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CURRENT OPINION

Prevention Studies in Alzheimer's Disease: Progress Towards the Development of New Therapeutics

Nicola Coley[1,2,3] · **Adeline Gallini**[1,2,3] · **Sandrine Andrieu**[1,2,3]

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Abstract Alzheimer's disease (AD) is the most common form of dementia and is a major cause of disability and dependency amongst older people. AD drugs approved so far are symptomatic treatments and are not thought to affect the underlying disease process. Trials conducted with agents aiming to slow or stop disease progression in patients with AD have all failed, perhaps because they were tested too late in the disease process. Therefore, there has been a move towards prevention of AD. This paper presents an overview of trials testing pharmacological interventions for sporadic AD prevention. Those tested to date were initially developed for the treatment of AD or for the treatment of other conditions, rather than being specifically developed for AD prevention. Associated issues, such as evidence of 'proof-of-concept,' doses and safety, are discussed. A major shift has taken place in the methodology of AD prevention trials since the results of the first trials were published in the 1990s. New directions that are currently being considered in ongoing or future prevention trials are discussed, in terms of endpoints, target populations, and study design. The use of AD-specific drugs to prevent AD in high-risk individuals is currently limited by a lack of validated predictive and surrogate markers. Population approaches, such as lifestyle changes, are an alternative strategy that could be of public health interest, but may provide only limited benefits for individuals. The best chance of preventing AD may come from a combination of individual and population prevention approaches.

Key Points

Following the failure of treatment trials in symptomatic Alzheimer's disease (AD), there has been a move towards prevention of AD.

To date, no specific pharmacological intervention has been developed for sporadic AD prevention and trial results have been disappointing.

A major shift has taken place in the methodology of AD prevention trials and new directions are being considered in terms of endpoints, target populations, and study design.

1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that affects memory and other cognitive domains, and is the most common form of dementia. It is a major cause of disability and dependency amongst older people, and has a huge impact on both families and society. There were an estimated 36 million cases of AD and other dementias worldwide in 2010, and this number is set to more than triple by 2050 due to demographic aging [1],

N. Coley and A. Gallini contributed equally to this work.

✉ Sandrine Andrieu
sandrine.andrieu@univ-tlse3.fr

[1] Inserm UMR1027, 31073 Toulouse, France

[2] University Toulouse III, 31073 Toulouse, France

[3] Department of Epidemiology and Public Health, CHU Toulouse, 31073 Toulouse, France

despite suggestions of a decrease in their incidence in western countries [2–4]. The annual global cost of dementia is estimated at more than US$600 billion [5].

The major pathological features of AD are cerebral plaques and neurofibrillary tangles, mainly comprised of β-amyloid (Aβ) and hyperphosphorylated tau, respectively. Other characteristics of this disease include synaptic dysfunction, neuronal and white matter loss, inflammation, and oxidative stress [6].

Drugs approved so far for AD are symptomatic treatments targeting cholinergic and glutamatergic neurotransmission and are not thought to affect the underlying disease process [7]. A number of phase III trials have been conducted using agents aiming to slow or stop disease progression (disease-modifying drugs), including six compounds, such as monoclonal antibodies or γ-secretase inhibitors, specifically targeting the amyloid cascade, but all have failed [8–12].

Various reasons may explain these failures. For instance, there may have been too much focus on Aβ, which may not be the right target for an effective AD treatment [13–15], or the drugs tested so far may not have been targeting the right form of amyloid [16]. Furthermore, the AD subjects recruited to these trials may have been very heterogeneous and not all may have had evidence of amyloid plaques [17]. Finally, a widely held belief is that intervening at the dementia stage may be too late, and that putative disease-modifying agents, particularly anti-amyloid therapies, should be initiated earlier in the disease process [18–21]. The recent solanezumab trials provided some support to this theory, since there was a suggestion of beneficial treatment effects in patients with mild AD but not in those with moderate forms [22].

Indeed, the physiopathological changes associated with AD are thought to begin decades before the onset of clinical symptoms [23]. Because of this long asymptomatic phase, AD may be particularly amenable to prevention. Furthermore, epidemiological studies have identified numerous modifiable factors, such as diet, physical exercise, cognitive reserve and cardiovascular risk factors, which are associated with AD risk [24]. It has been estimated that a preventive intervention able to delay disease (dementia) onset by just 1 year could result in 9 million fewer cases by 2050 [25].

2 Prevention Trials of Alzheimer's Disease (AD) with Pharmacological Agents

This paper does not aim to give a systematic review of prevention trials of AD. Such a review can be found in recent papers (e.g. Williams et al. [26]). Here we briefly describe pharmacological approaches (excluding vitamins and supplements) that have been tested or are currently being tested to prevent sporadic AD (excluding trials in prodromal subjects). Essentially, two types of drugs have been tested for AD prevention: drugs specifically designed to treat AD and other drugs (see Table 1).

2.1 AD-Specific Drugs

Cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) have been approved for the symptomatic treatment of AD since the late 1990s. In the following decade, these drugs were tested for AD prevention in randomized controlled trials (RCTs). Trials involved subjects with mild cognitive impairment (MCI) and showed possible positive effects on some but not all primary endpoints for donepezil [27–29] and rivastigmine [30]. However, to date, cholinesterase inhibitors are not approved for prevention. Trials with galantamine were negative [31, 32].

Among more recently developed AD-specific drugs, only one is currently being tested in sporadic AD prevention. The A4 Study plans to test the efficacy of solanezumab (a humanized monoclonal anti-Aβ antibody) in 1000 clinically normal older individuals identified as at-risk for progression to AD dementia due to brain amyloid accumulation on positron emission tomography (PET) imaging [33]. Furthermore, some prevention trials are testing anti-amyloid therapies in autosomal-dominant AD [34, 35].

2.2 Other Pharmacological Interventions

In accordance with AD risk factors and supposed physiopathology, observational studies have proposed that various drugs may be beneficial in AD prevention: antihypertensives [36, 37], hormone replacement therapy (HRT) [38, 39], non-steroidal anti-inflammatory drugs (NSAIDs) [40, 41], HMG-CoA reductase inhibitors (statins) [42–44], and antidiabetics [45]. All five therapeutic classes are very commonly used in the general population.

To confirm a hypothetical preventive effect on AD, large RCTs have been or are being conducted. However, apart from antihypertensive trials to some extent [46, 47], they have not demonstrated a protective effect of the candidate drugs.

Trials are still being conducted and ongoing RCTs are testing the efficacy of oral conjugated estrogens or estradiol in 700 recently post-menopausal women (KEEPS Cog (Kronos early estrogen prevention study cognitive and affective substudy) trial [48]), and of aspirin in 19,000 older subjects (ASPREE [ASPirin in Reducing Events in the Elderly] trial [49]).

More recently, other drugs already approved for the treatment of other conditions have been proposed for AD prevention and are being tested in ongoing trials.

Table 1 Randomized controlled trials testing pharmacological interventions for the prevention of Alzheimer's disease or cognitive decline

Trial name/author(s)	Sample size	Duration	Intervention	Main inclusion criteria
Trials with AD-specific drugs				
InDDEx [30]	1018	4 years	Rivastigmine (3–12 mg/day) vs. placebo	55–85 years old, MCI
Doody et al. [27]	821	48 weeks	Donepezil (5 mg/day) vs. placebo	45–90 years old, MCI
Donepezil 401 study [29]	270	24 weeks	Donepezil (5 mg/day then 10 mg/day) vs. placebo	55–90 years old, MCI
Petersen et al. [28]	769	3 years	Donepezil (10 mg/day) or vitamin E (2000 IU/day) vs. placebo	55–90 years old, MCI
Peters et al. [31]	*232*	*52 weeks*	*Galantamine (16 mg/day) or galantamine + memantine (20 mg/day) vs. placebo*	*Amnestic MCI*
GAL-INT-11/18 [32]	2048 (2 trials)	2 years	Galantamine (16–24 mg/day) vs. placebo	≥50 years old, MCI
A4[a] [82]	1000	3 years	Solanezumab (400 mg IV every 4 weeks) vs. placebo	65–85 years old, amyloid accumulation (PET)
Trials with AD non-specific drugs				
Antihypertensives				
Syst-Eur [47]	2418	2 years	Nitrendipine (10–40 mg/day) vs. placebo	≥60 years old, hypertension
AVEC [93]	53	1 year	Lisinopril (10–40 mg/day) or candesartan (8–32 mg/day) vs. hydrochlorothiazide	≥60 years old, early cognitive impairment
PROGRESS [46]	6105	4 years	Perindopril (4 mg/day) vs. placebo	History of stroke or TIA within 5 years
HYVET-COG [83]	3336	5 years	Indapamide (1.5 mg/day) vs. placebo	≥80 years old, hypertension
Hormone replacement therapy				
WHIMS [56, 94]	*4532*	*4 years*	*CEE (0.625 mg/day) + medroxyprogesterone (2.5 mg/day) vs. placebo*	*65–79 years old, post-menopausal women*
WHIMS [94]	*2947*	*5 years*	*CEE (0.625 mg/day) vs. placebo*	*65–79 years old, women with prior hysterectomy*
Tierney et al. [95]	142	2 years	17-β estradiol (1 mg/day) + norethindrone (0.35 mg for 3 days/week) vs. placebo	≥60 years old, post-menopausal women
KEEPS Cog[a] [48]	720	4 years	CEE (0.45 mg/day) + progesterone (200 mg/day for 12 days/month) or transdermal estradiol (50 μg/day) + oral progesterone vs. placebo	42–58 years old, recently post-menopausal women
Non-steroidal anti-inflammatory drugs				
TRIMCI [96]	*257*	*13 months*	*Triflusal (900 mg/day) vs. placebo*	≥60 years old, a*mnestic MCI*
Rofecoxib protocol 078 [64]	1457	4 years	Rofecoxib (25 mg/day) vs. placebo	≥65 years old, MCI
ADAPT [55]	*2528*	*18 months*	*Naproxen (200 mg bid) or celecoxib (220 mg bid) vs. placebo*	*≥70 years old, family AD history*
ASPREE[a] [49]	19,000	5 years	Aspirin (100 mg/day) vs. placebo	≥70 years old
Statins (HMG-CoA reductase inhibitors)				
SHARP[a] (NCT00939822) [99]	90	18 months	Simvastatin (40 mg/day) vs. placebo	45–65 years old, family AD history
SIMaMCI[a] (NCT00842920) [98]	640	4 years	Simvastatin (60 mg/day) vs. placebo	55–85 years old, MCI, high cholesterol level
SimBio[a] (NCT01142336) [97]	120	1 year	Simvastatin (40 mg/day) vs. placebo	45–64 years old

Table 1 continued

Trial name/author(s)	Sample size	Duration	Intervention	Main inclusion criteria
Peroxisome proliferator-activated receptor-γ agonists				
TOMMOROW[a] [51]	5800	5 years	Pioglitazone (low dose) vs. placebo	65–83 years old, at risk for AD (genetic biomarker)

Trials in italics have been halted prematurely

AD Alzheimer's disease, *ADAPT* Alzheimer's Disease Anti-inflammatory Prevention Trial, *ASPREE* ASPirin in Reducing Events in the Elderly, *AVEC* antihypertensives and vascular, endothelial, and cognitive function, *bid* twice daily, *CEE* conjugated equine estrogen, *GAL-INT* Galantamine-International, *HYVET-COG* Hypertension in the Very Elderly Trial cognitive function assessment, *InDDEx* Investigation Into Delay to Diagnosis of Alzheimer's Disease With Exelon, *IV* intravenous, *KEEPS Cog* Kronos Early Estrogen Prevention Study Cognitive and Affective substudy, *MCI* mild cognitive impairment, *PET* positron emission tomography, *PROGRESS* Perindopril Protection Against Recurrent Stroke Study, *SHARP* Statins in Healthy, At-Risk Adults: Impact on Amyloid and Regional Perfusion, *SIMaMCI* Trial of Simvastatin in Amnestic Mild Cognitive Impairment (MCI) Patients, *SimBio* Effects of Simvastatin on Biomarkers, *Syst-Eur* Systolic Hypertension in Europe, *TIA* transient ischemic attack, *TRIMCI* triflusal in mild cognitive impairment, *WHIMS* Women's Health Initiative Memory Study

[a] Ongoing trials

Despite no effect on disease progression in mild-to-moderate AD [12], three trials are currently investigating the efficacy of simvastatin on AD prevention in subjects with normal cognition (NCT01142336 [97]), MCI (NCT00842920 [98]), or with a parent with documented AD (NCT00939822 [99]). Proposed mechanisms of action for statins include a lipid-lowering action resulting in reduction of amyloid plaques, reduction of neurofibrillary tangles, and effects on inflammation and endothelial function [50].

Last, based on evidence of preclinical studies and from small AD treatment trials, pioglitazone is being tested for AD prevention in the ongoing TOMMOROW trial which plans to follow 5800 subjects for up to 5 years [51]. Only the subjects with the highest risk of developing MCI due to AD will be receiving pioglitazone. Mechanisms through which pioglitazone, a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist approved in diabetes mellitus, is thought to be effective include action on inflammation, mitochondrial dysfunction, and amyloid burden [52, 53].

3 Issues Related to the Re-Use of Existing Data

So far, no pharmacological intervention has been specifically designed for sporadic AD prevention. Tested drugs were either developed for the treatment of AD or for the treatment of other conditions. The lack of phase II trials brings various issues that could have contributed to the mostly negative findings of prevention trials, similar to the critique that some phase III trials in treatment of AD were conducted based on insufficient evidence from phase II trials [8].

3.1 Lack of 'Proof of Concept'

For AD-specific drugs, 'proof of concept' relied on transposing findings from phase II and III treatment trials in AD patients to prevention trials based on the reasonable hypothesis that targets identified for treatment were relevant in prevention and that they may be more beneficial at earlier stages of disease development [19].

For other drugs, the 'proof of concept' only relied on preclinical and/or observational studies and on the fact that the pharmacodynamic mechanism was compatible with AD physiopathology. The traditional phase II of drug development was therefore skipped. Furthermore, the timing of exposure and doses and/or the pharmacological ingredient tested in intervention trials were not necessarily those identified in observational studies [54]. Disappointing results from very large phase III trials emphasize the need for phase II data. Indeed, in two RCTs, not only did the candidate drugs not prevent AD, but, converse to the

hopes brought by observational studies, their use was associated with an increased risk of dementia [55, 56]. In WHIMS (Women's Health Initiative Memory Study) [56], this negative signal could be seen as early as 1 year after randomization and may therefore have been captured in short-duration trials, despite the small number of events, if preliminary trials had been conducted.

3.2 Dose Concerns

Current models suggest that the rate of change of AD biomarkers varies across different stages of disease development [23], which may reflect different underlying processes, and since experience from other fields has shown that determining preventive doses may be tricky (for instance, many doses have been used for aspirin in cardiovascular prevention [57]), one can only regret that no specific dose-finding trials have been conducted.

In trials investigating the effect of AD-specific drugs (cholinesterase inhibitors, solanezumab), the doses used in prevention trials were those recommended/tested in AD treatment (i.e., 400 mg intravenously every 4 weeks for solanezumab).

For other drugs, doses tested in AD prevention were also the ones routinely used for other conditions. Antihypertensive trials are particularly interesting since doses were determined according to the efficacy on blood pressure. However, some evidence suggests that the effect of antihypertensive drugs on AD prevention may be due to different mechanisms, independent of their blood pressure-lowering action [58, 59]. Thus, doses used in hypertension may not be the most appropriate and subjects in prevention trials could potentially have received lower doses if appropriate phase II trials were conducted. This is of concern since toxicity is almost always dose related and exposing individuals to the minimal effective dose should be a priority. If a beneficial effect were to be found with one dose, approval would probably be granted for that specific dose without testing if lower doses were equally effective.

3.3 Safety Concerns

So far, only one candidate drug (solanezumab) has been tested in well-conducted phase III RCTs for sporadic AD prevention without being already approved for another indication. Solanezumab has been used by approximately 1000 AD patients in prior phase III treatment trials [22], and safety findings did not retrieve any signal that met the investigator's pre-specified criteria. An increase in cardiac diseases was nonetheless seen in patients treated with solanezumab compared to those who received the placebo (3.1 vs. 1.6 %). As opposed to previous findings [60], there was no significant increase in amyloid-related imaging abnormalities with edema or hemorrhage associated with solanezumab in phase III trials [22].

Compared to developing new drugs, testing already approved drugs in new indications may seem relatively safe. Indeed, drugs must have demonstrated a favorable benefit–risk ratio in order to obtain market approval. However, the appreciation of the benefit–risk ratio strongly depends on the context of potential use and transposing benefit–risk ratios found in treatment situations to prevention situations is difficult. Indeed, in mass prevention each individual has only a small expectation of benefit and this small benefit can easily be outweighed by a small risk [61]. Therefore, safety must be a priority in prevention trials. Furthermore, drug safety profiles are likely to be imperfectly known in elderly subjects because phase III developments are usually conducted in younger populations with few elderly people who, furthermore, may be non-representative of subjects of the same age [62, 63].

In various instances, prevention trials of AD have been halted early for induced harm with long-time approved drugs. ADAPT (Alzheimer's Disease Anti-inflammatory Prevention Trial) (which aimed to study the effect of naproxen and celecoxib to prevent AD) [55] and WHIMS (testing the efficacy of conjugated equine estrogens ± progestin) [56] were discontinued for cardiovascular harm. One RCT investigated the effect of the blockbuster NSAID rofecoxib [64], which was later withdrawn from the international market due to an increased risk of cardiovascular events. Last, the safety of pioglitazone tested in the very large TOMMOROW trial has been questioned [35, 65] and this antidiabetic drug is no longer marketed in some countries (e.g., France).

Caution should prevail in prevention trials, even with drugs that have been marketed for a long time. Careful assessment of the benefit–risk ratio in the prevention context should be conducted considering the basal AD risk of the included population (i.e., high-risk individuals vs. low-risk population).

4 New Directions

There has been a major shift in the methodology of AD prevention trials since the results of the first trials were published a little more than 15 years ago [66]. In the late 1990s and early 2000s, trials essentially tested non-AD-specific drugs or re-tested approved AD drugs as 'secondary' prevention strategies. More recently, lifestyle interventions, including multidomain interventions, have prevailed and some have shown promising results [67–71]. Today, with our revised conceptualization of the disease process, and trial design improvements, pharmacological

interventions are once again being tested. Innovative design features developed for both pharmacological and non-pharmacological prevention trials are discussed below.

4.1 Endpoints

Initially, dementia (or, more specifically, AD-type dementia) incidence was generally used as the primary endpoint. Challenges, including large sample sizes and long follow-up periods, and the difficulty in establishing a reliable diagnosis and exact date of occurrence, as well as our increasing understanding of the AD continuum, meant that later trials primarily aimed to demonstrate improvement (or less decline) on measures of cognitive function. These measures target either specific cognitive domains, particularly memory, or global cognitive function measured by global tests, such as the Mini-Mental State Examination (MMSE), or batteries of multiple cognitive tests. Composite cognitive outcome measures, focusing in particular on memory and executive function, have recently begun to be developed, and constitute the primary outcome measure for several ongoing trials [33, 72–74]. Such measures aim to detect early cognitive changes and essentially serve as surrogate endpoints for AD incidence. However, to date there are only very limited data about trajectories of cognitive decline measured by these composite measures. Further validation is still required, especially in prospective studies, to determine the optimal weighting of the different components, responsiveness, the clinical relevance of cognitive changes on such measures, and whether or not a significant treatment effect would actually translate into a reduction in the number of cases of clinically apparent AD [72, 75, 76].

Biomarkers, including plasma and cerebrospinal fluid (CSF) measures of Aβ or tau, and functional, structural and amyloid brain imaging, have also received much attention as endpoints [77]. Several prevention trials have begun to use biomarkers as outcome measures [33, 34, 78–80], but predominantly as secondary rather than primary outcome measures because no AD biomarker has yet been validated as a surrogate endpoint [81, 82].

4.2 Target Population

There has also been a shift in target populations. Trials completed so far have included cognitively normal individuals or those with some form of objective cognitive impairment without dementia, e.g., MCI. Furthermore, some trials have targeted individuals with specific risk factors for AD, such as hypertension [83], a family history of AD [55], poor nutritional status [84], or those with an increased dementia risk score based on several factors [68]. Recent advances in biomarker and imaging techniques have also meant that it is now possible to identify cognitively normal individuals with evidence of brain amyloid, often considered to have 'preclinical' or 'asymptomatic' AD [85, 86]. Preventive interventions can, therefore, now be tested in pre-dementia stages of AD, which is now widely regarded as 'secondary' or 'tertiary' prevention, depending on whether or not cognitive impairment is also present [19]. The ongoing A4 trial is an example of such a trial [33]. Genetic inclusion criteria may also be used to target individuals at increased risk of AD. The apolipoprotein E (*APOE*) ε4 allele is the strongest genetic risk factor for sporadic AD [87], but no prevention trials to our knowledge have so far used *APOE*-based inclusion criteria. The TOMMOROW trial is developing a new algorithm, based on *APOE* and *TOMM40* genotype and age, for identifying subjects with increased personal risk of developing MCI due to AD as an enrichment strategy, and only the subjects with the highest risk will receive active treatment [51]. Another trial that will include only *APOE* ε4 homozygotes is in the planning stages [100].

4.3 Novel Trial Designs

Adaptive trial designs are beginning to be advocated in the AD field [88], based notably on experience from the breast cancer I-SPY 2 (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis 2) trial [89]. These trials aim to be more efficient, more likely to demonstrate a treatment effect if one exists, and/or more informative [90]. They can speed up the process of drug development, e.g., by using stratified trials, testing several different active treatment arms in the same trial, some of which may be discontinued based on the results of pre-defined interim analyses, or combining late phase II and III trials into 'seamless' studies, whilst maintaining scientific and methodological rigor [90]. Adaptive designs are already starting to be used in prevention by industry (NCT01767311 [101]) and the European Prevention of Alzheimer's Dementia (EPAD) consortium, a public–private partnership (http://www.synapse-managers.com/epad/). Such designs could also be applied in earlier-stage prevention trials, but their use in both clinical and preclinical stages of AD is currently limited by a lack of validated biomarkers. In particular, we do not have a clear and relatively near-term primary endpoint, nor do we have biomarkers able to predict treatment response [88].

AD is a multifactorial disease and may be a spectrum of neurodegenerative diseases that coexist and are influenced by other co-morbidities, rather than a single entity. Therefore, instead of a 'one size fits all' approach, personalized preventive interventions could also be considered, based on risk profiles that might take into account

lifestyle factors, co-morbidities, genetics, and/or biomarkers. More work is required to better define and validate such profiles. In such a context, adaptive interventions could be proposed, based not only on an individual's initial risk profile, but also on their response and/or adherence to interventions. Adaptive interventions could include combination therapies combining multiple pharmacological and/or lifestyle interventions [88, 91].

5 Conclusion

Using AD-specific drugs to reduce the risk of AD in high-risk individuals is an individual approach to prevention. If we want to prioritize such an approach, the use of novel trial designs could make the drug development process significantly more efficient. However, the use of such strategies is currently limited by a lack of validated predictive and surrogate markers [88]. Intensive collaboration, including the sharing of data, resources, infrastructure and expertise, across the whole scientific community, in both the public and private sectors, will be necessary for progress.

Lower-risk, population-based approaches, e.g., based around lifestyle changes or the treatment of cardiovascular risk factors, are an alternative approach that could provide substantial benefits for the population, but may only have limited benefits for individuals (the so-called 'prevention paradox'). Given the inherent difficulties with both individual and population approaches, as for many diseases, the best chance of preventing AD is likely to come from a combination of both [92].

Compliance with Ethical Standards

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