Prevention strategies for Alzheimer’s disease

Serge Gauthier¹,², Liyong Wu², Pedro Rosa-Neto¹ and Jianping Jia²

Abstract
Symptomatic treatment during the dementia stage of Alzheimer’s disease (AD) cannot delay or halt the progression of this disease. Therefore, prevention in the preclinical stage is likely the most effective way to decrease the incidence of this age-associated neurodegenerative condition, and its associated burden for individuals and society. Age, gender, family history, ApoE4, systolic blood pressure, body mass index, total cholesterol level and physical activity are all used as component of dementia risk score. There have been numerous challenges in conducting primary prevention trials in AD. Enrichment strategies for prevention studies include studying those subjects with more risk factors for AD, such as older age, those with a positive family history of late onset AD, and those who are ApoE4 positive. Each of these strategies is designed to increase the probability of developing AD thereby decreasing the sample size or the duration of follow up. Another strategy would be to target directly the pathophysiology of AD in its preclinical stages and use the biomarkers in prevention trial as surrogate markers. This will be done first in carriers of dominantly inherited early onset AD. As this research takes place networks of memory clinics must prepare to transfer new knowledge to persons interested in a preventive approach to AD.

Keywords: Alzheimer disease, Risk factor, Prevention, Clinical trial, Clinical practice

Introduction
Alzheimer disease (AD) is characterized by accumulation of amyloid plaques, neurofibrillary tangles and neuronal depletion associated with progressive deterioration of cognition and functional status [1]. AD is a catastrophic disease and symptomatic treatment (e.g. donepezil, rivastigmine, galantamine, memantine) during the different stages of dementia can only mildly ameliorate the symptoms and cannot delay or halt the progression of this disease, since extensive brain damage has already occurred prior to the dementia phase of AD [2]. Therefore, prevention in the preclinical stage is likely the most effective way to decrease the incidence of this age-associated neurodegenerative condition, and its associated burden for individuals and society [3]. There is great interest in prevention studies as a way to reduce the incidence and prevalence of dementias. This review will summarize the results of recent researches and outline some prevention strategies of AD for future research.

Risk factors of AD
Numerous risk factors for AD have been identified by epidemiologic studies [4,5]. Everyone is at risk if living long enough (33% of individuals have AD over age 85), but some persons are more at risk than others because of their family history (Table 1). Family history in first-degree relatives is the main factor, and the age of onset of the family member matters as well: apoE4 genotype is more likely to be a factor if one of parent had AD at age 70 rather than at age 85[6].

Other known risks include subjective cognitive complaints [7] and demonstrable decline on serial cognitive testing even if still within the normal range considering age and education [8]. Another approach has been the assessment of a variety of risk factors in mid-life, giving them relative weights, and adding them up in a “Dementia Risk Score” [5], as summarized in (Mid-life dementia risk score [modified from 5]).

Mid-life dementia risk score [modified from 5]
- Age at time of initial assessment
- Formal education level
- Gender
- Systolic blood pressure
for such individuals, as summarized in Table 2 [10].

posed by a National Institute on Aging (NIA) task force

marker positive

33% of cognitively normal persons over age 65 are

weight of these risk factors is still unknown, but at least

ography (FDG-PET) and structural MRI) [9]. The relative

imaging and/or a reduction in levels of Aβ42 in the cere-

brospinal fluid (CSF), [18 F]-fluorodeoxyglucose positron emission tom-

ography (FDG-PET) and structural MRI) [9]. The relative

weight of these risk factors is still unknown, but at least

33% of cognitively normal persons over age 65 are "biomarker positive". A new diagnostic category has been pro-

posed by a National Institute on Aging (NIA) task force

for such individuals, as summarized in Table 2 [10].

Prevention of AD

There have been numerous difficulties in conducting pri-

mary prevention trials in AD because of the unclear

pathophysiological mechanism of AD, the difficulty in ac-

curate selection of the target population, the need for a

large sample size, long duration of follow up, the high cost

of the prevention study, adverse events of the prevention

drugs being studied and the related ethical issues [11-15].

Who should be enrolled in the primary prevention trials

remains a very important but complex issue. The target

populations of primary prevention are usually the healthy

elderly. The subjects enrichment strategies include study-

ing those subjects with more risk factors for AD, such as

older people, those with a positive family history of AD,

and those who are Apo E4 positive [11]. Each of these

strategies is designed to increase the probability of de-

veloping AD thereby decreasing the sample size or the dur-

ation of follow up [11,16]. Another group of interest are

persons with memory complaints but no measurable cog-

nitive impairment (subjective cognitive impairment or "pre-

MCI"), at higher risk of progression to dementia [17].

Non-pharmacological interventions

Non-pharmacological interventions are possible: life

style changes are of great interest to modify risk factors

(predominantly vascular) and enhance protective factors

Biomarker positivity can be important in deciding

what population to enroll in a prevention study: more

risk of progression to dementia will shorten the study

but will limit the applicability of findings to the popula-

tion as a whole [15,22]. Diagnostic biomarkers play an

important role in population enrichment by refining se-

lection criteria, stratifying populations and increasing

the statistical power of trials. Endpoint biomarkers may

be used as outcome measures to monitor the rate of dis-

ease progression and detect treatment effects of drugs

[23].

The side effects of drugs are not negligible, particularly

in asymptomatic persons. These risk/benefit considera-

tions are very important to research ethics boards and

regulators: “safety must be the primary consideration

since an agent that will be administered to thousands of

healthy normal individuals, many of whom will never

develop disease, must be remarkably free of side effects”

[24].

Aims in prevention studies for AD

Delays biomarkers changes

The Alzheimer Disease Neuroimaging Initiative (ADNI)

has demonstrated that biomarkers change over time in a
predictable sequence [9]. This makes possible prevention studies looking at delaying biological progression over a relatively short time (12 to 18 months). For instance in early MCI (EMCI) there is already amyloid deposition but little PET-FDG changes and no atrophy on MRI [25]. Progression to late MCI (LMCI) will likely correlate with worsening of PET-FDG and early atrophy on serial MRI. This type of study would be considered as proof-of-concept and would be supportive for longer and larger clinical trials. Shorter (12 months) studies could even be done in APP or presenilin mutation carriers who are within 5 years of their expected time of dementia (ETD) based on their family history [16].

**Delaying cognitive decline**

Delaying decline of cognition using a standardized cognitive measure may be a valid primary outcome in primary or secondary prevention studies [15]. The CogState appears to be of interest for epidemiological studies in older people [26] and in MCI [27]. The episodic memory decline measured by the CogState correlates with findings on amyloid PET imaging [28], thus bridging cognition and biomarkers in pre-dementia stages of AD.

**Delaying dementia**

The studies comparing Ginkgo Biloba in France [29] and in the USA [30] are good examples of randomized studies where time to dementia was the primary outcome. The low incidence rate of dementia caused the US study to be prolonged from the original five years to seven. Thus although having a high face validity, a delay of incident dementia may not be the ideal outcome because of the duration of studies and the need for a conversion committee on top of an experienced clinician opinion.

**Clinical application of prevention**

There is a need for a structured approach to the prevention of AD as new data becomes available. Groups of persons at different level of risk are already seeking advice from their family doctor and memory clinics. The baby boomers may flood the resources of specialized centers for AD who are currently responsible for the diagnosis and symptomatic treatment of AD and other dementias, and who will also have to deal with the use of disease-modifying drugs in the near future, some requiring monthly intravenous infusions. Hopefully family doctors with interest in prevention of heart disease and stroke will also be interested in AD prevention, since these conditions share many risk factors.

**Conclusions**

The prevention of AD require large investment of time and money, but the return on investment may be huge, considering the projections of costs for patients with dementia in the near future. Regular meetings of clinical trialists and epidemiologists will facilitate the development of methodology for successful prevention studies.

### Table 2 Asymptomatic persons with positive biomarkers of AD [modified from 10]

| Stage                                    | Biomarkers or evidence                                      |
|------------------------------------------|------------------------------------------------------------|
|                                          | Aβ (amyloid PET or CSF) | Neuronal injury (tau in CSF, FDG-PET, structural MRI) | Evidence of cognitive decline |
| asymptomatic cerebral amyloidosis (ACA)  | positive           | negative                                         | negative                     |
| ACA + neuronal injury (NI)               | positive           | positive                                         | negative                     |
| ACA + NI + subtle cognitive decline      | positive           | positive                                         | positive                     |

### Table 3 Pathophysiology of AD and potential drug treatments

| Pathophysiology                  | Potential drug treatments                              |
|----------------------------------|-------------------------------------------------------|
| amyloid deposition               | beta and gamma secretase inhibitors active and passive immunotherapy |
| tau hyperphosphorylation         | methylene blue, lithium, memantine                    |
| microglial activation            | naproxen                                              |
| inadequate synaptic plasticity   | probuchol                                             |
as was recently done under the auspices of the Alzheimer Association [31].

Competing interests
The authors declare that they have no competing interest.

Authors' contributions
All authors contributing equally and having read and approved the manuscript.

Acknowledgements
Canadian Institutes of Health Research (CIHR)(MOP-11-51-31 to Pedro Rosano-Neto and Serge Gauthier), National Nature Science Foundation of China (NSFC) [30700241 to Liyong Wu]; and the Beijing Scientific and Technological New Star Program [2007B069 to Liyong Wu].

Author details
1 McGill Center for studies in Aging, McGill University, Montreal, Canada.
2 Neurological Department, Xuanwu Hospital, Capital University, Beijing, China. 3 McGill Centre for Studies in Aging (MCSA), McGill University, 682 S. Boul. LaSalle Blvd, Montreal, QC H4H 1R3, Canada.

Received: 20 April 2012 Accepted: 10 June 2012
Published: 28 June 2012

References
1. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E: Alzheimer's disease. Lancet 2011, 377:1019–1031.
2. Mangalashe F, Solomon A, Winblad B, Mecocci P, Kivipelto M: Alzheimer's disease: clinical trials and drug development. Lancet Neurol 2010, 9:702–716.
3. Khachatryan ZS, Petersen RC, Gauthier S, Buchholz N, Corey-Bloom JP, Evans B, et al: A roadmap for the prevention of dementia: the inaugural Leon Thal Symposium. Alzheimer's & dementia: the journal of the Alzheimer's Association 2008, 4:156–163.
4. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al: Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med 2002, 137:149–155.
5. Kivipelto M, Njardu T, Lastikainen T, Winblad B, Soininen H, Tuomilehto J: Risk score for the prediction of dementia risk in 20 years among middle-aged people: a longitudinal, population-based study. Lancet Neurol 2006, 5:735–741.
6. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S: Apolipoprotein E polymorphism and Alzheimer's disease. Lancet 1993, 342:697–699.
7. Reisdorf B, Gauthier S: Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. Int Psychogeriatr 2008, 20:1–16.
8. Vellas B, Andreu S, Cantet C, Dartigues JF, Gauthier S: Long-term changes in ADAS-cog: what is clinically relevant for disease modifying trials in Alzheimer? J Nutr Health Aging 2007, 11:338–341.
9. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al: Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010, 9:119–128.
10. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al: Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging- Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia: the journal of the Alzheimer's Association 2011, 7:280–292.
11. Thal LJ: Prevention of Alzheimer disease. Alzheimer Dis Assoc Disord 2006, 20(Suppl 2):S5–S9.
12. Feldman HH, Jacova C: Primary prevention and delay of onset of AD/ dementia. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques 2007, 34(Suppl 1):S84–S89.
13. Touchon J, Portet F, Gauthier S: Prevention trials in Alzheimer disease: one step forward? Neurology 2006, 67(Suppl 3):S21–S22.
14. Green RC, Dekosky ST: Primary prevention trials in Alzheimer disease. Neurology 2006, 67(Suppl 3):S52–S55.
15. Andreu S, Coley N, Aisen P, Carrillo MC, Dekosky S, Durga J, et al: Methodological issues in primary prevention trials for neurodegenerative dementia. Journal of Alzheimer's disease: JAD 2009, 16:235–270.
16. Bateman RJ, Xiong C, Benzinger TLS, Fagan AM, Goate A, et al: Clinical and biomarker changes in Dominantly Inherited Alzheimer's Disease. N Engl J Med 2012, doi: 10.1056/NEJMoa120753.
17. Loewenstein DA, Greig MT, Schinka JA, et al: An investigation of PreMCI: subtypes and longitudinal outcomes. Alzheimers Dement 2012, 8:172–179.
18. Carre I, Abellan Van Kan G, Gilette-Guyonnet S, et al: Recruitment strategies for preventive trials: the MAPT Study (Multidomain Alzheimer Preventive Trial). J Nutrition Health Aging 2012, 16:355–359.
19. Forette F, Sex S, Staessen JA, Thijs L, Bijnens WH, Babarskieni MR, et al: Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998, 352:1347–1351.
20. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, et al: Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 2008, 7:683–689.
21. Williams IM, Plassman BL, Burke J, et al: Preventing Alzheimer's disease and cognitive decline. Evidence Report/Technical Assessment no 193.; 2010.
22. Vellas B, Aisen PS, Sampiao C, Carrillo M, Scheltens P, Scherr B, et al: Prevention trials in Alzheimer's disease: an EU-US task force report. Prog Neurobiol 2011, 95:594–600.
23. Wu L, Rosa-Neto P, Gauthier S: Use of biomarkers in clinical trials of Alzheimer disease: from concept to application. Mol Diagn Ther 2011, 15:313–325.
24. Thal LJ: Potential prevention strategies for Alzheimer disease. Alzheimers Dis Assoc Disord 1996, 10(Suppl 1):1–8.
25. Wu L, Rowley J, Mohades S, Leuzy A, Daurat MT, Shin M, et al: Dissociation between brain amyloid deposition and metabolism in early mild cognitive impairment. PLoS One 2012, submitted.
26. Fredrickson J, Maruff P, Woodward M, Moore L, Fredrickson A, Sach J, et al: Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. Neuroepidemiology 2010, 34:65–75.
27. Snyder PJ, Jackson CE, Petersen RC, et al: Assessment of cognition in mild cognitive impairment: a comparative study. Alzheimers Dement 2011, 7:338–355.
28. Darby DG, Brodtmann A, Pietrzak RH, Fredrickson J, Woodward M, Vilemagne VL, et al: Episodic memory decline predicts cortical amyloid status in community-dwelling older adults. Journal of Alzheimer's disease: JAD 2011, 27:327–337.
29. Andreu S, Ousset PJ, Coley N, Ozud M, Mathieux-Fortune H, Vellas B: GuidAge study: a 5-year double blind, randomised trial of EGB 761 for the prevention of Alzheimer's disease in elderly subjects with memory complaints. 1. rationale, design and baseline data. Curr Alzheimer Res 2008, 5:406–415.
30. Dekosky ST, Williamson JD, Fitzpatrick AL, Ronmal RA, Ives DG, Saxton JA, et al: Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA 2008, 300:2253–2262.
31. Yaffe K, Tocco M, Petersen RC, et al: The epidemiology of Alzheimer's disease: laying the foundation for drug design, conduct, and analysis of clinical trials. Alzheimers Dement 2012, 8:237–242.