERAPY OF COGNITIVE SYMPTOMS;**

العلاج الدوائي ل الأعراض المعرفية/ الإدراكية

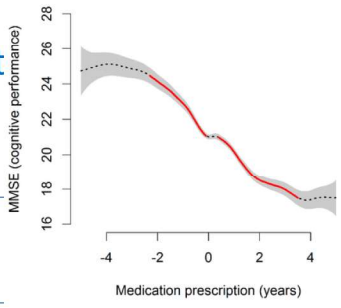
- **Cholinesterase inhibitors** and **NMDA-receptor antagonists** are indicated for treatment of AD.
  - **Current guidelines** do **not** have a **specific preference** for cholinesterase inhibitor initiation.
- Reasonable **expectations** of treatment may be a **slowed** decline in abilities and **delayed** long-term care placement.
- **Dosing** regimens should be **simplified** and **patient** and **caregiver** preferences considered in an effort **to improve medication adherence and persistence**. الالتزام والمثابرة.
- **Gaps in treatment** may be associated with a **loss of benefits** when medication is stopped but this is controversial.

1- Cholinesterase Inhibitors

- **No comparative trials** have assessed the effectiveness of one agent over another. **Donepezil**, **rivastigmine**, and **galantamine** are indicated in **mild-to-moderate** AD; **donepezil** is also indicated for **severe** AD.
- MMSE is practical to use in the clinical setting to measure changes in cognitive function. Successful treatment would show a decline in MMSE score of less than 2 points per year.
- The duration of benefit lasts **3-24 months**. Because of their short half-lives, if **rivastigmine** or **galantamine** treatment is interrupted for several days or longer, retitrate starting at the lowest dose. Gradual dose titration over several months improves tolerability. When switching from one agent to another, a washout period is recommended.

❑ **SE: *N.V.diarrhea,, Peptic ulcer disease***, GI bleeding, anorexia, weight

معظم الأعراض الجانبية هى على الجهاز الهضمى → **NAMZARIC®= Donepezil +*Memantine***



The average expected decline in an untreated patient is 2–4 points /year .
Successful **treatment** would **show a decline** in MMSE score of **less than 2 points /year**.

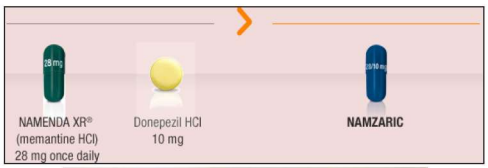
2- N-Methyl-D-Aspartate (NMDA) Receptor Antagonist

❑ **Memantine** (Namenda)® It is used as monotherapy and in combination with a cholinesterase inhibitor.

- ➢It is indicated for treatment of **moderate to severe AD**, but **not for mild AD**.
- ➢**Dosing** must be **adjusted in patients with renal impairment**. (It is not metabolized by the liver and is primarily excreted unchanged in the urine) → Kidney Ø **Dose adjustment !**
- ➢It is usually well tolerated; **side effects** include constipation, confusion, dizziness, and headache

❑ **Combination therapy** with **cholinesterase inhibitors + memantine**, individually or as **Namzaric®**, is generally prescribed for people with **moderate-to-severe AD** + **slow cognitive and functional decline** to a significant degree compared to cholinesterase inhibitor monotherapy or no treatment + **Memantine** may help **mitigate some of the GI adverse** effects seen with cholinesterase inhibitors (**Donepezil**)

NAMZARIC®= **Donepezil** +**Memantine**



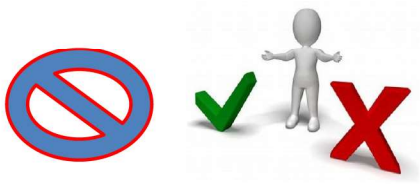
Donepezil المحدث بواسطة الآثار الضارة للجهاز الهضمي بعض **تخفيف** تساعد في **Memantine**

Other Drugs: احتياطات وممنوعات

1. Use of estrogen, **NSAIDS**, prednisone, statins, or **ginkgo biloba** is **not recommended** to prevent or treat dementia.
2. **Vitamin E** is under investigation for prevention of AD and is **not recommended** for treatment of AD. ما زال تحت الدراسات
3. **Do not** use **ginkgo biloba** in individuals taking **anticoagulants** or **antiplatelet** drugs, and use cautiously in those taking **NSAIDs**.

Ginkgo Biloba → increasing risk of bleeding of those drugs

4. There is currently insufficient evidence to recommend medical foods such as **Axona**, **Souvenaid**, and **Cerefolin NAC** for treatment of AD.



PHARMACOLOGIC THERAPY OF NON-COGNITIVE SYMPTOMS;

العلاج الدوائي ل الأعراض الغير معرفية/ غيرالإدراكية

No drug is FDA approved for the **treatment of AD behavioral and psychological symptoms** such as psychotic symptoms, inappropriate or disruptive behavior, and depression

- **General guidelines include**:
  (1) starting with **reduced doses** and **titrating slowly**; نبدأ بجرعة صغيرة ونزود ببطئ تدريجيا
  (2) **monitoring** closely; متابعة
  (3) periodically attempting/trying to taper and discontinue medication; and تناقص او وقف الدواء من حين الى اخر
  (4) careful documentation. توثيق

Some evidence supports that **cholinesterase inhibitors and memantine** may be **beneficial** in treating **non-cognitive symptoms**, but they **do not reduce acute agitation**. **Avoid anticholinergic psychotropic** medications as they may worsen cognition.

1. Antidepressants

- A selective serotonin reuptake inhibitor (**SSRI**) is usually given to **depressed patients with AD**, and the best evidence is for **sertraline and citalopram**.
  Tricyclic antidepressants (TCA) are usually avoided.

depression + AD → sertraline and citalopram - (not TCA)

2. Antipsychotics

Antipsychotic medications have traditionally been used for disruptive behaviors and neuropsychiatric symptoms, but the **risks and benefits** must be carefully **weighed**.

- Atypical antipsychotics (ie, **aripiprazole, risperidone, olanzapine**, and **quetiapine**) have been shown to be **more effective** compared to placebo; however, the **higher risk of adverse effects and mortality offset this benefit**. So, --→→
  - *Antipsychotics in AD* should be **restricted to patients with severe symptoms** that have not responded to other measures, and treatment should be tapered as early as possible and **rarely used beyond 12 weeks**. لايستخدم أكثر من 3 شهور
- **Common adverse events** include somnolence النعاس, extrapyramidal symptoms, abnormal gait, worsening cognition, cerebrovascular events, and increased risk of death.

3. Miscellaneous Therapies

- Evidence for **benzodiazepine** use is lacking and **not advised** due to significant adverse effects.
- Use of **antiepileptic medication** (ie, **carbamazepine** and **gabapentin**) may be **alternatives** for agitation الانفعالات, but evidence is conflicting. Use of **valproic acid** is no longer recommended due to severe adverse effects.

EVALUATION OF THERAPEUTIC OUTCOMES

- At baseline **interview** both **patient** and **caregiver** to identify target symptoms; define therapeutic goals; and document cognitive status, physical status, functional performance, mood, thought processes, and behavior.
- Use the MMSE for cognition, Bristol Activities of Daily Living Scale for activities of daily living, and Neuropsychiatric Inventory Questionnaire for assessment of behavioral disturbances to quantify changes in symptoms and functioning.
- Observe the patient carefully for potential side effects.
- Assess for drug effectiveness, side effects, adherence to regimen, and need for dosage adjustment or change in treatment at 2-4 weeks, and 8-12 weeks after initiation, followed by every 3-6 months thereafter. Several months to 1 year of treatment may be required to determine whether medications for cognition are beneficial.

Thank You !