Update on Prevention Trials in Alzheimer’s Disease

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Abstract

An evolving consensus about the need to treat AD in the presymptomatic phase has emerged following the disappointing results of several trials that enrolled subjects with mild to moderate disease, as well as accumulating research demonstrating that AD pathologic process begins decades before the appearance of symptoms. Several lessons can be learned from past prevention trials. The targeted populations were too diverse, the interventions probably not strong enough, and the time of exposure was most likely too short. We have learned from these trials that future prevention trials must be targeted, use strong interventions with known biological activity, and must be sustained with a long-term intervention.

In this paper, we focus on three prevention trial approaches:

A. Targeted therapy: Preventing AD by targeting a specific population with a specific intervention. Such preventive approaches and trials must be based on biomarkers and imaging to select a study population in accordance with the mechanism of the specific intervention;

B. Multi-domain interventions targeting a larger, more diverse population over a longer time period with long-term exposure to non-specific, multi-domain intervention. The rationale for this approach stems from studies showing that several environmental factors are associated with the risk of developing dementia. These factors may include educational level, vascular and metabolic risk factors, physical activity, cognitive stimulation, and nutritional status. It may also be possible to identify healthy adults at high risk of AD and likely to benefit from intervention based on subjective memory complaint, ApoE4 carriage, family history of AD, or the presence of frailty; and use multidomain interventions to compensate for low specificity;

C. What will be probably the future of the clinical practice: A preventive approach, integrated into primary care settings that begins with longitudinal monitoring of memory function in a general population to identify decliners, followed by a specific intervention based on biomarkers and imaging discussed case by case. Finally, preventing AD will require new and improved infrastructure.

Key words: Alzheimer, primary care, drug trials, intervention trials, prevention.

In worldwide efforts to address the oncoming public health and economic crisis resulting from the rising prevalence of Alzheimer’s disease (AD), prevention has been recognized as a key goal (1, 2). Primary prevention by targeting modifiable risk factors could potentially reduce disease incidence by millions of cases by 2050 (3). Meanwhile, the field has coalesced around the idea of secondary prevention, which involves diagnosing and treating the disease before symptoms become apparent (4). An evolving consensus about the need to treat AD in the presymptomatic phase has emerged following the disappointing results of several trials that enrolled subjects with mild to moderate disease (e.g., (5-7)), as well as accumulating research demonstrating that AD pathologic process begins decades before the appearance of symptoms (e.g., (8)).

Several lessons can be learned from past prevention trials. For example, the GuidAge clinical trial -- the largest preventive trial conducted in the EU -- tested whether long-term use of a Ginkgo biloba extract could reduce the risk of progression to AD among subjects over age 70 who spontaneously subjective memory complaints reported to their primary-care physician (9). This randomized, placebo-controlled trial enrolled 2840 individuals and followed them for five years. At the end of the study, there were no statistically significant differences in AD incidence between the two groups. Three reasons were cited as contributing to these disappointing results: the targeted population was too diverse, the intervention with Ginkgo biloba was probably not strong enough, and the time of exposure was most likely too short. The population of individuals with subjective memory complaints is highly variable, with the overall incidence of dementia quite small, making it difficult to achieve statistical significance. In addition, progression to dementia is slow, so in order to demonstrate a slowing of progression, one would likely need either an intervention with a very robust effect or exposure for a very long time, taking into account that the impact of exposure may not be proportional but may increase over time. Taken together, these factors suggest that future preventive trials will need to consider novel statistical approaches with pre-defined endpoints that take into consideration the fact that the impact of intervention could depends on the time of exposure.

Phase 3 trials of solanezumab and bapineuzumab, both monoclonal antibodies directed against beta-amyloid (Aβ), provide additional lessons (6, 7). Despite the fact that both trials enrolled subjects who met criteria for mild-to-moderate AD, biomarker studies revealed that a substantial number of subjects (nearly 30% of those with mild dementia) had no amyloid in the brain (10). Moreover, amyloid-negative subjects receiving placebo...
showed almost no disease progression during the 18-month study period, suggesting that they did not have AD. After this trial, the sponsor Eli Lilly launched a third, targeted solanezumab trial (Expedition III), which enrolled only individuals with biomarker evidence of brain amyloid. Interestingly, the practice of conducting targeted trials in other disease areas such as oncology is credited with much of the progress achieved in developing effective drugs.

We have learned from these trials that future prevention trials must be targeted, must use strong interventions with known biological activity, and must be sustained with a long-term intervention. Here, we propose three prevention trial approaches:

- Targeting a specific population with a specific intervention
- Multi-domain interventions on a large, more diverse population over a longer time period.
- What will be probably the future of clinical practice: A preventive approach, integrated in primary care setting that begins with longitudinal monitoring of memory function in a general population to identify decliners, followed by a specific intervention based on biomarkers and imaging if the disease progress

Targeted therapy: Preventing AD by targeting a specific population with a specific intervention

One approach to the development of an effective disease-slowing therapy is to select a study population in accordance with the mechanism of a specific intervention (11). Targeting therapies in this way depends on identification of biomarkers or genetic markers that provide evidence of the stage or type of disease, as hypothesized by Jack and colleagues (12) and demonstrated in subsequent studies (8, 13). For example, trials of anti-amyloid therapies would enroll subjects at early disease stages when deposition of amyloid is underway, but not so far along that neurodegeneration has ensued.

In 2011, the National Institute on Aging and the Alzheimer’s Association (NIA-AA) proposed modifications to the diagnostic criteria for AD, which included a category called “preclinical AD,” subdivided into three stages based on biomarker findings (Figure 1): stage 1 is defined by the presence of amyloid, evidenced using PET imaging or a CSF analysis; stage 2 by the presence of amyloid plus markers of neurodegeneration, indicated by hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET), elevated CSF tau or phospho-tau, or structural MRI findings of hippocampal atrophy or cortical thinning; or stage 3, where in addition to amyloidosis and neurodegeneration, there is evidence of subtle cognitive decline (14). Subsequent refinement of the criteria added two additional preclinical stages: stage 0, where all biomarkers are normal and there is no cognitive impairment; and suspected non-Alzheimer’s pathophysiology, i.e., markers of neurodegeneration but not amyloidosis (SNAP) (15).

Vos et al. used these criteria to classify 311 cognitively normal (CDR 0) subjects living in the community. They found that 41% were classed as stage 0, 15% as stage 1, 12% as stage 2, 4% as stage 3, 23% as SNAP, and 5% remained unclassified. They also determined the 5-year progression rate to symptomatic AD (CDR ≥ 0.5). Only 2% of stage 0 subjects progressed, whereas, 11% of stage 1 subjects, 26% of stage 2 subjects, 56% of stage 3 subjects, and 5% of SNAP subjects progressed (16). These data support the temporal order of biomarkers proposed Jack et al, and its relevance for clinical progression (12, 13), in particular that amyloid accumulation begins in the preclinical stage of the disease and that this could be the appropriate time to intervene with anti-amyloid therapies.

Johnson et al. used florbetapir PET imaging to assess amyloid load in healthy controls, demonstrating that the mean SUVR increases with age even among cognitively normal subjects, from 5.3% positive in those aged 50 to 59, 10.5% in those 60-69, 15.0% in those 70-79, and 33 % in those 80 years or older (17). These results suggest that it may be possible to enroll subjects based on the presence of brain amyloid (by CSF or amyloid PET), with no objective cognitive decline, possible subjective memory complaints, and preserved activities of daily living. The advantages of such a trial targeting amyloid are its specificity and the ability to treat at a very early stage before non-reversible lesions have developed. The drawbacks are the difficulty of demonstrating a slowing of cognitive decline in an already slowly-declining...
population and the low conversion rate to dementia. These drawbacks result in long and costly trials.

Nonetheless, a trial based on this strategy already started this year. The Anti-Amyloid Treatment in Asymptomatic Alzheimer’s (A4 trial) will be the first prevention trial in subjects determined to be at risk based on brain amyloid demonstrated with PET imaging (18). This placebo-controlled trial will use solanezumab as the treatment and a composite of well-validate neuropsychological tests known to be sensitive in the early stages of cognitive decline as the primary outcome.

The A4 trial aims to exclude older persons without cognitive impairment who, based on the absence of brain amyloid, are much less likely to develop AD. Overall, in our point of view, amyloid PET or CSF seems to be best for selecting trial participants. As tau PET imaging continues to develop, it may be useful for assessing disease-stage and perhaps response to treatment.

We must underline, however, that such trials are expensive and raise cost effectiveness issues. It will be hard to use such treatment for very long period of time, e.g., decades. There are also ethical concerns raised by treating individuals who may never develop AD with drugs that have unknown long-term safety profiles, particularly in people who may develop other chronic diseases. Moreover initiating treatment based on biomarker findings has the potential to affect the life and well-being of subjects. For example, when we detect amyloid and propose treatment in still-normal older adults, we will likely induce stress and other life-altering decisions, which must be taken into consideration. While we hope to prevent the development of AD in some older people, we must realize that not all would have gone on to develop AD and that many other diseases can also occurs at this age.

Other trials targeting the preclinical stages of AD have also begun enrolling subjects. These trials – conducted by the Alzheimer’s Prevention Initiative (API) (19) and the Dominantly Inherited Alzheimer’s Network Trials Unit (DIAN-TU) (20) are targeting individuals with autosomal dominant mutations that make them almost certain to develop early-onset AD (EOAD). A third trial, also by API, will target ApoEε4 carriers, who are at elevated risk of developing late onset AD (LOAD). All of these trials will test the efficacy of active immunotherapeutic agents.

Another possible target population for preventive trials is late MCI due to AD. Individuals at this stage have objective decline in memory, for instance evidenced by low scores in logical memory testing, and a positive amyloid signature (CSF or amyloid-PET), but generally preserved activities of daily living. The advantage of targeting this population is the fact that they have a higher likelihood of converting to AD and, because they are already symptomatic, are more likely to comply with the study protocol. However, they are difficult to screen due to the low prevalence and the high cost of screening with imaging, CSF biomarkers, or extensive cognitive testing. Moreover the cut-off at which cognitive

### Table 1. Drug trials

<table>
<thead>
<tr>
<th>Population</th>
<th>Dvt</th>
<th>Identifier</th>
<th>Clinical trial.gov</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Mechanism of action</th>
<th>Sponsor</th>
<th>N</th>
<th>Primary endpoint</th>
</tr>
</thead>
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<tr>
<td>MCI-AD and mild to moderate AD</td>
<td>I</td>
<td>NCT01837641</td>
<td>Amyloid PET</td>
<td>LY3002813</td>
<td>Nootropic</td>
<td>Eli Lilly</td>
<td>100</td>
<td>Safety</td>
<td></td>
</tr>
<tr>
<td>Prodromal AD</td>
<td>I</td>
<td>NCT01978548</td>
<td>Amyloid PET or CSF Aβ1-42</td>
<td>JNJ-54861911</td>
<td>BACE inhibitor</td>
<td>Janssen</td>
<td>24</td>
<td>Pharmacokinetics and dynamics</td>
<td></td>
</tr>
<tr>
<td>MCI-AD and mild AD</td>
<td>I</td>
<td>NCT02094729</td>
<td>CDR-0.5 WMS-R memory II</td>
<td>BAN2401</td>
<td>Monoclonal antibody anti-Aβ</td>
<td>Eisai</td>
<td>24</td>
<td>Safety</td>
<td></td>
</tr>
<tr>
<td>MCI-AD</td>
<td>II</td>
<td>NCT01255163</td>
<td>CSF Aβ1-42</td>
<td>Exendin-4 (Exenatide)</td>
<td>Neuroprotective action</td>
<td>NIA</td>
<td>100</td>
<td>Safety</td>
<td></td>
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<tr>
<td>MCI-AD and mild AD</td>
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<td>NCT01767311</td>
<td>CDR-0.5 WMS-R Amyloid PET</td>
<td>BAN2401</td>
<td>Monoclonal antibody anti-Aβ</td>
<td>Eisai</td>
<td>800</td>
<td>Derived Composite Clinical Score</td>
<td></td>
</tr>
<tr>
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<td>CDR-0.5 Amyloid PET</td>
<td>ACC-001</td>
<td>Active immunotherapy Anti-Aβ</td>
<td>Pfizer</td>
<td>63</td>
<td>Safety</td>
<td></td>
</tr>
<tr>
<td>MCI-AD and mild AD</td>
<td>II</td>
<td>-</td>
<td>Amyloid PET or CSF Aβ1-42</td>
<td>AZD3293</td>
<td>BACE inhibitor</td>
<td>Astra</td>
<td>1310</td>
<td>ADAS-Cog FAQ</td>
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<td>MK-8931</td>
<td>BACE inhibitor</td>
<td>Merck Serono</td>
<td>1500</td>
<td>CDR-SB</td>
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<td>Prodromal AD</td>
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<td>Amyloid PET</td>
<td>Gantenerumab</td>
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<td>Hoffmann-La Roche</td>
<td>770</td>
<td>CDR-SB</td>
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<tr>
<td>Prodromal AD</td>
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<td>LipidDiet</td>
<td>Dubois et al, 2007</td>
<td>Souvenaid</td>
<td>Medical Nutrition (omega-3)</td>
<td>Nutricia</td>
<td>312</td>
<td>NTN</td>
<td></td>
</tr>
</tbody>
</table>
improvement represents MCI is still unclear, and is impacted by education, sleep, general health, life events, and other factors. Finally the learning effect must be taken into consideration in this population when a repetitive test is used as a screening tool. In the GuidAge trial, for example, the learning effect with the free and cued selective reminding test (FCSRT) was observed over 2 years both in subjects with CDR 0 and CDR 0.5 (personal data). CDR-SB may be a reasonable end point in late MCI, (ADNI and MAPT personal analysis), while in those with early MCI, a composite score appears to be more appropriate. Recently a composite score composed of tests for Word Recall, Delayed Word Recall, Orientation, the CDR-SB, and the FAQ was proposed (21).

Several drugs with varying mechanisms of action have been, or plan to be, used in preclinical, MCI, and AD trials. A phase 3 trial of the gamma-secretase inhibitor semagacestat was tested in patients with mild-to-moderate AD but did not improve cognition and, in fact, was associated with a worsening of functional abilities among those receiving a high dose of the drug. There were also more adverse side effects among those receiving drug compared to placebo (5). Beta-secretase inhibitors may be more efficacious (22). Despite evidence of hepatic toxicity with some of these compounds, at least one (MK-8931) is recruiting subjects for a phase 3 study. Other approaches include monoclonal antibodies such as solanezumab and gantenerumab, which are also in phase 3 studies. Less advanced molecules targeting alpha secretase or tau protein, as well as neuroprotective compounds still in early development. Some studies have been terminated, for example a study of the microtubule stabilizer epothilone D.

Table I summarizes prevention trials in MCI due to AD and prodromal AD currently underway. However, questions remain about whether treating at these stages is too late. While it makes sense to treat before neurodegeneration begins, the progression of the disease is still slow in prodromal AD and MCI, suggesting that there may be some benefit to treating at these stages.

**Alzheimer Prevention Trials: Larger Target, Non Specific but Multi-Domain Intervention, Long-Term Exposure**

An alternative approach for prevention trials is to have a larger more diverse population group with long-term exposure to non-specific, multi-domain intervention. The rationale for this approach stems from studies showing that several environmental factors are associated with the risk of developing dementia. These factors may include educational level, vascular and metabolic risk factors, physical activity, cognitive stimulation, and nutritional status. In addition, recent studies suggest a declining incidence and prevalence of AD over the last ten years, thought to be due to improvements in overall health and educational levels (23, 24). Finally, a recent autopsy study of 1599 older people compared amyloid deposition in subjects 65 yrs. and older who died between 1972 and 2006. Lower amyloid deposition was seen in the 2006 cohort and was particularly marked in the oldest age groups, providing preclinical evidence supporting recently described decreases in AD incidence (25). These accumulating data recently led the U.S. National Institute on Aging (NIA) to encourage all adults to exercise regularly, eat a healthy diet rich in fruits and vegetables, engage in social and intellectual activities, control type 2 diabetes, lower high blood pressure, lower cholesterol levels, maintain a healthy weight, stop smoking, and get treatment for depression.

Targeting the general population for interventional AD prevention trials may not be feasible or even desirable, although there is the potential to promote more informed decision-making by the general public on low-risk approaches that could improve brain health and reduce the risk of dementia (26). In addition, it may be possible to identify healthy adults at high risk of AD and likely to benefit from intervention based on subjective memory complaints (SMC, also called subjective memory impairment [SMI] or subjective cognitive impairment [SCI]), ApoEε4 carriage, family history of AD, or the presence of frailty. Multidomain interventions may compensate for low specificity in these populations.

We would like to propose two specific approaches, targeting 1) those with subjective memory complaints, and 2) physically and cognitively frail older adults.

Individuals with SMC have, by definition, no objective cognitive decline and preserved activities of daily living (ADL). The prevalence has been estimated at between 11% in 65-85 year olds (27) to over 88% in those over age 85 (28), and some studies have suggested that the presence of SMC may predict subsequent dementia (29). Progression to dementia among those with SMC is elevated in individuals with a family history of dementia, expressed concern about memory, onset over the previous 5 years, and when the concern is severe enough to motivate consultation with a primary care provider (PCP).

The advantages of targeting individuals with SMC are that there are large numbers of potential subjects who are relatively easy to identify through PCPs, and that engaging PCPs in the process may increase compliance. Disadvantages of this approach include very high heterogeneity, slow decline, and minimal conversion to MCI or AD. The endpoint for a trial in this population could be a composite score including measures of logical memory or the FCSRT and measures of executive function.

Another large population that could be targeted for non-specific multi-domain trials are older persons with
physical and/or cognitive frailty. In the longitudinal Rush Memory and Aging study, frailty was shown to be associated with both cognitive decline and incident AD (30). Indeed, the definition of frailty -- increased vulnerability resulting from decline across multiple physiologic systems (31) -- has recently been expanded to include cognitive decline (32). In 2013, a consensus group organized by the International Academy on Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) proposed a definition of cognitive frailty that includes both physical frailty and cognitive impairment (e.g., CDR 0.5) in the absence of dementia (33). Individuals meeting this definition are typically 80 yrs. or older with preserved basic ADLs, but some decline in instrumental ADL (IADLs), due mostly to physical frailty.

The advantages of targeting frail older adults for multi-domain prevention trials include the importance of intervening and potentially slowing or reversing the frailty syndrome, the large numbers of persons affected, and the ability to target these individuals through PCPs. Disadvantages include the broad heterogeneity and presence of multiple morbidities within this population and the likelihood of poor compliance to intervention. In addition the neurobiology of frailty has yet to be defined. Endpoints of a study in this population could include both physical (e.g. gait speed) and cognitive functions (memory plus executive functions).

Multi-domain prevention trials in these two populations should include both pharmacological and non-pharmacologic therapies. Possible pharmacotherapies include anti-diabetic drugs such as pioglitazone. This drug is used in the oncoming TOMMORROW trial (34), which will enroll subjects based on their APOE and TOMM 40 genotype. Other agents that could be considered for prevention trials include insulin (35), selective serotonin receptor agonists (SSRIs) (36), and a variety of nutrients such as resveratrol (37), the Ginkgo biloba extract EGB 761 (38), Vitamin D (39), B vitamins, including folate (40), and omega-3 fatty acids (41).

Omega-3 fatty acids (ω-3) are poly-unsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that are found in cold-water fish and fish oil and have been associated, in a number of epidemiologic studies, with a reduced risk of dementia (42). Based on the results of a pilot study (43), the NIA has funded a study to test the potential of ω-3 PUFAs to prevent vascular cognitive impairment. This 3-year, randomized, placebo-controlled trial of ω-3 PUFA will enroll 150 subjects age 80 and older with a CDR ≤ 0.5 (non-demented), low plasma ω-3 PUFA, and white matter hyperintensities (WMH) on MRI scans. Outcome measures include progression of WMH, progression of blood-based markers of inflammation, and cognitive decline (executive function and processing speed)

Physical exercise has been studied extensively in recent trials and found to be associated with both cognitive function (44), decreased MRI hippocampal brain atrophy (45), improved brain metabolism and some in amyloid deposit (ref...). Cognitive stimulation has been largely shown to improve cognition (46) and lower amyloid burden (47) in older adults.

Multi-domain intervention aims to bring together the benefits of nutritional intervention, physical exercise, cognitive stimulation, social activities, and vascular and metabolic risk control to increase the effect of each intervention, reach a threshold, and achieve clinically significant effects. The first and largest trial to have been designed is the Multi-domain Alzheimer’s Prevention Trial (MAPT) (48), a randomized, placebo-controlled study of 1680 subjects, 70 years of age or older living in the community and presenting with SMC (99% of subjects). The cohort was enriched for frail subjects with slow walking speed (4 meters test) in 11.9% of the sample and limitation in one IADL in 11.2%. Demented patients as well as those dependent for basic ADL were excluded. Subjects were randomized into four treatment arms: Omega 3 alone, Placebo alone, Omega 3 plus multi-domain intervention, and Placebo plus multi-domain intervention. The multi-domain intervention included physical and cognitive exercises, dietary counseling and weight maintenance, increased social activities, control of vascular and metabolic risk factors, and correction of vision and hearing impairments. The length of the intervention was 3 years plus 2 years of observational follow-up. Outcome measures included cognitive decline using the FCRST, cerebral and hippocampal volumes (n=500), cerebral glucose metabolism using FDG-PET (n=68) and amyloid PET scanning with florbetapir (n=271).

The MAPT multi-domain intervention was shown be feasible with good compliance demonstrated by only 22.5% drop outs over the 3-year study. The MAPT trial is now completed and results will be released shortly.

Other multi-domain trials include the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER Study), a 2-year intervention trial targeting 1200 subjects at risk for dementia (49), the Prevention of Dementia by Intensive Vascular Care (Pre-DIVA) trial, the Vitamin D3, Omega-3, Home Exercise Healthy Ageing and Longevity Trial (DO-HEALTH), and the Healthy Aging through Internet Counseling of the Elderly (HATICE) program (50). Results presented from the FINGER study at the 2014 Alzheimer’s Association International Conference (AAIC) indicate positive effects on cognitive function (51). The Pre-Diva, MAPT and FINGER trials have been brought together under the umbrella of the European Dementia Prevention Initiative in order to share data and collaborate on new studies.

The advantages of multi-domain trials with large population targets and non-specific but multi-domain
intervention delivered over a long time period are that these interventions are likely to be less expensive, easier to implement in daily clinical practice or at the population level, and safe for long-term exposure; and may act on different therapeutic targets. The disadvantages are interventions themselves are non-specific, the cohorts are highly variable and with different risks of developing dementia, and the potential for low compliance with the study protocol. For example, with regard to the variability in risk of dementia, amyloid PET scans performed in 271 subjects enrolled in the MAPT trial showed that 38.0% had significant brain amyloid (cortical SUVR > 1.17). Moreover these individuals were found to have lower cognitive function at baseline and more cognitive decline over the trial period, similar to what has been seen in observational studies (48).

In fact, these two preventive approaches: targeting a specific population with a specific intervention or targeting a larger at risk population with a multi-domain intervention are complementary and may both be appropriate at different time-points over the life time of an older adult. Indeed, this may be what is required in future clinical practice.

The future of clinical practice: A preventive approach, integrated in primary care setting that begins with longitudinal monitoring of memory function in a general population to identify decliners, followed by a specific intervention based on biomarkers and discussed case by case if the disease progress (FIG 2)

A prevention approach could start by making general recommendations to a large, diverse population (e.g., those age 50 years or older with normal cognition) on diet, physical and cognitive exercise, and risk factor control; then identify decliners through longitudinal monitoring of biomarkers or cognitive markers; and finally test interventions targeted specifically. These preventive approaches must start in primary care settings and integrate the family practitioners.

Among those with SMC and/or a family history of dementia, a tailored multi-domain intervention might be proposed, including nutrition, physical and cognitive exercise, and risk factor control; the use of the MAPT or FINGER trials. Ideally, these interventions could be delivered by PCPs who, at the same time, could begin longitudinal monitoring of cognition as a way to identify decliners for the next level of prevention trials. Some web resources will be probably helpful in the near future, such as the Brain Health Registry (www.brainhealthregistry.org)

If subjects with early MCI, biomarkers (e.g., CSF amyloid, tau, as well as PET scans) may be considered despite the fact that they are expensive and invasive. Plasma biomarkers would greatly enhance the ability to conduct large, longitudinal progression studies. A recent study identified 10 plasma proteins that are strongly associated with structural MRI findings and appear to be able to predict conversion from MCI to AD with an accuracy of 87%, sensitivity of 85%, and specificity of 88% (52). In another study, a set of ten peripheral plasma phospholipids were identified that predicted conversion to MCI or AD over a 2-3 year timeframe with over 90% accuracy (53). However these findings have to be replicated and their clinical utility validated. At that point, it should be possible to offer multi-domain interventions to those who are biomarker-negative and oral drugs such as anti-amyloid drugs to those who are biomarker positive or those who transition to biomarker positivity during the trial. However, as mentioned earlier, there are those who believe that the MCI stage is too late to begin treatment with anti-amyloid therapy and that what is needed is better characterization of the transition from amyloid negativity to amyloid positivity. Anti-amyloid monoclonal antibodies will be also probably useful if the ongoing clinical trials of these drugs are successful.

If the disease progress to late MCI/prodromal AD stages of the disease, new therapies are needed, such as those that target tau; or it may be necessary to use combination therapies that simultaneously act on multiple therapeutic targets (e.g., amyloid plus tau). Anti-amyloid monoclonal antibodies may also be useful in these patients, depending on the outcome of ongoing studies of these agents. However these results will have
to be scrutinized closely to assess the real impact of such therapies (54).

Comments and Research Directions

To achieve our goal of preventing AD, changes are needed in the way clinical trials are designed and conducted:

- Clinical trials must target specific populations according to the intervention.
- The interventions need to be robust and appropriate for the targeted population, e.g., a multi-domain intervention for a large heterogeneous population vs. an intervention with a specific mechanism of action for targeted populations.
- Trials must be of sufficient length to assess long-term exposure to intervention.
- Trials will need to be implemented in clinical settings, beginning with the involvement of general practitioners and other primary care providers. These providers are in an ideal position to monitor longitudinally the cognition of elderly patients and identify decliners who can then be referred for more intensive assessment of progression using biomarkers.
- Trial designs are needed that will enable the testing of combined approaches, including multi-domain approaches as well as combined pharmacotherapy against multiple therapeutic targets.

Moreover, preventing AD will require new and improved infrastructure. In the war against AD we need not only new weapons (drugs) but also the fleet (infrastructures, clinical research facilities) and the framework for the international battle against Alzheimer's disease. Alzheimers Dement. 2013;12(10):207-16.


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