Preventing Dementia

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ABSTRACT: Primary prevention will become increasingly important as dementia prevalence increases and effective retardive therapies are developed. To date, only one randomized controlled trial (involving treatment of systolic hypertension) has demonstrated that the incidence of dementia can be reduced. Physicians should remain alert to possible secondary causes of dementia and correct these whenever possible. Primary and secondary prevention of stroke should reduce dementia related to cerebrovascular disease either directly or as a comorbid factor in Alzheimer's disease (AD). Epidemiological studies have revealed a number of risk factors for AD including genetic mutation, susceptibility genes, positive family history, Down's syndrome, age, sex, years of education, head trauma and neurotoxins. In case-control studies non-steroidal anti-inflammatory medication and estrogen replacement therapy appear to decrease the relative risk of developing AD. Further research to develop and test preventative therapies in AD and other dementias should be strongly encouraged.

RÉSUMÉ: Prévention de la démence. La prévention primaire va devenir de plus en plus importante à mesure que la prévalence de la démence augmente et que des stratégies efficaces pour en retarder l'apparition sont développées. Pour l'instant, une seule étude randomisée contrôlée (traitement de l'hypertension systolique) a démontré que l'incidence de la démence peut être réduite. Les médecins devraient demeurer vigilants pour détecter la présence causes secondaires de démence et les corriger si possible. La prévention primaire et secondaire de l'accident vasculaire cérébral devrait diminuer l'incidence de la démence reliée à la maladie cérébrovasculaire, soit directement ou comme facteur de comorbidité dans la maladie d'Alzheimer (MA). Des études épidémiologiques ont identifié certains facteurs de risque de la MA, dont des mutations génétiques, des gènes de susceptibilité, une histoire familiale positive, le syndrome de Down, l'âge, le sexe, la scolarité, les traumatismes crâniens et des neurotoxines. Dans les études cas-témoins, les anti-inflammatoires non stéroïdiens et l'oestrogénothérapie de remplacement semblent diminuer le risque relatif de développer la MA. On devrait encourager les recherches pour développer et évaluer des mesures thérapeutiques préventives dans la MAet les autres démences.

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The concept of primary prevention of dementia is relatively new but will assume increasing importance as dementia prevalence increases in our graying population[1] and as the etiological factors and molecular pathogenetic mechanisms of primary degenerative dementias become better understood.[2] Current definitions of dementia require memory impairment and cognitive dysfunction in at least one other domain of sufficient degree to interfere with social functioning.[3] In this review we emphasize prevention of dementia in individuals who are cognitively normal but may be at risk for dementia, or who are cognitively impaired but not yet demented. Potential preventative measures include avoidance or control of modifiable risk factors to prevent progression to clinically manifest dementia. Secondary prevention of the degenerative dementias is equivalent to treatment, which is discussed in a companion article in this series. Recent clinical trials have provided evidence for modest symptomatic stabilization with so-called cognitive enhancing agents. If effective retardive therapies or neuroregenerative strategies are developed, in the future it may be possible to delay progression or even partially reverse dementing illness.

In reviewing this topic based on Medline searches of dementia risk factors and prevention, the following rules of evidence were applied. Level I evidence is derived from at least one properly conducted randomized controlled trial (RCT). Randomization of administration of a particular intervention makes it possible to infer causality, if a statistically significant difference is found. Level II evidence lacks the randomization maneuver but can be used to suggest an association between certain factors and outcomes. A causal inference cannot be drawn from such evidence. Three types of well-designed Level II studies are considered: controlled trials without randomization (Level II-1); retrospective case-control or prospective cohort analytic studies, preferably multicentre (Level II-2); and

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comparisons between times or locations where the intervention was or was not given (Level II-3). Dramatic findings in uncontrolled experiments such as the discovery of penicillin would be an example of landmark Level II-3 evidence. Level III evidence is derived from expert opinion based on descriptive reports, clinical experience, reports of experts, etc. Potential interventions to prevent neurodegenerative dementias arise primarily through Level II-2, 3 evidence; i.e. associations between certain risk factors or interventions and Alzheimer's disease (AD) have been uncovered but causal links have not been established.

Primary prevention of dementia

Until recently it has been difficult to identify individuals at sufficient risk of dementia to warrant the potential risks of pharmacotherapy, even if an effective agent were available. With identification of highly penetrant, autosomal dominant genetic mutations in familial AD[4] and better understanding of genetic susceptibility and other epidemiological factors, individuals at high risk of developing dementia can now be identified and could be candidates for preventative treatment if neuroprotective agents emerge.[5] Elderly individuals with mild memory complaints, called Mild Cognitive Impairment, are at high risk for dementia, with conversion rates to dementia of 25-50% over two to four years, depending on the series.[6,7] Certain neuropsychological measures[7-9] and/or quantitative brain imaging techniques can help to predict which individuals are likely to develop dementia.[10-14] Thus, it is possible to identify a high risk group who would benefit if safe prophylactic interventions to prevent dementia become available. Studies comparing possible treatments (vitamin E, donepezil, rivastigmine, cox II inhibitors) to placebo are currently underway with up to three years follow-up. Cohort and case-control studies (Level II–2 evidence) suggest that estrogen replacement (ERT) and nonsteriodal anti-inflammatory therapy (NSAIDs) may already be serving a protective role in AD (see sections VI and VII below). The period of observation needed to establish a Level I claim for prevention would be longer (three to five years) than is currently feasible or ethical for randomized, placebo-controlled clinical trials of clinically diagnosed AD. A challenge facing such endeavours is that the advent of dementia may be an elusive end-point modified by individual factors such as genotype, education, age, sex and concomitant illness (eg. cerebrovascular disease). Dementia is an outcome measure more complex than those commonly studied, such as death, heart attack, stroke, in other disorders. Despite these impediments, the increasing ability to identify profiles of individuals at high risk for dementia and the emergence of neuroprotective strategies will continue to stimulate such prevention trials in the near future.

Primary prevention in Alzheimer's disease in relation to risk factors

A number of risk factors for AD have been identified and are listed in Table I.[15] Some of these are potentially modifiable but so far there have been no published clinical trials investigating primary prevention. Not all studies agree on the importance of all the factors; the Canadian Study of Health and Aging (CSHA), for example, examined over 16 factors but only five emerged as significant, namely family history, education, NSAID use or arthritis, head injury (borderline), and occupational exposure to glues, pesticides and fertilizers.[15]

Table I: Putative Risk Factors for Dementia due to Alzheimer's Disease)

Increases Risk
Genetic mutations[1,14,19,22]
Genetic susceptibility (apolipoprotein E e4)
Diabetes mellitus
Positive family history
Substandard education
Older age
Female Sex
Significant head injury
Cerebrovascular disease
Decreases Risk
NSAID use
Estrogen use
Uncertain
Alcohol
Cigarette smoking
Toxins – aluminum, glue, fertilizers, pesticides

I. Genetic factors

a) Mutations: Individuals at highest risk for AD are those with a family history of the early-onset, autosomal-dominant forms of the disease, which account for less than 1% of cases.[4] In these families, children are at 50% risk of developing the disease. Thus, if a safe prophylactic therapy were available, it would be logical to target these individuals. Now that certain gene mutations can be identified, these odds could be changed in some family members to the normal life-time risk of developing AD in the general population (15%),[16,17] or to 100% in family members with the pathologic mutation, since the gene mutations, for example, on chromosome 1 and 14 are highly penetrant.

b) Susceptibility Genes – Apolipoprotein E (ApoE): Another important genetic risk factor for AD, working synergistically with environmental factors such as trauma or stroke, is the ApoE genotype. There are three ApoE alleles in the human genome, ApoE e2, e3 and e4.[18] Biologically, ApoE e4 has been found to increase neurofibrillary tangle formation and amyloid plaque density[16-18] and to decrease compensatory synaptogenesis especially in the hippocampus.[19] There is now solid epidemiological evidence (Level II-2) that the presence of the e4 allele is associated with an increased risk of AD. One e4 allele increases the risk of AD three times and the presence of both e4 alleles increases the risk up to 30 times.[17,18] This striking allelic association with AD has been replicated in many studies across all populations despite ethnic variation in the frequency of the different genotypes.[20-22] The presence of an e4 allele shifts the onset of AD forward by a decade but does not appear to change

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the rate of progression once the disease manifests.[17,21,23,24] To put the ApoE influence in the perspective of the 15% life-time overall risk of AD in the general population, the presence of an e4 allele increases this to 29% and its absence reduces the risk to 6%.[17] Recent evidence suggests that apolipoprotein status accounts for cases of AD with onset before age 70,[24] who represent only 10% of the AD population. Thus, ApoE appears to be a genetic susceptibility factor which makes the individual more vulnerable to other environmental risk factors. Currently, ApoE status is not regarded as predictive of AD but it may be useful in diagnosis.[25]

c) Family History: It has been recognized that a family history of AD present in approximately a quarter of AD subjects, depending on the series[15] increases the risk of the disease and recent surveys have allowed quantification of that risk. In the CSHA, the odds ratio for AD was increased to 2.4 (CI: 1.3 – 4.3) with one first degree relative affected and 4.2 (CI: 1.2 - 14.7) for two or more relatives with AD.[15] A meta-analysis of seven case-control studies with respect to family history revealed similar results; the odds ratio was 3.5 (CI: 2.6 – 4.6) for one first degree relative and 7.5 (CI: 33 – 16.7) for two or more.[26] Interestingly, although the relative risk decreased with increasing age of onset, even with age of onset greater than 80, the relative risk was still elevated (2.6, CI: 1.3-5.2). There was an increased risk of similar magnitude with a family history of Down's syndrome and Parkinson's disease.[26]

d) Down's Syndrome: It has been recognized for some years that almost all individuals with Down's syndrome over age 40 have neuropathological changes typical of AD[27] but dementia does not usually develop until the 50s and 60s, with varying incidence depending on the series.[28-30] In one of the largest prospective studies in this population (N=307), monitored by serial clinical, cognitive and EEG assessments, 56 Down's syndrome individuals developed dementia with a mean onset of 56 years. Prevalence increased from 11% in the 40-49 age group to 77% in those 60-69 years of age and the one individual surviving to age 70 was demented.[31] Other factors, in addition to triplication of the beta amyloid gene located on chromosome 21, likely play a role in the clinical expression of Alzheimer's pathology in Down's syndrome. Clearly, aging individuals with Down's syndrome are at high risk for AD with an earlier age of onset than is typical for the disease. As a high-risk group, persons with Down's syndrome will obviously be an important target population for prevention trials. In the meantime, however, more studies are required to determine incidence and risk factors and to develop reliable screening tools to detect cognitive decline in these subjects.[28]

II. Demographic factors

Increasing age is a potent risk factor for AD, in which prevalence climbs from 2% for those aged 65 to 43% for those aged 95.[1] The prevalence of AD is higher in women consistently throughout each age decade,[1] a finding which does not appear to be simply attributable to greater longevity, though this finding is not unanimous.[15,32] Several well-designed cohort and case-control studies also suggest that substandard education is associated with a higher incidence of AD.[15,33,34] The extent to which this is related to indigenous factors such as synaptic connectivity and inborn intellectual capacity or exogenous factors such as socio-economic status, nutrition in early life, and the opportunity for mental stimulation throughout the life-span, has not been delineated. More recent longitudinal studies have not confirmed the relationship between AD and fewer years of formal education. Nevertheless, one implication of available evidence is that increasing standards of education could be considered a public health measure for the prevention of dementia in later life.

III. Head trauma and other brain injuries

Head injury with loss of consciousness has emerged in several epidemiological studies as a risk factor for AD.[15] A meta-analysis of 11 such studies yielded a pooled relative risk of 1.82 (CI: 1.3 – 2.7).[35] Amyloid deposits have been demonstrated to occur within days of severe traumatic brain injury as part of an acute phase response to neuronal injury. Dementia pugilistica (punch drunk syndrome), presumably due to repeated traumatic brain injury, is associated with neurofibrillary tangles histologically indistinguishable from AD.[36,37] This has fuelled the epidemiological search for a link between traumatic brain injury and AD. Some recent studies suggest that the association between AD and head trauma exists primarily for ApoE e4 carriers[38,39] but another study did not confirm this[40] or found only a trend.[41] In contrast, longitudinal prospective studies, such as the Rotterdam Study, concluded that head trauma does not increase the subsequent risk of AD or other causes of dementia.[42]

With respect to possible infectious etiologies, some studies suggest that herpes simplex labialis might signify subclinical brain reactivations, which may play a role in the pathogenesis of AD in ApoE e4 carriers.[43,44] This is partly based on the fact that abnormal amyloid precursor protein processing is facilitated by ApoE e4 in normal cellular repair reactions triggered by environmental factors, such as head injury, herpes simplex reactivations or stroke.[45,46]

Based on some case-control studies, prevention of head trauma could be considered primary prevention for dementia, particularly in individuals with increased genetic susceptibility such as the presence of ApoE e4. The use of helmets for sports activities, safety belts in cars and maneuvers to reduce falls in the elderly are worthy in themselves and may, in addition, reduce later risk of dementia.

IV. Exposure to neurotoxins

a) Aluminium: Aluminum has been implicated as a potential neurotoxin in AD, although this remains controversial.[15,47-50] Increased aluminum content in the nuclei of AD neurons has been reported and it has been hypothesized in individuals predisposed to AD that aluminum enters neurons more readily, binds to their nuclei and accelerates cell death.[51] A follow-up study of miners subjected to aluminum dust as a putative prevention measure for silicosis in the MacIntyre mines in northern Ontario, has revealed an increased incidence of dementia in the miners so exposed.[52] Furthermore, aluminum levels in the local water supply appear to correlate with the incidence of AD in that location.[53] One study has suggested that decreasing aluminum levels in the water supply could reduce the incidence of AD[53] but this would be a costly public health measure. Not all forms of aluminum appear to be equally absorbed and because of ongoing dispute concerning the validity

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of these epidemiological studies,[48-50] public health authorities have so far not acted on this information. A double-blind, randomized, placebo-controlled pilot study of aluminum chelation with deferoxamine in advanced AD reported a slower decline in patients receiving deferoxamine injections compared to controls who received an oral placebo.[54] Chelation treatment is associated with some toxicity and can only be delivered by injection but further study in a larger sample has not been undertaken.

b) Other chemicals: In their investigation of possible risk factors for AD, the Canadian Study for Health and Aging found that exposure to glues, chemical fertilizers or pesticides was associated with an increased risk of AD.[15] Thus, reduction in chronic exposure to these compounds could be a preventative measure for the development of AD.

c) Cigarettes/Smoking: The relationship between cigarette smoking and AD has been studied in several case-control surveys.[55-57] However, the gene pool of surviving smokers is different from that of nonsmokers and the difference in survival of smokers and nonsmokers at older ages, when AD most frequently occurs, may be sufficient to account for this apparent negative association.[58] Stimulation of nicotinic cholinergic receptors could provide a rationale for a negative association of smoking with AD. Recently, a prospective population study of 6,870 people over age 55 followed for a mean of 2.1 years revealed that smokers had a higher risk of AD (relative risk 2.3, 95% CI: 1.3 – 4.1), particularly in those not carrying the ApoE e4 allele (relative risk 4.6, 95% CI: 1.5 – 14.2).[59] While the evidence remains contradictory, the potential for serious harm to health caused by smoking outweighs any potential benefit and all tobacco use should be discouraged.

V. Anti-inflammatory medications

Inflammatory cells and acute phase proteins are found in amyloid plaques in AD. Activated microglia cells aggregate in the area of amyloid plaques and complement activation, including membrane attack complex, is present around neurofibrillary tangles and dystrophic neurites.[60,61] The release of toxins by these inflammatory cells, including free radicals, leukotrienes and cytokines may further contribute to ongoing neuronal damage.[60-63] Thus the concept that NSAIDs might slow down or prevent the development of AD has emerged and has inspired several retrospective case-control studies, which have suggested that anti-inflammatory drugs may be protective in AD.[15,60,63-65] McGeer et al[66] critically reviewed 17 such studies, in which arthritis and use of NSAIDs or steroids were evaluated as risk factors for AD. The combined data from the population-based studies of rheumatoid arthritis revealed an odds ratio of 0.19 for AD (CI: 0.09 – 0.41) and for use of NSAIDs, the odds ratios was 0.50 (CI: 0.34 – 0.72).[66] Case-control studies of steroids or NSAIDs revealed statistically significant risk reduction to 0.66 (CI: 0.43 – 1.0) for steroids and 0.56 (CI: 0.42 – 0.74) for NSAIDs.[66] Thus, according to this meta-analysis, NSAID use was associated with approximately 50% relative risk reduction for AD. A subsequent longitudinal study tracked NSAID use in 1,686 participants and found that NSAID use of > two years yielded a relative risk for AD of 0.40 (CI: 0.19 – 0.84), compared to 0.65 for < two years (CI: 0.33 – 1.29).[67] The strength of this study was that information on NSAID use was gathered prospectively. Another noteworthy report involved 50 elderly twin pairs (26 monozygous) who were discordant for the onset of AD symptoms by three or more years.[68] History of arthritis and anti-inflammatory drug use was carefully documented. The onset of AD was inversely associated with steroid or NSAID drug use with an odds ratio of 0.24 (CI: 0.07 – 0.74), even after controlling for arthritis.[68] Finally, in a group of AD subjects, those taking NSAIDs (N=32) performed better on cognitive tasks compared to nonNSAID users (N=177) and showed less decline over one year, further supporting the possibility that NSAIDs may serve a protective role in AD.[69] A preliminary observation that histamine – H_2 blockers might also provide a protective effect, independent of NSAID use, was not confirmed in a subsequent population study.[70]

The limitations of the case-control and population methods are best overcome by a hypothesis-driven, randomized, placebo-controlled trial but efforts in this direction have been very limited. Indomethacin is a lipophilic NSAID which readily crosses the blood brain barrier.[71] A pilot study of 44 demented subjects with AD, with an entry Mini Mental State Examination (MMSE) greater than 16, were given placebo or 100-150 mg of indomethacin per day for a period of six months. The Alzheimer's Disease Assessment Cognitive Scale (ADAS-Cog), language tests, MMSE and percentage change from baseline were used as outcome measures. Only 28 subjects completed the trial due to a high dropout rate attributed to side-effects (10/24 in the treatment group and 2/20 on placebo). Nevertheless, the treated group showed less decline ($p<0.03$).[72] A recent trial with diclofenac, however, showed no benefit,[73] and in another double-blind RCT of 138 AD patients who received either placebo or prednisone 20 mg daily for one month followed by 10 mg daily for one year, there was no measurable cognitive benefit at the completion of the study in the prednisone treated group.[74] Glucocorticoids should be used cautiously as they are known to affect hippocampal function adversely.[75] A recent study of chronic prednisone treatment in elderly subjects revealed selective impairments on tests of explicit memory, which are known to relate to hippocampal function.[76] The authors concluded that any potential benefit of steroid treatment might be outweighed by adverse iatrogenic effects on memory.

In summary, epidemiological studies and a small randomized, placebo-controlled pilot study suggest the anti-inflammatory drugs may be beneficial in retarding progression in AD. The toxic side-effect profile of these agents (particularly with respect to gastro-intestinal side-effects and potential gastro-intestinal hemorrhage) have tempered enthusiasm for their use in AD. A large scale, multi-centre study would be warranted if gastroprotective measures can be combined, or if a safer anti-inflammatory agent can be found.[77] The new generation of anti-inflammatory drugs, which selectively antagonise the secretion of the anti-inflammatory enzyme cyclo-oxygenase (Cox II inhibitors), may obviate these side effects and clinical trials are underway in AD and MCI.

VI. Estrogen replacement therapy (ERT)

Estrogen is more than a reproductive hormone. Ironically, postmenopausal women experience an estrogen-withdrawal state, while men continue to have estrogen available due to

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conversion of testosterone to estradiol in the brain. Estrogen has neurotrophic effects, especially on hippocampal neurons,[78] as well as anti-oxidant, neuroprotective actions.[79] The gene sequence for nerve growth factor contains an estrogen response element.[80,81] Estrogen and nerve growth factor receptors coexist on basal forebrain neurons, suggesting a synergistic action in maintaining neuronal viability.[82] Estrogen enhances synaptogenesis in hippocampal neurons[80] and may up-regulate choline acetyltransferase thereby enhancing cholinergic function.[80] It reduces the toxicity of beta-amyloid *in vitro*[83] and enhances cleavage of amyloid precursor protein into soluble form.[80,84] Furthermore, estrogen may modulate neurotransmission by increasing D_2 striatal receptors and 5-HT_{2A} receptors in the anterior frontal, cingulate and olfactory cortex of rodents.[85] In animal models it improves cerebral blood flow and cardiac output[80] and it may also have beneficial effects on platelet aggregation and serum lipids, all of which contribute to reducing the risk of stroke.[86]

An increasing number of human studies provide converging evidence for the importance of estrogen as a cognitive and mood enhancing agent.[85,87,88] Recent studies of cognitive patterns in men and women have demonstrated clearly that cognitive performance may be influenced by fluctuations in hormone levels.[89] Estrogen enhances mood state and selective aspects of memory in surgically or naturally postmenopausal women.[87,88,90] Sherwin and colleagues[91] have shown enhancement of verbal episodic memory using parenteral estrogen administered pre- and postsurgery in women undergoing ovarectomy. In a study of nondemented postmenopausal women, a higher index of estrogen exposure, based on age at menarche and menopause, time since menopause, time on ERT, postmenopausal weight and number of children breast fed, was found to be associated with better performance on verbal cognitive tasks and measures of attention after controlling for age and education.[92] The authors concluded that longer lifetime estrogen exposure improved later-life cognitive functioning. In another study of postmenopausal women, estrogen users performed better than non-users on all neuropsychological tests, particularly conceptualization and visuoconstructive skills, after correcting for multiple comparisons and controlling for age, education, blood pressure and activity levels. There were fewer white matter hyperintensities in estrogen-treated women on quantitative MRI as well.[93] However, in a large prospective US study of 6,110 women aged 48-67, performance on cognitive tests, including verbal memory and fluency tasks, did not differ in relation to ERT.[94]

In case-control studies, with one exception,[95] a number of different lines of evidence consistently point to beneficial effects of estrogen on cognitive function in women.[96-99] In most of these studies, the odds ratios for developing AD have been calculated for subjects who are taking or not taking ERT, based on retrospectively or prospectively acquired information and reductions in the 50% range have been reported.[96-99] However, a recent meta-analysis of ten studies of postmenopausal ERT involving over 3,000 women (including cross-sectional, case control and clinical trials), concluded that the relative risk of developing AD after exposure to estrogen was .71 (95% CI .53-.96).[100] The risk reduction provided by ERT in AD may also extend to Vascular Dementia (VaD). In a study of 93 subjects with probable AD, 65 subjects with VaD and 148 normal control subjects, logistic regression revealed that ERT was associated with almost 50% reduced risk for dementia in both etiologies.[86]

In a trial of tacrine for probable AD with MMSE scores between 10-26, there were 343 women, 150 of whom were on ERT. The authors found that prior and continuing ERT enhanced the response to tacrine and recommended further randomized trials to investigate this.[101] Whether estrogen should be a component in chemotherapeutic options in AD remains to be determined in properly designed clinical trials. The potential benefit of estrogen alone as a cognitive enhancer in AD has been cast in doubt by a double-blind, placebo-controlled study of estrogen in 120 women with probable AD. After one year, there was no evidence of improvement in cognitive, functional or global measures in those treated with estrogen.[102]

In summary, the majority of case-control studies have shown a reduced risk for AD in postmenopausal women using ERT but not always in relation to duration of use. This is true not only in retrospective surveys, with all the attendant problems in retrospective determination of drug use, diagnosis etc. but also in the few prospective studies that have been published, suggesting a true association for AD and possibly VaD, though the latter has been less studied. An RCT in postmenopausal AD women showed no benefit but prevention of disease may be a different matter and trials are underway to investigate this. Community surveys suggest that 10-20% of older women and 50% of younger postmenopausal women are on ERT.[103] Present evidence is insufficient to guide clinical practice, which will continue to be individualized, based on patient preference and risk calculation weighing potential beneficial effects of ERT in reducing osteoporosis, cardiovascular and cerebrovascular disease and possibly dementia, against the potential increased risk of breast and uterine cancer.

Prevention of secondary dementias

With respect to "secondary" dementias in which a proximate cause such as infection, drugs, metabolic derangement or mood disorder can be detected by appropriate investigation, prevention of dementia would be considered standard care without the need for clinical trials, particularly in the case of disorders which can be identified and treated on the basis of systemic symptomatology prior to the development of cognitive impairment. For example, timely treatment of hypothyroidism prevents the dementia that might supervene if the condition were overlooked. Similarly, B_{12} deficiency can manifest as anemia or subacute combined degeneration of the spinal cord prior to dementia; it can be readily detected by a blood test and effectively treated, thereby avoiding emergence of dementia. Normal pressure hydrocephalus can be suspected on the basis of a triad of gait disorder, incontinence and cognitive impairment in the presence of ventricular enlargement disproportionate to sulcal atrophy on a structural brain scan. If shunting is successfully carried out in a timely manner, dementia may be avoided or ameliorated. Likewise, effective treatment of infectious diseases of the central nervous system such as syphilis, herpes simplex encephalitis and human immunodeficiency virus may prevent or delay development of dementia. Treatment of depression can reverse the significant cognitive decline that sometimes accompanies

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mood disorder. However, it is noteworthy that depression in the elderly may be the harbinger of a dementing illness,[104] particularly when poorly responsive to treatment.[105] Avoidance of drugs with anticholinergic side-effects as well as sedative medications can preserve cognitive function in elderly individuals. Prolonged use of alcohol can also lead to dementia or to the disabling amnestic syndrome seen in Korsakoff's psychosis. Thus, treatment of alcohol addiction and control of alcohol intake can be viewed as a dementia prevention strategy, although a recent case-control study in France reported that moderate consumption of wine (three to four standard glasses per day) in the elderly was associated with a reduced odds ratio of 0.25 for AD.[106] (See also the new guidelines for low-risk drinking issued by the College of Family Practice of Canada.) In summary, the identification and appropriate treatment of secondary causes of dementia can be considered standard care, which, when successfully implemented, constitutes primary prevention of dementia.

Prevention of dementia due to stroke

The prevention of dementia related to cerebrovascular disease warrants special consideration. Careful management of cerebrovascular risk factors, insofar as this may prevent recurrent stroke and/or reduce progression of small vessel disease, could be regarded as a preventative treatment for VaD.[107] However, there are few long-term studies that actually confirm this, although one study is currently underway.[108]

In a recent review of key studies on risk factors for dementia associated with stroke, only age emerged as a clearly documented factor. Based on Level II evidence, ethnicity, education, hypertension, cigarette smoking, alcohol use, exposure to pesticides, liquid rubber or plastics, heart attack, diabetes, high cholesterol, size and number of infarcts and cerebral atrophy were also contributing factors[109-113] (see Table II). If multiple cortical and/or subcortical strokes can cause dementia - and this may be less common than once thought,[109,114] then reduction in the number of such events may reduce cognitive morbidity, although the relationship of hypertension and dementia is complex and may be age-dependent.[114,115]

Evidence that blood pressure control prevents the long-term development of dementia is gradually accumulating. Some prospective cohort studies have suggested that not only is higher blood pressure associated with a higher likelihood of dementia but also that the type of antihypertensive used may play a role. Specifically, in a longitudinal study of risk factors for coronary artery disease and stroke in men and women over age 65, performance on the modified Mini Mental State Examination (3MS) and severity of white matter hyperintensities on MRI were compared in 1,268 subjects on antihypertensive drugs. The use of calcium channel blockers or loop diuretics was associated with a significantly poorer 3MS score and more severe white matter disease than use of beta blockers, with no association found for thiazides or angiotensin converting enzyme (ACE) inhibitors.[116] Data from CSHA suggest that the use of calcium entry blockers is associated with more cognitive decline than other antihypertensive agents.[117] The reasons for these possible differential antihypertensive effects are not clear and more study is needed to determine if these findings relate to drug effects, including hypotension, patient selection or other factors.[115] In a Swedish study of 382 elderly nondemented subjects over age 70, followed for 15 years, subjects who developed dementia between ages 79-85 had significantly higher systolic (mean 178 vs. 164 mmHg) and diastolic (mean 101 vs. 92 mmHg) blood pressure at age 70 than those who did not become demented.[118] Presence of white matter lesions on CT at age 85 was also associated with higher blood pressure at age 70. Higher diastolic blood pressure at age 70 was noted in those later developing Alzheimer's dementia and at age 75 in those later developing VaD, further suggesting synergistic effects of cerebrovascular and AD.[118]

The most persuasive evidence that treating hypertension reduces the risk of dementia comes from the Syst-Eur trial.[119] In this study, over 2,000 cognitively intact older individuals with systolic hypertension (SBP 160-219: DBP less than 95 mmHg) were randomized to receive either nitrendipine (a calcium channel blocker) together with enlapril and hydrochlorthiazide if necessary to reduce SBP to below 150 mmHg, or placebo. After a mean follow-up of two years, the incidence of dementia in the placebo group was 7.7 per 1,000 patient years but was 3.8 per 1,000 patient years (50% reduction p=0.05) in the treated group. Interestingly, the numbers of VaD and AD were both reduced.[119,120] It was postulated that the calcium entry blocker nitrendipine may have exhibited neuroprotective effects.[119] Interestingly, while treatment of systolic hypertension in the SHEPstudy reduced the incidence of stroke, there did not appear to be any reduction in the incidence of dementia.[121]

A trial to investigate whether lowering blood pressure prevents cognitive decline in patients with cerebrovascular disease is currently underway. It incorporates genotyping to stratify risk and quantitative neuroimaging as a parallel outcome measure.[108] An ACE inhibitor (perindopril) is being compared to placebo in 6,000 patients considered to be at risk of cognitive impairment due to a history of stroke or transient ischemic attack. The follow-up will be for four years. A sub-study will be conducted on the effects of treatment on cognitive decline in relation to white matter hyperintensities on MRI.[108] This is one of the first and largest studies to target primary prevention of dementia in a cerebrovascular disease population.

Recent evidence suggests that cerebrovascular disease is a potent synergistic factor with Alzheimer pathology in the production of cognitive decline sufficient to classify as dementia.[122] In the "nun" study, quantitative neuropathological postmortem investigation showed that clinical dementia was more frequent (75%) when cortical infarcts were combined with AD pathology than with AD pathology alone (57%). The presence of lacunar infarcts in the basal ganglia and deep white matter made clinical dementia even more likely (93%).[109] The presence of any stroke increased the relative risk of clinical dementia in those with Alzheimer's pathology to 20 times. Also less AD pathology was required for the expression of dementia in the presence of cerebrovascular disease. Subjects with cerebrovascular disease alone, on the other hand, had a low incidence of dementia.[109] Thus, reduction in cerebrovascular disease may also be considered an important preventative measure for the dementia associated with AD; this may apply particularly to individuals with ApoE e4.[45]

Treatment of hypertension, heart disease, hypercholesterolemia, diabetes and reduction of smoking all contribute to the

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Table II: Summary of Risk Factors for Stroke-Related Dementia Based on Level II Evidence

Hypertension
Diabetes
Age
Sex
Race
Genetic factors
Education
Smoking
Heart attack
Cholesterol
Size and location of infarct
Infarct number
Cerebral atrophy
Periventricular white matter disease

reduction of stroke and indirectly of dementia. Stroke prophylaxis in individuals who present with cerebrovascular events, either as transient ischemic attacks (TIAs) or as strokes, could be considered secondary prevention of dementia as well as stroke.

In the context of stroke prevention, Level I evidence is available from several secondary prevention trials beginning with the demonstration that aspirin reduces stroke incidence by about 25%.[123-125] The reader is directed to other sources for a comprehensive review of these studies.[126] Level I evidence also exists that use of other antiplatelet agents can also reduce the frequency of stroke after TIA or completed stroke, for example, ticlopidine,[127] clopidogrel[128] and an aspirin-dipyrimadole combination.[129] Anticoagulation is indicated for prevention of stroke in chronic atrial fibrillation as both primary and secondary stroke prevention.[130] The NASCET study proved that for symptomatic carotid stenosis greater than 50% endarterectomy is beneficial in stroke prevention.[131,132] Endarterectomy may also reduce stroke incidence in patients with asymptomatic stenosis of the carotid arteries although the clinical utility of this remains controversial.[133] None of these studies, however, have specifically targeted prevention of dementia as an outcome; end points have usually included heart attack, stroke and death.

Numerous studies have been conducted primarily in Europe on the efficacy of various agents hypothesized to be useful in treatment of VaD. Pentoxifylline,[134] nimodipine,[135] hydergine,[136] propentofylline,[137] gingko biloba extract[138] and aspirin[139] have been investigated in this context. These trials have involved patients already diagnosed with dementia and are therefore classified as secondary prevention. Most studies have been small and although many positive results have been reported, few have met the rigorous design criteria required by drug approval agencies in North America. Very few studies have investigated these medications in nondemented subjects. One exception was a six week, placebo-controlled, randomized, double-blind study of pentoxifylline in 120 elderly subjects with cerebrovascular disorders. In addition to the treated and placebo groups, a third group received pentoxifylline plus psychological training. The results showed superior mental performance in the pentoxifylline groups and it was suggested that its therapeutic benefit could be improved by a simultaneous mental training program.[140]

Antioxidants

Oxidative stress may be important in the pathogenesis of AD. The oxidative damage induced by β-amyloid, the principal component of neuritic plaques and integral to the pathological changes in AD, can be reduced in cell culture by vitamin E and vitamin E can delay memory deficits in animal models.[141] An RCT comparing vitamin E (2,000 units), selegiline (5 mg bid), both drugs or placebo, conducted in over 400 individuals with moderately severe AD, showed benefit from both vitamin E and selegiline in delaying the end points of death, institutionalization or severe dementia by about one year, after correcting for initial MMSE, which was maldistributed by the randomization process.[142]

The theoretical benefits, spurred on by the results of this clinical trial, have led to the hypothesis that vitamin E may retard the progression of MCI to dementia. This is being investigated in a large RCT currently in progress in North America. A weakly positive RCT of gingko biloba extract in AD[143] has also led to a large US study now in progress.

Conclusion

In summary, despite an increasing ability to identify individuals genetically at risk or to detect preclinical disease, there is sparse evidence for primary prevention of dementia. For so-called secondary dementias, treatment of the proximate cause may prevent, partially reverse or stabilize cognitive impairment. Thus, family physicians should be alert to possible secondary causes of cognitive impairment and correct them where appropriate. In the particular case of preventing dementia related to cerebrovascular disease either directly or as a comorbid factor for AD, Level I evidence exists for both primary and secondary prevention of stroke and a large study is addressing prevention of dementia as an explicit goal.[108] This study underscores the importance of detecting and treating systolic hypertension and provides a promising means of reducing the incidence of dementia. Prudent physicians should detect and control risk factors for cerebrovascular disease and, in the presence of TIAor stroke, initiate appropriate investigations and secondary prevention procedures.

With regard to AD, numerous risk factors have been established mostly by case-control methodology and justify cautious action to modify such factors whenever possible. So far, Level I evidence to strengthen the rationale for such interventions is lacking with the exception of treatment of systolic hypertension. Clinicians should base decisions on the risk-benefit ratio for each individual, for example with NSAID or ERT use. Estrogen use in postmenopausal women may be justified on other grounds. Risk factors for less common primary degenerative dementias such as Frontal Temporal Degeneration (FTD).[144] and Lewy body disease[145] are as yet unknown, though a positive family history is present in approximately half of the subjects with FTD.

Table III summarizes the recommendations that can be made based on the available studies but it is clear that primary prevention for Alzheimer's and other degenerative dementias is

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Table III: Recommendations

1. Secondary Dementias	
When clinical conditions that can lead to cognitive impairment are uncovered by clinical and laboratory assessment, appropriate corrective treatment should be instituted, for example, thyroid replacement, alcohol abstinence programs, etc.	**LEVELIII, B**
2. Cerebrovascular Disease	
a) Treatment of systolic hypertension has been demonstrated to reduce the incidence of dementia.	**LEVELI, A**
b) By effectively treating other vascular risk factors such as cholesterol, diabetes, smoking cessation and prophylactic anticoagulation for chronic atrial fibrillation to prevent stroke, the risk of vascular and Alzheimer's dementias may also be reduced.	**LEVELIII, B**
c) The decision to treat TIAs and stroke by secondary prevention measures such as antiplatelets and anticoagulants (and carotid endarterectomy as appropriate) may likewise lower risk of Vascular and Alzheimer's dementia.	**LEVELIII, B**
3. Demographic and Environmental Risk Factors forAD	
Physicians should be aware of genetic risk factors for AD and follow recommendations under genetic screening. Evidence suggesting that substandard education (<6 years) and head trauma may increase the risk of AD would lend support to advocacy programs for minimum standards of education and for head injury prevention (such as the use of seatbelts when driving and helmets for cycling or other sports).	**LEVELIII, B**
4. Non-steroidal Anti-inflammatory Medication in AD	
The use of NSAIDs cannot be recommended on the basis of available evidence for dementia prevention but, if required for arthritis or other conditions, may afford some protection against the development of AD.	**LEVELII-2, C**
5. Estrogen Therapy	
Physicians should provide counseling on the risk and benefits of estrogen therapy in peri-menopausal and postmenopausal women. Although current evidence does not support the use of estrogen specifically for dementia prevention, the reduced risk of AD associated with estrogen use in epidemiological studies may provide an additional potential benefit to consider when weighing the pros and cons of estrogen therapy.	**LEVELII-2, B**

still in its infancy and warrants serious attention especially as retardive therapies are developed. Physicians are encouraged to support and encourage the large-scale clinical trials that will need to be mounted to address more definitely these issues.

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