Primary Prevention and Delay of Onset of AD/Dementia

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ABSTRACT: Prevention in Alzheimer's disease and other dementias (AD/dementia) is defined on the basis of clinical states and their expressed symptoms. Primary prevention refers to delaying the development of the full-blown state of clinically expressed disease in normal individuals. Current primary prevention research is driven by evidence of AD/dementia protective factors that have emerged from epidemiological studies. The first randomized controlled trials (RCTs) of primary AD/dementia prevention have been designed to test the efficacy and safety of NSAIDs, hormonal therapy, antihypertensive drugs and antioxidants. The experience of these trials has indicated safety concerns as a key issue and highlighted significant design challenges in this type of research. These trials have required large sample sizes and unsustainable costs. There should be consideration given in future trials to enriching study samples with risk factors to increase progression rates to AD/dementia. Innovative strategies will also be needed to recruit and retain subjects given the long follow-up periods, modest perceived benefit and the potential for the risk-benefit ratio to change during the trial. It is foreseeable that regulatory authorities will be presented with primary prevention RCTs for approval and labelling, and that criteria to evaluate such evidence still need to be developed.

RÉSUMÉ: Prévenir et retarder l'apparition de la MA/démence. La prévention de la maladie d'Alzheimer (MA) et des autres démences (MA/démence) se définit sur des bases cliniques et symptomatiques. En prévention primaire, on cherche à retarder l'apparition de la maladie avérée au point de vue clinique chez des individus normaux. Actuellement, la recherche en prévention primaire est basée sur des données provenant d'études épidémiologiques sur les facteurs de protection contre la MA/démence. Les premiers essais contrôlés randomisés (ECRs) en prévention primaire sur la MA/démence ont été conçus pour évaluer l'efficacité et la sécurité d'AINSs, de traitements hormonaux, d'antihypertenseurs et d'antioxydants. L'expérience acquise au cours de ces études a soulevé des questions importantes concernant la sécurité et a fait ressortir des défis importants quant au plan de ce type de recherche. Ces essais nécessitent de très grands échantillons et entraînent des coûts prohibitifs. À l'avenir, on devrait considérer enrichir les groupes en incluant des sujets ayant des facteurs de risque afin d'augmenter le taux de progression à la MA/démence. Des stratégies novatrices seront également nécessaires pour recruter et maintenir la participation des sujets aux études étant donné le suivi à long terme, les bénéfices perçus comme étant modestes et le taux de risques/bénéfices qui peut changer pendant l'étude. Il est à prévoir que des ECRs en prévention primaire seront présentés aux organismes de régulation pour approbation et étiquetage du conditionnement des médicaments et que des critères d'évaluation des données ainsi générées devront être développés.

There are approximately 350,000 Canadians estimated to be suffering from dementia today, the majority (65%) from Alzheimer's disease (AD). The incidence rate of dementia in Canada is estimated at 20.6 new cases per 1,000 per annum. With the projected growth of the senior population, the number of affected individuals is predicted to increase to over a million in the next three decades.[1] The associated costs of dementia are incalculable for the patients and their families, and are anticipated to be staggering for Canada's health system. In 1991 a conservative health-economic study from the Canadian Study of Health and Aging (CSHA) estimated the cost of care at $3.9 billion per year, with anticipated escalating forward costs.[2] Taken together, these data provide a pressing target for aging and dementia research directed at enabling individuals to maintain

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their cognitive capacity into old age, delaying the onset of impairment, and reducing the number of people affected by dementia. In this context, research strategies are now aiming at the prevention of AD and other dementias (AD/dementia). This paper proposes a framework for studies on the prevention of AD/dementia, examines candidate interventions for prevention and addresses the challenges that research will face in testing their efficacy.

WHAT IS MEANT BY PREVENTION OF AD/DEMENTIA

Primary prevention in AD/dementia refers to delaying the development of the full-blown state of clinically expressed disease in normal individuals, while secondary prevention refers to delaying the progression from earliest symptom expression to an overt disease state. Tertiary prevention coincides with treatment, aiming to slow, stop or reverse the progression of overt clinical disease. Because the pathogenesis of AD/dementia is believed to begin years before symptom expression and its onset is impossible to date, the lines between the state of normal, early and overt disease are imprecise. At present the clinical states of AD/dementia and its expressed symptoms are the only available endpoints for prevention studies.
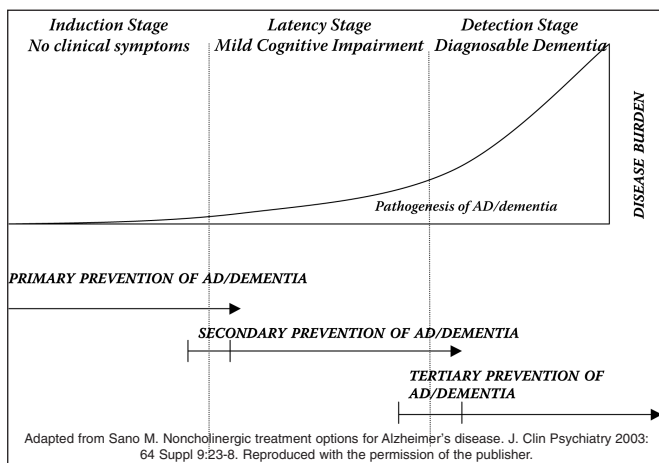
Figure: *Pathogenesis, clinical states and prevention approaches to AD/dementia.*

The Figure presents the conceptual model of the relationship between the clinical stages of disease development and the three preventive approaches, set against the continuum of the pathological process underlying dementia.[3] At the induction stage there are no clinical symptoms present despite the early subtle brain changes that are believed to occur in individuals who are eventually destined to develop the disease. At the latency stage, there are clinical symptoms, currently known as Mild Cognitive Impairment (MCI)[4] or Cognitive Impairment Not Dementia (CIND).[5] These symptoms can be accompanied by

more defined pathological processes measurable on MRI,[6,7] PET,[8,9] and post-mortem neuropathology.[10] The percentage of MCI cases that advance to AD/dementia is 10 to 15% per annum,[11] compared to 1 to 2% for normal subjects.[1] Mild Cognitive Impairment is therefore an ideal stage for secondary preventive interventions. Where MCI does advance to AD/dementia, the detection stage of diagnosable AD/dementia is reached, with its pathological cascade of apoptosis, inflammatory changes, increasing amyloidopathy and tangle formation.

There is an important current assumption underlying primary prevention of AD/dementia. For successful prevention to occur, the onset of the disease would have to be delayed in a sizeable group of at-risk individuals some of whom will die of other causes prior to the diagnosable AD/dementia state. It has been calculated that interventions capable of producing even a modest delay in onset, such as 1 year, would reduce AD/dementia prevalence by 7% in 10 years and by 9% in 30 years. Delaying the onset by 5 years could potentially reduce the prevalence by 40% in 10 years and by as much as 50% in 30 years.[12]

HOW TO IDENTIFY CANDIDATE INTERVENTIONS

Research on prevention of AD/dementia has been —and will likely continue to be— driven by evidence of protective factors emerging from retrospective case-control and prospective cohort studies of dementia. A large number of medication, health and lifestyle factors including the use of statins,[13-15] non-steroidal anti-inflammatory (NSAID) drugs,[16,17] vitamins,[18] estrogens,[19,20] participation in cognitively demanding activities,[21-23] and physical exercise,[24] have been associated with a reduced risk of dementia. These associations suggest that a spectrum of interventions —pharmacological treatments, nutritional supplements and lifestyle modifications— might have preventive effects. However, these association studies must be tested through randomized controlled trials (RCTs) before any intervention can be scientifically accepted and considered for widespread application within the healthy population. The Women's Health Initiative Memory Study (WHIMS) found that treatment with conjugated equine estrogen, alone or in combination with medroxyprogesterone, was associated with an increased risk of developing cognitive impairment and dementia.[25,26] The WHIMS outcome serves as a vivid reminder that factors identified as protective of AD/dementia in association studies do not necessarily have a preventive effect when tested more definitively in an RCT.

Beyond the epidemiological leads, the risk-benefit ratio of candidate interventions must be carefully considered. Primary prevention interventions should be sufficiently safe to be given to healthy normal individuals without causing harm. They should be affordable such that widespread use can follow. In addition, compliance needs to be high and maintained over long periods of time. Lastly, any such intervention should ideally have a biologically plausible mechanism of action within the framework of AD/dementia pathogenesis.

CURRENT STATUS OF PRIMARY PREVENTION TRIALS

To identify primary prevention RCTs of AD/dementia, PubMed and the US National Institutes of Health clinical trials

web site (www.ClinicalTrials.gov) were searched. The search yielded eight primary prevention RCTs summarized in the Table. These trials address the efficacy and safety of NSAIDs (Naproxen and Celecoxib), hormonal therapy (estrogen and progesterone), antihypertensive drugs (Nitrendipine, Enalapril and Hydrochlorothiazide; Candesartan), antioxidants (Ginkgo Biloba) and supplements (Vitamin E and Selenium). The antihypertensive drug trials (Syst-Eur and SCOPE) have been completed, with mixed results. In Syst-Eur a reduction in dementia incidence was observed in the treated group,[27] whereas in SCOPE there was no difference in incident cases between the treated and control group.[28] Three RCTs (ADAPT, WHIMS and PREPARE) have been halted because of emerging safety concerns. ADAPT was discontinued for reasons of unacceptable toxicity, where a risk of cardiovascular events in association with naproxen arose.[29] The WHIMS and PREPARE trials of conjugated equine estrogen alone, or in combination with medroxyprogesterone acetate, have been halted because of increased risks of breast cancer and cardiovascular problems.[25] GEMS,[30] GuidAge,[31] and PREADVISE[32] are in process, with results not anticipated for some considerable length of time.

This first generation of trials does not address the full range of potentially efficacious preventive strategies. Of potential interest for future primary prevention trials will be agents with anti-amyloidogenic action, hyperlipidaemia-lowering drugs including statins,[33,34] and agents capable of reducing hyperhomocysteinemia, neuronal DNA damage and apoptosis.[35]

DESIGN AND METHODOLOGICAL CHALLENGES FOR PRIMARY PREVENTION RCTs

Prevention RCTs face unique challenges, some of which have already emerged from the first generation of trials.
(1) Sample sizes and costs: As seen in the Table, primary prevention RCTs have required very large sample sizes (n=900

Table: Placebo-controlled AD/dementia prevention RCTs (ongoing and completed)

Trial (Acronym)	Status	Intervention	Subject selection criteria	Duration (years)	Overall estimated incidence rate (% per year)	Planned sample size
PREPARE	Discontinued	Conjugated equine estrogen alone Conj. equ. estrogen + medroxyprogesterone acetate	Female sex Family history of AD Age ≥ 65	3	5	900
ADAPT	Discontinued	Naproxen or Celecoxib	Family history of dementia Age ≥ 70	5 – 7	3 - 3.4	2,800
SYST-EUR	Completed	Nitrendipine and/or Enalapril and/or Hydrochlorothiazide	Systolic hypertension Age ≥ 60	5	1.6	3,000
SCOPE	Completed	Candesartan cilexetil	Systolic hypertension Age 70 to 89	3 - 5	2.4	4,000
GEMS	Ongoing extended	Ginkgo biloba	Age ≥ 75 (≥ 71 if of African ancestry)	5	4	3,000
GUIDAGE	Ongoing	Ginkgo biloba	Age ≥ 70 Memory complaints	5	Not available	2,800
WHIMS	Discontinued	Conjugated equine estrogen alone Conj. equ. estrogen + medroxyprogesterone acetate	Female sex Age ≥ 65	6	2	8,300
PREADVISE	Ongoing	Vitamin E or Selenium or Both	Age ≥ 62 (≥ 60 if of African or Hispanic ancestry)	9-12	1	10,700

to 10,700, average roughly 4,500) and long follow-up times (3 to 12 years, average roughly 6 years). These numbers have been necessary because of the low projected incident rate of dementia (range 1 to 5% per year) in the study populations. In turn the costs have been formidable, not likely sustainable in the Canadian funding environment. The two largest trials (WHIMS and PREADVISE) have targeted entirely non-selected study populations whereas the other trials have enriched their study samples with a limited number of AD/dementia risk factors to increase the incidence rate and reduce the number of required participants. These enriching risk factors have included a family history of AD/dementia in a first-degree relative,[29] old age,[30] systolic hypertension[27,28] and memory complaints.[31] Efforts will be warranted in future trial designs to increase the rate of dementia progression by further enrichment techniques, that might include a larger number of risk factors related to demographics, genomic profiles, vascular history and neuroimaging. The settings of the research study and the source of recruited subjects likely impact progression to AD/dementia rates and should also be carefully considered as a potential enrichment technique.

Enrichment of study samples with AD/dementia risk factors can be viewed as a potential strategy to optimally investigate putative preventive agents. Smaller samples could establish proof-of-principle as a prelude to larger-scale studies. This would also allow a range of existing/emerging epidemiological leads to be pursued within a reasonable time frame. Within enriched studies the magnitude of treatment effect sizes could be assessed.

(2) Projected rates of progression to AD/dementia: The projected progression rates appear likely to have been overestimated in the initial primary prevention RCTs. This raises important considerations for future studies with some speculation. The participation in a prevention trial may carry with it a beneficial impact on subjects' health that extends beyond the intervention that is being tested. Subjects may become more motivated to engage in health promoting behaviours including diet, exercise patterns and other risk-modification. They benefit from receiving careful medical follow-up within the trial over long periods of time, with appropriate identification and treatment of new health problems. In interventions that are non-prescriptional, the non-protocol use of the target treatments cannot be precluded as these are usually readily available and subjects may wish to 'hedge their bets'. By their nature, prevention trials may attract highly health-conscious subjects who are not representative of the populations from which the initial AD/dementia incidence rates have been derived. Taken together, these factors may culminate in unattainable projected rates of AD/dementia progression, resulting in the need for additional time and further resources to complete trials (see Table).

(3) Recruitment and retention: Innovative strategies will be needed to recruit and retain subjects in prevention trials. The recruitment of elderly participants into long-term studies is known to be problematic,[36] yet this is the group with the highest risk of progression to AD/dementia. As previously pointed out, there may be a potential problem of over-representation of very successfully aging subjects. This has already been reported in the Syst-Eur trial where subjects' median MMSE score at study entry was 29.[27] Recruitment problems may be further

exacerbated by the requirement of an informant for participation in the trial.

Retention of subjects will also pose problems, given long follow-up periods, modest perceived benefit and the potential for the risk-benefit ratio to change during these periods (e.g. NSAIDs in ADAPT, and estrogens in PREPARE and WHIMS). The first generation of trials underscores that non-adherence and loss to follow-up will be significantly higher than predicted. Provisions will have to be made for sample sizes that preserve adequate power through trials. To enhance compliance, follow-up strategies that do not involve on-site visits (e.g., telephone interviews) may be useful, as might the conduct of the study within usual care settings, i.e. General Practitioner offices.

(4) Study endpoints: The clinically defined endpoints of AD/dementia prevention RCTs have intrinsic limitations. The validity of clinical states (normal, MCI, dementia) and state transitions is limited by the absence of conclusively established biological markers within a continuous disease process. Yet, time to diagnosis of AD/dementia is the primary outcome measure in RCTs and its accurate determination is critical. In multi-centre RCTs, rater and centre biases in the measurement of time to diagnosis can be anticipated. On the horizon, biomarkers in development[37-39] may assist, or even become surrogate outcomes; however at present they cannot provide evidence of efficacy independent of clinical criteria.

(5) Timing of interventions: Prevention RCTs will have to systematically investigate the relation between time of intervention and treatment effect. The WHIMS trial found that treatment with estrogen plus progestin was unsuccessful in reducing the incidence of AD/dementia in women aged 65 years or older,[25] though it has been suggested that if such treatment were initiated around menopause (10 years earlier), there might have been a positive treatment effect.[40] There have been suggestions that also other pharmacological interventions may exert their most significant effects in midlife, long before the age of concern for AD/dementia.[41]

CONCLUSIONS

Research on the therapeutics of AD/dementia has traditionally focused on treating diagnosed disease. However researchers in the field have increasingly advocated that attention be turned to the possibility of preventing dementia.[42-44] Currently the primary prevention of AD/dementia should be understood as delaying the onset of diagnosable disease. In turn this delay will effectively eliminate a number of AD/dementia cases as individuals die of other causes before they cross the threshold of diagnosable disease. Evidence of protective factors already exists and offers good leads as to candidate interventions that might be effective. The first prevention RCTs have been designed to test NSAIDs, hormonal therapy, antihypertensive drugs, antioxidants and supplements. The experience of these RCTs has indicated safety concerns as a key issue in research on preventive interventions. Significant design and methodological challenges have been highlighted that will need to be addressed in future trials.

It is foreseeable that regulatory authorities will be presented with primary prevention RCTs for approval and labelling. The regulatory criteria to evaluate such evidence will need to be developed. These decisions about approval and labelling of

preventive interventions will have to define the acceptable risks and the standards for minimum treatment effect sizes.

DECLARATION

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