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Alzheimer's disease: only prevention makes sense.

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Abstract

Alzheimer's disease therapeutics is one of the most important endeavours in today's clinical investigation. Over more than thirty years of research, no disease-modifying treatment has been approved by either the FDA or the EMA to treat Alzheimer's disease. Recently, evidence of pathological alterations in the brain tissue has been gathered showing that the signs of brain damage appear more than twenty years before the onset of Alzheimer's dementia.

The major aim of this review is to underpin the idea that in Alzheimer's therapeutics, only prevention makes sense. It is difficult to visualise that would-be patients may be treated with endovenous administration of antibodies for several years to delay the onset of dementia.

Rather, changes in lifestyle that should be specific, stratified and personalised are a likely alternative to delay the transition from asymptomatic Alzheimer's to minimal cognitive impairment and from there to dementia. These efforts are of the utmost importance. If we could delay the onset of full-blown dementia by five years, the number of demented patients would be almost halved.

Thus, emphasis on preventive measures that can be implemented for decades, must be supported. This approach, where even mild changes in cognition are of the greatest importance, cannot be underestimated in terms of both the individual and society's viewpoints.

Keywords: Dementia, Lifestyle, Clinical trials, Animal models, Vitamin E.

1.- Introduction: Only prevention makes sense

Alzheimer's disease poses a huge problem to society and especially to the individual patient and his or her caretakers. The epidemiological features of the disease and the challenges that it presents to society have been broadly reviewed before[1]. Therapeutics can be approached from two sides: treatment and prevention. It is the main idea of this review to state that only prevention makes sense and that when patients suffer from overt Alzheimer's disease, successful treatments are unlikely to occur.

2.- Failure of previous attempts to treat Alzheimer's disease.

In spite of the impressive efforts carried out by both academia and pharma industry to treat Alzheimer's disease, in the last thirty years there has not been any significant improvement in disease-modifying treatments.

On some occasions, for example in the case of some of the therapies directed against amyloid-β (Aβ), impressive decreases, determined by positron emission tomography (PET), were observed. However, the effects of such treatments on cognitive decline were disappointing[2].

Researchers have tried several approaches to treat Alzheimer's. Table 1 reports only clinical trials that have been published at phase 3, i.e., when efficacy of the drug was being tested, without any success in terms of cognition.

Monoclonal antibodies against Aβ both soluble and non-soluble, have been tested. Solanezumab, a monoclonal antibody against soluble Aβ was tested in patients with mild to moderate Alzheimer's and did not show any benefit in terms of cognition. Increased levels of Aβ in cerebrospinal fluid (CSF) were detected. However, no effect on amyloid accumulation was evident using florbetapir (PIB) as a tracer for PET[3].

A different approach was tested using Bapineuzumab. This was tested in patients carrying APOE4 allele as well as in non-carriers. No significant changes were observed in cognition in patients with mild to moderate Alzheimer's disease. No significant lowering of CSF phospho-tau (P-tau) concentration was observed in APOE4 non-carriers. However, in APOE4 carriers, a reduction of CSF P-tau concentration was observed and a decrease in the accumulation of amyloid in the brain was determined by PET. As stated earlier, these favourable effects were not accompanied by any improvement in cognition[4].

An entirely different approach was used when researchers tried to modulate γ-secretase activity. Two trials have been published, one of them using a γ-secretase inhibitor (Semagacestat). Not only did the drug produce no improvement in cognition,

but on the contrary, a clinical worsening in multiple primary and secondary measures could be observed. Moreover, treatment was associated with more adverse events, including skin cancers[5].

Another trial using Tramiprosate, an aβ aggregation inhibitor, offered some hope in that hippocampal volume loss was diminished when compared with placebo, but unfortunately, no significant effects on the primary outcome, the loss of cognitive function, could be found[6].

The general conclusion that can be drawn from these studies is that so far, no attempt to improve cognition has been effective even though different approaches modulating different pathophysiological features of the disease were used.

Even if we have just limited our comments to phase 3 clinical trials, we would like to comment on the relatively recent report of a phase Ib study that has offered some hope in terms of improving cognition. We refer to Aducanumab, a monoclonal antibody directed against aggregated Aβ. The results in terms of lowering the Aβ deposition in brain were spectacular. The loss of cognition as determined by the mini-mental state examination (MMSE) was significantly lower when compared with placebo, and some improvement in the clinical dementia rate – sum of boxes (CDR-SB) was found[7].

In this particular case, patients with prodromal or mild AD were treated, supporting the idea that we need to treat the disease in the earlier stages if we want to observe some clinical benefit.

These are results of a phase Ib trial, the definitive answer as to whether Aducanumab is effective in improving cognition, even in a moderate manner, has to wait for the results of phase 3 clinical trials that are now ongoing.

3.- Alzheimer's disease: Diagnostic problems

A major problem when analysing previous treatments as well as when proposing new ones for Alzheimer's is that we have serious difficulties in obtaining a proper diagnosis of the disease.

The clinical diagnosis of Alzheimer´s dementia show a specificity and sensitivity of around 60-70%[8], and therefore there are about 30% of persons who are diagnosed with Alzheimer´s that would be misdiagnosed.

When cognitive impairments are associated with changes in P-tau or Aβ in cerebrospinal fluid, the specificity of the diagnosis increases to approximately 80-90%[9]. However, these are invasive techniques, not devoid of secondary effects, and on many occasions, patients are reluctant to take those analyses.

Quite recently, PET analysis with specific radiotracers for Aβ have been developed. These methods offer a specificity and sensitivity similar to the determination of Aβ in CSF, i.e. around 80 – 90%[9]. A major problem with this methodology is that it is very expensive, making it not always easily accessible to investigators trying to propose clinical trials for different drugs or even lifestyle changes.

The general consensus is that around 30% of the patients who are diagnosed with Alzheimer's disease did not suffer from a pure form of Alzheimer's disease. On many occasions, the patients suffer from not only Alzheimer's but also different forms of vascular dementia[10]. We must take into consideration that dementia is multifactorial and not always related exclusively to Alzheimer's.

Any researchers or government agencies trying to evaluate the efficacy of preventive measures or of treatments for dementia should be aware that progress may be hindered by the lack of a proper diagnosis of Alzheimer's dementia.

4.- Prevention: New effects of old drugs

Early disruption of neural networks is a constant feature in patients with AD, the hippocampus becomes disconnected from the rest of the brain early in the symptomatic disease process[11]. As the disease advances and neurons begin to die, more and more networks get disrupted. At the mild to moderate AD stage, almost all networks show decreased functional connectivity[12]. That makes extremely difficult to cure patients in later stages of the disease, as we can get rid of the damaging agent (Aβ), but we are unable to restore those connections.

The advent of non-invasive methods to identify amyloid plaques, most significantly the identification of plaques using specific radiotracers by PET, has shown that many individuals develop amyloid plaques decades before the onset of the earliest form of minimal cognitive impairment (MCI)[13]. It is true that some people who have plaques die before developing dementia, however, the fact that a person has evidence of amyloid plaques in their brain should prompt physicians and other healthcare professionals to establish preventive measures in order to delay the development of dementia.

Figure 1 gives an indication of our view of when we should intervene in the natural history of Alzheimer's, taking into account the ideas presented in Jack et al [13].

Two ways of prevention come to mind: one is more aggressive and one is less so. The first can be to provide antibodies, anti-amyloid plaques that have shown to be effective in lowering the amyloid load in the brain. The idea would be to treat patients with several intravenous injections of antibodies when they are still healthy, which might not be devoid of secondary effects.

Another, in our opinion, safer way would be to treat patients with substances that are associated with lifestyle. Among these we can consider Genistein, Curcumin, and others. Moreover, changes in lifestyle themselves may be useful in the prevention of the development of dementia as we will underpin below.

New effects of old drugs

We would like to make a special mention to a drug that has been very useful in animal models but whose efficacy in humans is still under debate. In 2012, a paper by Gary Landreth and his colleagues described that an old drug used for cancer treatment, Bexarotene, could be useful in the treatment of Alzheimer's disease. It binds to a retinoic receptor that activates the production of ApoE. The results in mouse models of Alzheimer's were spectacular, Aβ load in brain was lowered, and cognition was clearly improved in the treated animals[14]. For a clear comment on this paper, see Laferla, New England Journal of Medicine[15].

Retinoic acid receptor dimerizes with PPARγ, thus, we thought that by activating the production of ApoE not via retinoic acid but via PPARγ one could find a treatment alternative to Bexarotene that could be far less toxic. One such treatment is Genistein, which is a soya component. We have previously shown that Genistein binds PPARγ and exerts its favourable effects by a multi-modal mechanism. One is increasing the production of ApoE, but also lowering inflammation and by activating antioxidant genes via estrogen receptor β[16]. When we tested Genistein in the APP/PS1 model of Alzheimer's disease, a very clear lowering of the amyloid load was observed and an increase in cognition similar to that observed with Bexarotene was found[17].

These are promising old drugs that could be used in this devastating disease, but importantly they have to be tested in humans. As stated below, animal models are

only models and even if the results of old drugs that are now applied for Alzheimer's disease therapeutics are very encouraging, only tests carried out in humans suffering from the disease will provide a definitive answer as to whether these old drugs can be used for Alzheimer's therapeutics.

As we will discuss, a crucial point in the treatment of AD is the need of an early treatment, even before the onset of symptoms, thus we need to find drugs devoid of secondary effects, as we are likely to treat our patients for many years.

5.- Prevention based on lifestyle changes.

Because prevention must occur when the patient starts being at risk, and this is decades before the onset of the disease, we can only be successful in treating patients with lifestyle changes. It is very unlikely that intravenous injections of molecules such as antibodies will be of practical use if they have to be injected periodically for very prolonged periods of time spanning from years to decades.

There is well-established evidence that AD can be modified by lifestyle factors, around a third of Alzheimer's diseases cases worldwide might be attributable to potentially modifiable risk factors[18]. Vemuri et al. in 2012 showed that lifestyle activities such as education, cognitive activity and physical activity, may delay the onset of dementia[19]. Many studies have shown an association between cardiovascular risks and dementia[20], and there is no doubt that these risks are affected by lifestyle factors (i.e. nutrition and physical exercise).

The effects of Alzheimer's are so devastating that attempts to treat the disease have come from many alleys of research. One interesting report that has shown to have promising results is to treat the disease with a multi-domain approach using essentially lifestyle changes. This is the FINGER study, a multi-national attempt to find treatment for Alzheimer's led by the Karolinska Institute in Sweden, which consisted of a two-year treatment using nutritional, exercise, cognitive, and general control of health in patients with MCI, that the authors reported to be at "risk of dementia". The essential results of the study were that patients who received the intervention had a better outcome in terms of cognition after two years than those who did not receive it[21].

Other researchers have proposed multi-domain treatments, Dr. Bredesen, from the Buck Institute in California, has created the "MEND" program, a personalised multi-domain treatment. The author reports evidence from a little group of patients who have improved their cognition very significantly[22, 23]. Needless to say, we still need a double-blind placebo-controlled study, but the anecdotal evidence shown by Dr. Bredesen is encouraging.

A recently published study of a two-year treatment with a specific multinutrient in individuals with prodromal Alzheimer's disease has shown some encouraging results that need to be confirmed in further research. Although the multinutrient intervention had no significant effect on the neuropsychological test battery (NTB) primary endpoint, potential benefits could be observed; the group who received the nutritional treatment had better results on the cognitive-functional measure CDR-SB and less brain atrophy assessed by magnetic resonance imaging (MRI)[24].

On the other hand, some multi-domain approaches have not shown clinical benefits. A 6-year multi-domain vascular intervention did not result in a reduced incidence of all-cause dementia, nevertheless, the study included an unselected population of older people (i.e. not at risk of dementia) and future studies might assess the efficacy in more selected clusters of patients[25].

And we would like to add a commentary to this. There is now evidence that amyloid plaques can be detected in brains of otherwise normal persons using PET with specific radiotracers, even ten years before the onset of Alzheimer's memory complaints[13].

Therefore, one given person can be considered at risk of the disease because they have amyloid plaques decades before the actual onset of dementia or even of MCI. It is understandable that patients at risk could decide to undertake serious lifestyle changes (like performing exercise, engaging in cognitive exercises, changing their diet, taking melatonin supplements, etc). However, it would be much more difficult to treat a person, who otherwise feels normal, with aggressive treatments such as monoclonal antibodies.

We believe, therefore, that personalised lifestyle changes are a likely possibility to exercise prevention of the progression from what has been called prodromal Alzheimer's to MCI and eventually dementia. There has been estimated that delaying onset of AD for 5 years would result in 41% lower prevalence[26]. The

possible favourable effects in terms of personal and public life of these changes are of such magnitude that this approach deserves much intense research support in the near future.

6.- The case of vitamin E in Alzheimer's disease.

Vitamin E offers a significant case of study because of the following reasons: Alzheimer's disease has been correlated with oxidative stress in brain; vitamin E is a lipophilic antioxidant that is likely to enter the brain and prevent oxidation; clinical studies performed by the Alzheimer's disease cooperative study; an important group of researchers into Alzheimer's, have reported that vitamin E can be considered as a treatment of AD[27], and finally, there may be subgroups of patients who are responsive to vitamin E and others who are not.

Indeed, pioneering work of Mark Smith and George Perry showed that there was oxidative stress in the brains of Alzheimer's patients, and that in fact the majority of the pathophysiological changes that occur in Alzheimer's could be traced back to oxidative stress[28].

Furthermore, several groups, including our own, have shown that Aβ affects neurons because it enters the cell and then exerts significant damage to mitochondria. Work of Catarina Oliveira and her colleagues showed that mitochondria-devoid cells were much more resistant in vitro to Aβ peptide than cells containing mitochondria[29]. It was shown that the mitochondrial respiratory chain is impaired by the presence of

Alzheimer's peptides and in fact we showed that the rate of production of free radicals by mitochondria was increased in the presence of Aβ. This was due to the fact that Aβ binds to heme and lowers the rate of the mitochondrial respiration[30]. Therefore, there were experimental basis of pathophysiological importance to propose that indeed oxidative stress is associated with Alzheimer's.

Vitamin E can be considered as a two-sided coin. The "positive one" is that it acts as a powerful antioxidant; the "negative one" is that because it is such a powerful antioxidant, it blunts the antioxidant response to mild oxidative stresses, i.e., the hormetic antioxidant response[31]. There have been a number of clinical studies showing that vitamin E can be considered as a treatment of Alzheimer's. In 1997, Sano and co-workers reported that vitamin E could be deemed a treatment for Alzheimer's because patients who had taken vitamin E showed a significant delay in the progression of loss of cognition associated with the disease[32]. These results were more recently confirmed by the same group and the major conclusion was that patients receiving α-tocopherol had lowered cognitive decline measured by ADCS-ADL than those receiving placebo[27].

These facts have been questioned by other research groups. Petersen et al. in 2005 reported that there was no benefit attributable to vitamin E in patients with MCI[33]. Moreover, a recent systematic review by Farina et al. reported that there was not enough evidence that vitamin E given to persons with MCI may delay the progress of the disease or improve cognitive functions[34].

In many other diseases, it has been shown that persons do not respond uniformly to treatment with vitamin E. Individual responses could be traced to the expression of alpha-tocopherol-transporting proteins (α-TTP)[35]. This led us to consider the possibility that there might be two different sub-populations in terms of the reaction to vitamin E as a treatment for Alzheimer's. A rather preliminary study that we conducted in which we treated patients with vitamin E showed that this may be the case, and that there may be a paradox that we call "the vitamin E paradox in Alzheimer's". In the study, when vitamin E acted as an antioxidant in vivo (lowering the GSSG/GSH ratio in blood) patients showed an improvement in cognition. However, when vitamin E did not prevent the oxidation of glutathione as determined in blood, patients showed no improvement[36].

Therefore, we believe there may be some room for hope, at least in the sub-group of patients that may be responsive to vitamin E.

7.- Animal models: Are they useful?

It has been many years since the first successful attempts to cure AD in animal models, mainly mice, took place[37, 38]. Many of the drugs used to effectively treat AD do so by targeting several pathways[14, 39]. In fact, on some occasions they proved effective in fully restoring cognition in mice. Despite these encouraging results, translation to the clinics has proven to be elusive. No new treatments have been approved by FDA for AD since the introduction of Memantine in 2003.

AD models that have been developed in the last decades are not able to reproduce the full variety of pathogenic mechanisms of human AD. They usually focus on one or a few pathophysiological aspects of the disease[40].

There are obvious differences between mice and human AD. First of all, they are primarily models of familial AD, which are not the best models of late-onset AD, the most common form of the disease. In addition, mice have a brain anatomy and a cognitive capacity so different from human´s that makes it impossible to study superior cognitive functions that are exclusive to us.

Cognitive tests commonly used in mice mainly assess different types of memory (reference, recognition and working)[40]. However, the human condition is much more complex, it is associated with a vast range of different symptoms, including neuropsychiatric impairments, such as sleep disorders, depression or agitation, which are hard to evaluate in the murine models[41].

As we have seen, mice can be fully restored to their previous cognitive function, but this is not what we find in clinical trials. This might be explained because AD mouse models do not display irreversible neurodegeneration[42], their neural networks are affected, but unlike in humans, this can be reversed.

It is important to point out that our animal models of AD might be representing an early stage of the disease, when there is Aβ deposition but no neuronal loss. Thus, they cannot recapitulate the whole brain damage that humans suffer along the progression of the disease. In general terms, at least with the widely used APP/PS1 model of AD, amyloid derived damage, but not irreversible neuronal death, is observed even in old mice.

The problems we have described do not mean that our models are useless. Mice have been of inestimable value to our understanding of the Alzheimer's pathophysiology.

If the majority of the existing animal models do not exhibit neuronal death, and we can promote recovery of their previous cognitive abilities, we should use information derived from models to try and treat patients in the earlier stage of the disease, i.e. at the prodromal level or even to promote secondary prevention.

8.- Conclusion: Importance of early detection and prevention

Ever since the discovery of the disease by Alois Alzheimer, the diagnosis was based on pathological findings post-mortem. The advent of biochemical and molecular imaging techniques that are useful to help in the diagnosis, i.e. the determination of Aβ and P-tau in the cerebrospinal fluid and the identification of amyloid plaques in the brain of patients has meant an enormous advance in the diagnosis of the

disease. But this has underpinned the fact that persons may show signs of amyloid deposition in brain even decades before the first cognitive complaints occur.

It is at this particular time, before the first symptoms of cognitive impairment appear in people who already show Aβ deposition, that physicians and other health caretakers should act to prevent the onset of MCI and dementia.

Aggressive treatment methods are unlikely to be useful when the patient is decades away from the first symptoms of cognitive impairment. Therefore, we believe that the onset of preventive measures, especially associated with changes in lifestyle including exercise, control of sleep and the supplementation with nutritional components may be extraordinarily useful to delay the onset of MCI and especially its transition to dementia.

We hypothesize that even if neurons were regenerated after treatment with regenerative medicine, the neuronal connexions and networks would still be lost and therefore it would be impossible to restore cognition.

In our understanding, it makes little sense to treat patients when they have severe brain damage and when dementia has already been established. It is in the interest of the patients and also society in general to understand that only prevention makes sense in the case of Alzheimer's, and that when preventive measures are taken, the benefits for patients and society are likely to be enormous.

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46 Jones RW. Dimebon disappointment. *Alzheimers Res Ther* 2010;**2**:25.

Figure 1:

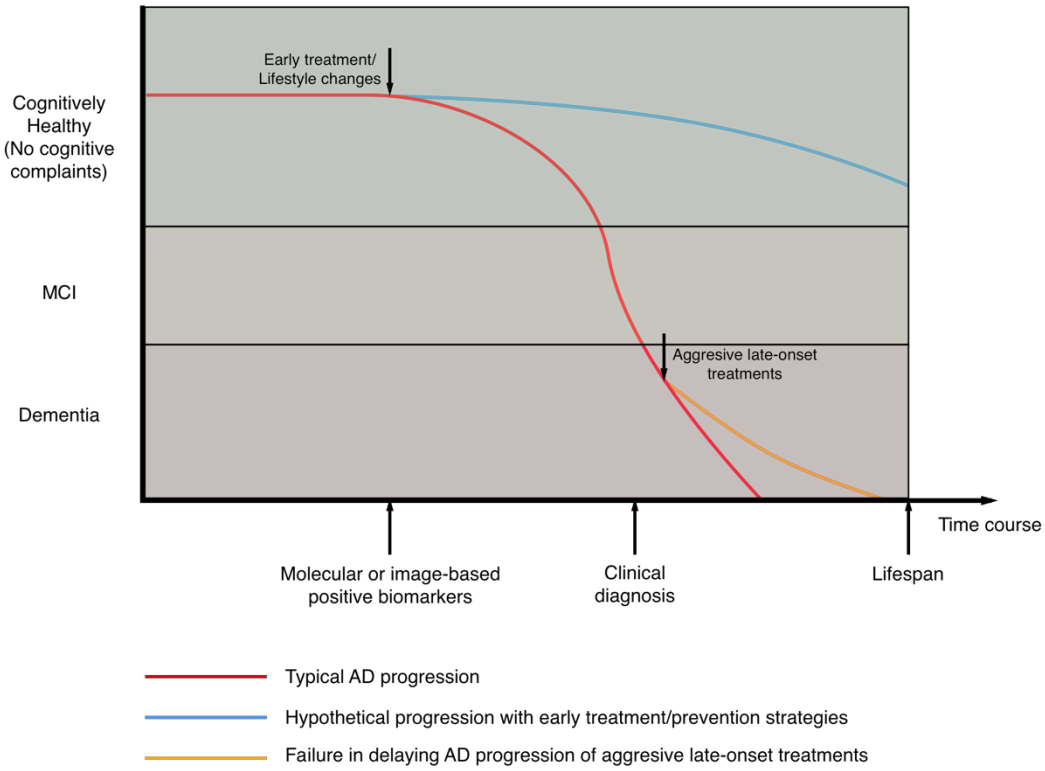

Figure 1.- Graphical representation of when-to-treat according to our understanding of the disease.

The horizontal axis represents disease progression expressed as a function of time.

Cognitive performance of the individual assessed by the Clinical Dementia Rating is divided in Cognitively Healthy (green area), Minimal Cognitive Impairment (yellow area) and Dementia (red area). As cognition declines, the individual goes through the three phases.

Red line **represents the history of the disease, with the individual staying cognitively healthy and asymptomatic (green area) for a long period of time**. Biomarkers (CSF or PET Aβ and later CSF p-Tau) are detectable in the green area, before the onset of clinical symptoms and diagnosis, allowing to intervene in the progression of the disease, before reaching MCI and dementia.

Blue line shows the desired progression with prevention strategies, with the individual dying cognitively healthy. Orange line shows the impossibility of late-onset treatments to reverse cognitive decline.

Table 1: **Selection of finished Alzheimer's clinical trials in phase 3, with no observable efficacy in terms of congnition in either of them.**

Reference	Drug	Inclusion Criteria	Effects on cognition	Other effects
Salloway 2014[4]	**Solanezumab:** Monoclonal antibody against soluble Aβ.	Patients 55 years of age or older who had mild-to-moderate Alzheimer's disease without depression. MMSE of 16-26.	No changes from baseline in scores on the ADAS-cog11 and the ADCS-ADL scale.	No effects on amyloid accumulation with the use of PIB-PET. Increase of Aβ in plasma. Reduction in CSF levels of free (unbound) $A\beta_{40}$. Increase in CSF levels of total (bound and unbound) $A\beta_{40}$ and $A\beta_{42}$.
Doody 2014[3]	**Bapineuzumab:** N-terminal–specific anti-Aβ monoclonal antibody.	Patients from 50 to 88 years of age, met the criteria for probable Alzheimer's disease, and had a MRI scan that showed results consistent with Alzheimer's disease. MMSE of 16-26. APOE4 non-carriers.	No significative changes in scores on the ADAS-cog11, nor in the DAD. No significant differences in the scores on the NTB, CDR-SB, MMSE, or Dependence Scale.	No significant lowering of CSF phospho-tau concentrations. It did not affect the rate of accumulation of amyloid in the brain on PIB-PET.

Doody 2013[5]	**Semagacestat:** γ-secretase inhibitor.	Patients 55 years of age or older who had mild-to-moderate Alzheimer's disease without depression. MMSE of 16-26	No significant differences in scores on either the ADAS-cog or the ADCS-ADL scale. Clinical worsening on multiple primary and secondary outcome measures, including ADCS-ADL, CDR-SB, MMSE, and quality of life (EQ-5D) with the higher dose of the drug.	Reduction in plasma levels of Aβ40 and Aβ42. No reduction in CSF levels of these Aβ proteins. Absence of changes in FDG-PET, amyloid imaging with PET, and MRI studies. Treatment was associated with adverse events, including skin cancers and infections.
Green 2009[43]	**Tarenflurbil:** γ-secretase modulator.	55 years or older and living in the community, meeting criteria for dementia by the DSM-IV, and having probable AD.	No significant effects on primary outcome measures on ADAS-cog, ADCS-ADL and MMSE.	
Aisen 2011[6]	**Tramiprosate:** Aβ aggregation inhibitor.	Patients 50 years or older with diagnosis of probable AD. MMSE of 16-26.	No significant effects on primary outcome measures on ADAS-cog and CDR-SB.	Significantly less Hippocampal Volume loss for tramiprosate 100 mg and 150 mg compared to placebo.
Ostrowitzki 2017 [44]	**Gantenerumab:** Human monoclonal antibody that binds aggregated Aβ.	Patients 50–85 years of age who met International Working Group criteria for prodromal AD.	No differences between groups in the primary CDR-SB change from baseline or secondary clinical endpoints were observed.	Amyloid concentration in brain determined by PET PET SUVr was reduced from baseline by an average 4.8% (absolute mean difference −0.09, $p = 0.1$ vs placebo) at week 100 in the 225-mg dose group.
Relkin 2017 [45]	**IV immunoglobulin**	Patients aged 50–89 years, diagnosed with probable AD dementia. MMSE between 16-26.	No beneficial effects were observed in the primary outcome measures.	Significant decreases in plasma Aβ42 levels were observed in treated participants
Jones	**Latrepirdine:**	Patients 50 Years and	Lack of	

2010[46]	Antihistamine drug	older with Mild-to-Moderate Alzheimer's disease. MMSE score 10-24 inclusive	demonstration of efficacy in clinical outcomes.	