

## New Strategies for Treatment of Alzheimer's Disease

Mennat- Allah Abdelsamed\*

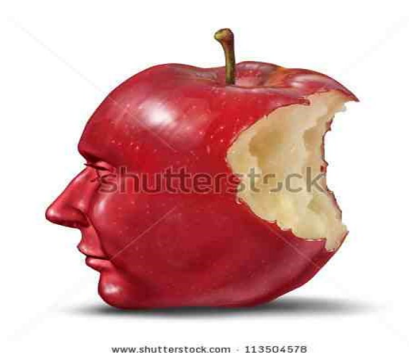
Faculty of Pharmacy , Minya University, Egypt

**Corresponding Author:** Mennat- Allah Abdelsamed, Faculty of Pharmacy, Minya University, Egypt

**Citation:** Mennat- Allah Abdelsamed (2017), New Strategies for Treatment of Alzheimer's Disease. Int J Pharm Sci & Scient Res. 3:2, 37-45. DOI:10.25141/2471-6782-2017-2.0036

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**Received:** March 26, 2017; **Accepted:** April 4, 2017; **Published:** May 16, 2017



### New Strategies for Treatment of Alzheimer's disease

#### Abstract

Alzheimer's disease is a degenerative disease and one of diseases that related to ageing and mostly happened with elderly people, and one of diseases that has no determinant treatment, but now a days many new strategies have been discovered in the treatment of Alzheimer include drugs reduced amyloid peptide (AB) production, drugs prevent AB aggregation, drugs reduce inflammation associated with Alzheimer, cholinesterase inhibitor and N-methyl-d-aspartate (NMDA) antagonist like memantine, Indoleamine 2,3-dioxygenase (IDO) inhibitor such as Coptisine which is a traditional Chinese medicinal prescription, and others some of it be approved in clinical trial and others still under investigation.

#### Introduction:

##### Definition :

Alzheimer's is a degenerative disease due to a marked atrophy of the cortical gyri, this tissue loss results from a combination of cell death and the loss of neuronal synapses and fibers, and a type of dementia that causes problems with Memory, Thinking, Behavior.



It is a progressive disease, It develops slowly and gets worse over time, becoming severe enough to interfere with daily tasks. And dementia means general term for memory loss.

### warning signs of AD's:

- 1- Memory loss that disrupts daily life
- 2- Challenges in planning or solving problems
- 3- Difficulty completing familiar tasks at home, at work or at leisure
- 4- Confusion with time or place
- 5- Trouble understanding visual images and spatial relationships
- 6- New problems with words in speaking or writing
- 7- Decreased or poor judgment
- 8- Withdrawal from work or social activities
- 9- Changes in mood and personality



### Typical ages of the majority of people who develop AD's :

Major of people are 65 and older , but people in their 40s or 50s can also develop early onset Alzheimer's Disease.

### diagnostic tests for AD's :

- 1- Medical exam
- 2- Cognitive tests



- Alzheimer has bad effects on patients on social , mental and physical sides , due to danger of Alzheimer's disease and there is no effective cure for it ,and most drug which available now is

symptomatic relief , all of this become good reason which make scientists start to discover new treatment to help patient of Alzheimer's disease .

- 3- Neurological exam
- 4- Brain imaging

### Diagnosis of Alzheimer's disease :

New blood test can detect alzheimer's with almost go percent accuracy



this test could be ready in 2 years , researchers in UK work on blood test can predict Alzheimer in people with mild memory problems

\* Identifies 10 proteins in the blood that are associated with tau and amyloid proteins both found in brain tissue with Alzheimer

" this test is a technical tour de force " , that is mean " For every 10 people who take the test , one will get an incorrect result "

- Another scientist and his colleagues analysed 26 proteins in blood from 1148 people including 476 people with Alzheimer , 220 with mild cognitive impairment and 452 elderly healthy controls , almost half of the particip in each gp also had an MRI brain scan

- There are other blood tests like test using the level of 10 lipids in the blood to identify people who will go on to get Alzheimer's two or 3 years later with an accuracy of 96 percent. (1)

### Treatment:

#### A - Cholinesterase inhibitors for Alzheimer's disease :

\* It is the first strategy used in treatment of Alzheimer and the introduction of first cholinesterase inhibitor (ChEI) was in 1997

\* These drugs inhibit the breakdown of acetylcholine , as we know that AD can happen due to low level of acetylcholine which is an important neurotransmitter associated with memory ,so we must stop cholinesterase activity that use to breakdown acetylcholine .The most that these drugs could achieve is to modify the manifestations of Alzheimer's disease and symptomatic relief but poorly affect the progression of the disease , and they are the first line pharmacotherapy of mild to moderate AD (2- 3 )

#### ex for drugs us this strategy in it's work

- 1- donepezil
- 2- galantamine
- 3- rivastigmine
- 4- Tacrine

### B) N-methyl-d-aspartate (NMDA) antagonist memantine:

The other drug approved for the treatment of Alzheimer is (memantine) , it is oral active antagonist at NMDA receptors (4) , with weaker blocking action on various other amine receptors (5)

Excitotoxicity : it is a concept mean excessive exposure to the neurotransmitter glutamate or overstimulation of its membrane receptors, leading to neuronal injury or death .

Excitotoxic neuronal cell death is mediated in part by overactivation of N-methyl-d-aspartate (NMDA)-type glutamate receptors, which results in excessive  $Ca^{2+}$  influx through the receptor's associated ion channel many previous NMDA receptor antagonists have disappointingly failed advanced clinical trials for a number of neurodegenerative disorders because they block virtually all NMDA receptor activity and NMDA receptor has physiological activity, however, is also essential for normal neuronal function , but memantine, more approved in clinical trials as it blocks excessive NMDA receptor activity without disrupting normal activity. Memantine does this through its action as an uncompetitive, low-affinity, open-channel blocker and it shows that it is well tolerated .<sup>(6)</sup>

### c- Nasal insulin-anew discovery:

-insulin is a hormone that helps regulate blood sugar levels and appears to play an important part in normal brain function .

Defects in insulin's function are suspected as contributors to the cognitive dysfunction and brain changes associated with Alzheimer's disease.

- neurons need insulin in order to absorb glucose and obtain energy, and research had shown deficits in glucose uptake and utilization in the brains of patients with AD. Thus, investigators had suspected a connection between insulin and AD for some time, but prior to the emergence of IN therapy this association was clinically moot.

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- Intranasal insulin when taken as a nose spray reaches the brain rapidly through nerves that serves our sense of smell, and can reach the brain without altering blood sugar levels as it will not travel to blood stream , making this available technique to help both diabetics and non diabetics .

Studies suggest that insulin protects against  $A\beta$ 's neurodegenerative effects and that  $A\beta$  interferes with normal insulin signaling , researchs show that Amyloid beta oligomers cause impaired insulin signaling at IRS-1 via mechanisms of TNFalpha and JNK activation. Attenuation of PI-3 kinase pathway.

- Studies suggest that insulin protects against  $A\beta$ 's neurodegenerative effects and that  $A\beta$  interferes with normal insulin signaling.

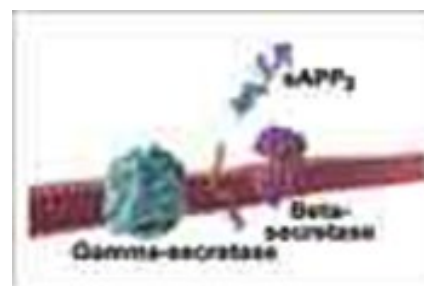
-In 2011 studies demonstrated improved memory and cognition

among individuals with AD or amnesic mild cognitive impairment (MCI) after IN insulin treatment. In this trial, insulin therapy was also associated with reduced loss of glucose uptake and utilization

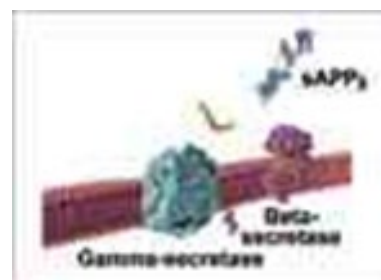


### D) Drugs to reduce AB production:

generation of  $A\beta_{40}$  or  $A\beta_{42}$  is the result of two sequential cleavages of the amyloid precursor protein (APP). First, extracellular cleavage of APP by  $\beta$ -secretase 1 (also termed beta-site amyloid precursor protein cleaving enzyme 1 or BACE1) produces a soluble extracellular fragment and a cell membrane-bound fragment referred to as C99. Subsequent cleavage of C99 within its transmembrane domain by  $\gamma$ -secretase releases the intracellular domain of APP and generates  $A\beta$  .

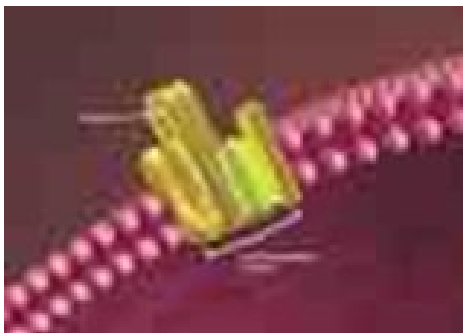


It is  $\beta$ -secretase cleaving APP molecule



Beta amyloid peptide released

In contrast, initial cleavage of APP by  $\alpha$ -secretase prevents generation of  $A\beta$ , Therapeutic attempts have targeted inhibition of  $\beta$ -secretase and  $\gamma$ -secretase .



**It is gamma secretase**

in brain areas linked to disease, other studies say that intranasal insulin treatment for four weeks normalized AKT and GSK-3 $\beta$ , as well as reduced tau hyperphosphorylation in T2D rat brains, (7-9)

**EX : Novoline R**

**B-secretase inhibitor:**

tested for AD in randomized controlled trials (RCTS) may in part act as suppressors of B- secretase expression. The administration of B-secretase inhibitor rescued cognitive decline and brain AB in AD mice tg2276 with no toxicity over 7 month time period, Up to now no efficacy data are available from phase 3 clinical trials of  $\beta$ -secretase inhibitors. Specific problems in developing safe, non-toxic  $\beta$ -secretase inhibitors are related to blood-brain barrier (BBB) penetration and reasonable selectivity.

- Rosiglitazone is an antidiabetic drug that has been tested in AD, it was shown to improve spatial learning and memory abilities, slightly decrease A $\beta$ 42 concentrations in brain (but not A $\beta$ 40) and induce insulin-degrading enzyme (IDE), without affecting the amyloid plaque burden in Tg2576 mice.

**Ex : Thiazolidinedione, rosiglitazone, pioglitazone**

**Table 1**  
Current status of clinical development of some disease modifying drugs for treat disease (AD)

Drug	Mechanism of action relevant for AD	Phase of study	Result of study
Rosiglitazone	$\beta$ -secretase inhibition (?)	3	Ineffective
Semagacestat	$\gamma$ -secretase inhibition	3	Premature end
Tarenflurbil	$\gamma$ -secretase modulation	3	Ineffective
Tramiprosate	Inhibition of A $\beta$ oligomerization	3	Ineffective
Scyllo-inositol	Inhibition of A $\beta$ oligomerization	2	Ineffective
Bapineuzumab	A $\beta$ clearance	3	Ongoing

**$\gamma$ -secretase inhibitor :**

$\gamma$ -secretase is a protease complex that cleaves proteins at residues within their single membrane spanning domain. The most known substrate of  $\gamma$ -secretase is APP, whose cleavage produces A $\beta$ . The  $\gamma$ -secretase complex consists of four individual proteins, (



presenilin, nicastrin, APH-1 and PEN-2. A fifth protein, known as CD147).

Presenilin is the catalytic subunit and mutations in the presenilin gene represent a major genetic risk factor for AD, Although  $\gamma$ -secretase mutations that completely knock out enzyme function prevent generation of A $\beta$ , mutations that only partially knock out enzyme function often enhance generation of A $\beta$ .

-  $\gamma$ -secretase inhibitors may enhance the production of A $\beta$ 42 while blocking other  $\gamma$ -secretase activities, thus mimicking the effects of PS mutations.

ex;

**1- Semagacestat :**

was the first  $\gamma$ -secretase inhibitor to undergo extensive clinical testing and was shown to reduce A $\beta$  concentrations in plasma and A $\beta$  production in the central nervous system (CNS)

but it is stopped as shown a serious collateral adverse effect like : haematological, gastrointestinal and skin toxicity

**2- Notch-sparing  $\gamma$ -secretase inhibitors :**

(second generation inhibitors) and/or modulators (agents that shift  $\gamma$ -secretase cleavage activity from longer to shorter  $\beta$ -amyloid species, without affecting Notch cleavage are in clinical development)

for ex :

**3- non-steroidal anti-inflammatory drugs (NSAIDs):**

act as  $\gamma$ -secretase modulators, decreasing A $\beta$ 40 and A $\beta$ 42, while increasing A $\beta$ 38,

ex:

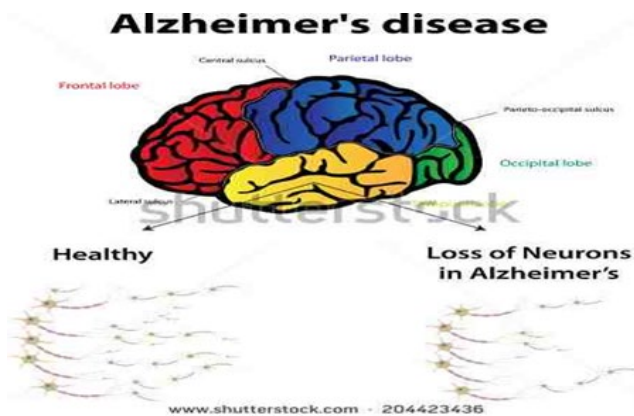
Tarenflurbil (the R-enantiomer of flurbiprofen) was tested in phase 3 RCTs but did not appear to slow cognitive decline, while increasing frequency of dizziness, anaemia, and infection

- cyclo-oxygenase inhibition in microglia may result in inhibition

of A $\beta$  clearance 1,4-dihydropyridine (DHP) L-type calcium channel blockers are known to interfere with A $\beta$  production, such as nilvadipine, can reduce the risk of developing AD,

.Recent studies suggest that such benefits are not related to the drug's blood pressure lowering function. Both nilvadipine and amlodipine decrease A $\beta$  production from APP in vitro, but only chronic oral treatment with nilvadipine reduces A $\beta$  accumulation in a transgenic model of AD, by targeting both production and clearance of A $\beta$  across the BBB.

In a small study, nilvadipine slowed cognitive decline in MCI patients with hypertension Nilvadipine stabilizes cognition and is



well tolerated, with no dangerous blood pressure lowering effects. A multicentre phase 3 clinical trial started in January 2012 to assess the efficacy of nilvadipine as a disease modifying drug in AD patients<sup>(10)</sup>

### E ) Drugs to prevent A $\beta$ aggregation

#### \* It prevents

Aggregation of monomeric A $\beta$  species into higher molecular weight oligomers that produces the primary neurotoxic species in AD

ex:

#### \* Tramiprosate (3-amino-L-propanesulfonic acid) :

is a glycosaminoglycan that binds to A $\beta$  monomers and prevents formation of oligomers, thus enhancing A $\beta$  clearance from the brain

- phase 2 study showed that tramiprosate reduces A $\beta$ 42 concentrations in CSF, but phase 3 study, however, tramiprosate did not determine clinical improvement, although a recent subanalysis suggests that it may exert some beneficial effects on memory, language and praxis skills, requiring further clinical evaluation.

#### \*There is another strategy can use to avoid aggregation :

we can use a chelating agent that removes copper and zinc from CSF, so promotes A $\beta$  oligomer clearance and restores cognition in AD mouse models as zinc and copper are catalysts for A $\beta$  aggregation and stabilization of amyloid plaques, and this agent

may be effective in dissolving amyloid deposits in vitro and in vivo.,

ex:

#### 1 - PBT2 is an 8-hydroxy quinolone :

orally administered, can penetrate BBB, in a recent phase 2a study, PBT2 lowered A $\beta$ 42 in CSF and improved cognition, but no correlation was found between A $\beta$  in CSF and cognitive changes

#### 2-Scyllo-inositol (scyllo-cyclohexanehexol, AZD-103, ELND-005)

can cross the BBB by inositol transporters and orally administered, can directly bind to A $\beta$  oligomers promoting dissociation of A $\beta$  aggregates, and this drug can prevent the transition from A $\beta$  monomers to A $\beta$  oligomers

- scyllo-inositol has a sustained ability to treat animals at advanced stages of AD-like pathology. Significant decreases in insoluble A $\beta$ 40, A $\beta$ 42, and plaque accumulation were observed in the brains of treated versus untreated TgCRND8 mice, and the growth of plaques of all sizes was inhibited. A phase 2 clinical trial evaluating safety, efficacy and effects on biomarkers of ELND-005 in mild to moderate AD patients has been completed. Of the three tested doses, 250, 1000 and 2000 mg, only 250 was well tolerated, and shows reduction in CSF B42 and patients who receive this dose have increasing in their brain ventricular volume, but the two higher dose groups show side effects like early discontinuation. In spite of lack of significant clinical improvement Large-scale phase 3 clinical studies are needed to evaluate the clinical efficacy of ELND005.

#### 3- polyphenolic compounds :

such as

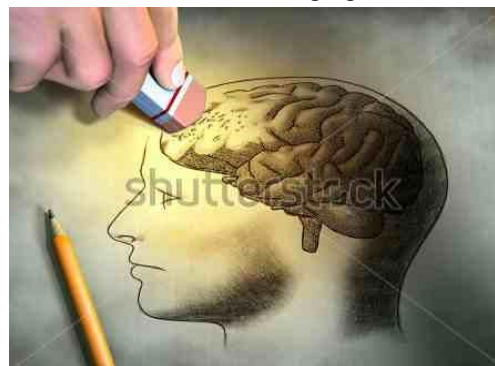
curcumin (-)

-epigallocatechin-3-gallate (EGCG) and grape seed extract

can reduce A $\beta$  aggregation. EGCG has shown good tolerability and is currently evaluate in phase 2, 3 RCT

#### 4- The amoebicidal drug clioquinol :

this metal chelating agent that causes regression of amyloid deposits in animal models of AD, and showed some benefit in initial clinical trials. clioquinol has known toxic effects in humans, but less toxic metal-chelating agents are under investigation



(11:13)

### F- Indoleamine 2,3-dioxygenase (IDO) Inhibitor :

Studies showed that Indoleamine 2,3-dioxygenase (IDO) is one of the causes involved in the pathogenesis of Alzheimer's disease (AD), IDO is a rate-limiting enzyme in the kynurenine pathway (KP) of tryptophan catabolism, so we use IDO inhibitor.

Ex :

Coptisine : is a traditional Chinese medicinal prescription Oren-gedoku-to (OGT) -

- recent studies show that OGT has effect on human IDO activity and can use as uncompetitive IDO inhibitor, that can inhibit IDO in the blood and decreased the activation of microglia and astrocytes, so prevented neuron loss, reduced amyloid plaque formation, and ameliorated impaired cognition.

Neuronal pheochromocytoma (PC12) cells induced with amyloid- $\beta$  peptide 1-42 and interferon- $\gamma$  showed reduction of cell viability and enhancement of IDO activity, its four main constituents (i.e., berberine, palmatine, jatrorrhizine, and baicalein) and they are potent IDO1 inhibitor, Jatrorrhizine and palmatine exhibited irreversible inhibition of rhIDO-1, whereas berberine and baicalein behaved as uncompetitive, reversible inhibitors. so OGT shows

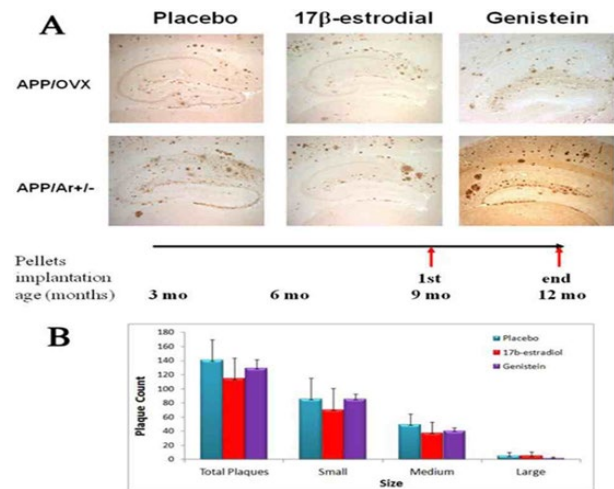


strong IDO1 inhibitory action and may have important therapeutic effect in AD (14-15)

### G) Estrogen replacement therapy for treatment of AD:

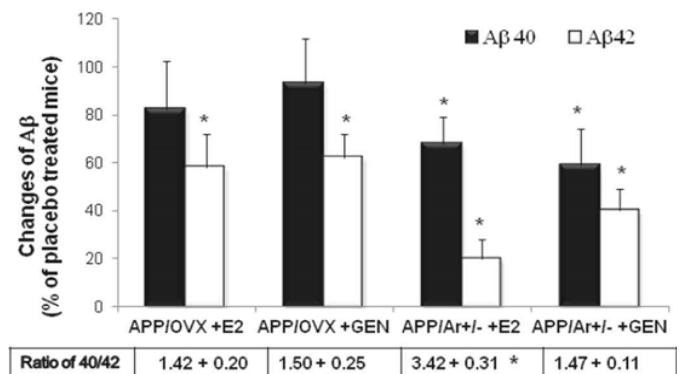
Studies showed that Alzheimer's disease (AD) is associated with age-related loss of sex steroid hormones in both women and men, but more in postmenopausal women due to depletion of estrogen and progesterone which showed that can increase susceptibility to AD pathogenesis as studies showed that brain estrogen deficiency inhibits IDE activity in female APP transgenic mice because insulin-degrading enzyme (IDE) and neprilysin (NEP) can be clear and degrade AB. so results of studies which worked on this point told us that we can use estrogens in treatment to improve memory and reduce risk of dementia. early and long-term treatment with 17 $\beta$ -estradiol (E2) or genistein could reduce brain amyloid levels and may prevent AD pathologies in a dependent manner on endogenous brain estrogen levels in aged females, some studies say that estrogen work by using strategy of increasing A $\beta$  clearance in both APP23 mice with genetic deficiency of

aromatase and promoting NEP, but most data suggest that estrogen increases the  $\alpha$  secretase pathway of APP processing via activation of extracellular-regulated kinase 1 & 2 (ERK1 & ERK2) signaling and by this will stop pathway that produce amyloid peptide but conjugated equine estrogen (CEE), a synthetic form of estrogen doesn't show the same result but cause reduction of cognitive



activities and increased risk of dementia As E2 is a natural form of estrogen that exists in the human body while CEE is not.

This figure shows effect of late and short term treatment of E2 and genistein on brain plaque formation. At an age of 9 months old, female mice were treated with 17 $\beta$ -estradiol (18.8ug/day), Genistein (26ug/day) or placebo for 3 months. At an age of 12 months, brain tissues were harvested. (A) Immunostaining of A $\beta$  plaques as shown in dark brown in the images. (B) Plaque count was performed by Image-pro Plus Analysis (media Cybernetics)



with three sizes as large (>20  $\mu$ m diameter), medium (10–20  $\mu$ m diameter) and small (>10  $\mu$ m diameter). \* P<0.05 compared to placebo groups

THIS figure shows Level of A $\beta$  in APP/OVX and APP/Ar+/- mice with estrogen treatment. Experimental mice received continuous treatment with placebo, E2 or genistein (Gen) from 3 months old and tissue was harvested at age of 12 months as described in the method. Brain tissue from total of 48 mice (n=8 each treatment group) were processed and measured for A $\beta$ 40 and A $\beta$ 42 by ELISA

kits. Data presented as percentage of placebo treated APP/OVX or APP/Ar+/- mice. \* indicates  $P < 0.05$  compared to placebo treated mice (16 -17) .

### H- cox-(1) inhibitor strategy in AD :

studies indicate that COX-1 is actively involved in brain injury induced by pro-inflammatory stimuli including  $A\beta$ , lipopolysaccharide (LPS) and  $TNF-\alpha$ . In some models of neuroinflammation . Reduction in cognitive decline in AD patients was observed in a 6-month, double-blinded, placebocontrolled study with indomethacin, a non-selective, but a potent COX-1 inhibitor , and neurons treated with COX-1 selective inhibitors are resistant to  $A\beta_{1-42}$  .Moreover, COX-1 inhibition produced a profound inhibition of either LPS- or arachidonic acid-induced PGE2 synthesis in human microglia (18) ,and other studies demonstrated a marked reduction in both amyloid burden and cognitive deficits. a platelet anti-aggregant and irreversible COX-1 inhibitor, prove that could rescue cognitive deficits by reducing the dense-core amyloid plaque load . (19)

### Combination:

1- a platelet anti-aggregant and irreversible COX-1 inhibitor, prove that could rescue cognitive deficits by reducing the dense-core amyloid plaque load .

2- placebocontrolled study with indomethacin, a non-selective, but a potent COX-1 inhibitor , this combination shows reduction in cognitive decline in AD patients in a 6-month .

### Strategies and drugs which under investigation:

1- Tramiprosate :

follow drugs prevent AB aggregation strategy ,and phase 2 study showed that tramiprosate reduces  $A\beta_{42}$  concentrations in CSF , but phase 3 study, however, tramiprosate did not determine clinical improvement , although a recent subanalysis suggests that it may exert some beneficial effects on memory, language and praxis skills , requiring further clinical evaluation

.2- Scyllo-inositol (scyllo-cyclohexanehexol, AZD-103, ELND-005 )

Follow drugs prevent AB aggregation strategy , a phase 2 clinical trial evaluating safety, efficacy and effects on biomarkers of ELND-005 in mild to moderate AD patients has been completed, but phase 3 clinical studies are needed to evaluate the clinical efficacy of ELND005.

3- polyphenolic compounds :

Follow drugs prevent AB aggregation strategy such as epigallocatechin-3-gallate (EGCG) can reduce  $A\beta$  aggregation . EGCG has shown good tolerability and is currently evaluate in phase 2, 3 RCT

4- Estrogen replacement therapy for treatment of AD :

EX :  $17\beta$ -estradiol (E2) or genistein

5- kinase Inhibitors as Drugs for Alzheimer's Disease:

studies showed that kinase inhibitor can use to prevent tau phosphorylation , but also showed that the large number of phosphorylation sites and different kinases make this a different approaches . (20)

6- Phosphodiesterase 7 inhibitor :

Inflammation as we know is pathological hallmarks in Alzheimer's disease (AD). So Phosphodiesterase 7 (PDE7) can use to regulate the inflammatory response through the cyclic adenosine monophosphate signaling cascade and plays a central role in AD .

ex s14

When APP/Ps1 mice treated daily for 4 weeks with S14 show :

- 1) significant attenuation in behavioral impairment
  - 2)decreased brain  $A\beta$  deposition
  - 3) enhanced astrocyte-mediated  $A\beta$  degradation; and
  - 4)decreased tau phosphorylation (21)
- ( 7- Drugs to promote  $A\beta$  clearance (7)

8- Strategies targeting tau (7)

NFTs are intracellular aggregates of paired helical filaments whose main constituent is a hyperphosphorylated form of the protein tau . Expression pattern of NFTs correlates with the clinical onset and progression of AD .

Recent efforts in drug discovery have been therefore directed to develop inhibitors of tau-phosphorylation and compounds that prevent tau aggregation

ex : Methylthioninium chloride (MTC ) which possesses antioxidative properties, reduces  $A\beta$  oligomerization and, most importantly, binds to the domain responsible for tau aggregation ( 22)

9- a new pharmacological target proposed for developing neuroprotective drugs in AD is the receptor for advanced glycation endproducts (RAGE), a transmembrane protein that belongs to the immunoglobulin superfamily localized in neurons, microglia, astrocytes and the BBB , RAGE mediates the effects of  $A\beta$  on microglia, the BBB and neurons through different signaling pathways. RAGE enhances generation and accumulation of  $A\beta$  in the CNS by modulating BACE1 (23- 24 )

10 - Deep brain stimulation (DBS) of memory circuits has been proposed as an alternative, non-pharmacological approach for AD treatment , studies suggest that DBS can revert impaired glucose utilization in the temporal and parietal lobes as assessed by PET and also slows cognitive decline but Additional studies are needed to confirm these preliminary results (25)

o we focused on available strategies that will help us in the treatment of Alzheimer's disease , but we still need approved drugs to give better effect in treatment , and we still hope that more strategies will discovered to treat Alzheimer's disease.

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