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Management of Dementing Disorders

Conclusions from the Canadian Consensus Conference on Dementia

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The recognition, assessment and management of dementing disorders: conclusions from the Canadian Consensus Conference on Dementia

Special Supplement

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These conclusions have been peer reviewed.

Members of the Steering Committee appear at the end of the article.

Abstract

Objective: To develop evidence based consensus statements on which to build clinical practice guidelines for primary care physicians toward the recognition, assessment and management of dementing disorders and to disseminate and evaluate the impact of these statements and guidelines built on these statements.

Options: Structured approach to assessment, including recommended laboratory tests, choices for neuroimaging and referral, management of complications (especially behavioural problems and depression) and use of cognitive enhancing agents.

Potential outcomes: Consistent and improved clinical care of persons with dementia; cost containment by more selective use of laboratory investigations, neuroimaging and referrals; and appropriate use of cognitive enhancing agents.

Evidence: Authors of each background paper were entrusted to perform a literature search, discover additional relevant material, including references cited in retrieved articles, consult with other experts in the field and then synthesize information. Standard rules of evidence were applied. Based on this evidence, consensus statements were developed by a group of experts, guided by a steering committee of 8 individuals, from the areas of Neurology, Geriatric Medicine, Psychiatry, Family Medicine, Preventive Health Care and Health Care Systems.

Values: Recommendations have been developed with particular attention to the context of primary care, and are intended to support family physicians in their ongoing assessment and care of patients with dementia.

Benefits, harm and costs: Potential for improved clinical care of people with dementia. A dissemination and evaluation strategy will attempt to measure the impact of the recommendations.

Recommendations: Forty-eight recommendations are offered that address the following aspects of dementia care: early recognition; importance of careful history and examination in making a positive diagnosis; essential laboratory tests; rules for neuroimaging and referral; disclosure of diagnosis; importance of monitoring and providing support to caregivers; cultural aspects; detection and treatment of depression; observation and management of behavioural disturbances; detection and reporting of unsafe motor vehicle driving; genetic factors and opportunities for preventing dementia; pharmacological treatment with particular emphasis on cognitive enhancing agents.

Validation: Four other sets of consensus statement or guidelines have been published recently. These recommendations are generally congruent with our own consensus statements. The consensus statements have been endorsed by relevant bodies in Canada.

Sponsors: Funding was provided by equal contributions from 7 pharmaceutical companies and by a grant from the Consortium of Canadian Centres for Clinical Cognitive Research. Contributions were received from 2 Canadian universities (McGill, McMaster). Several societies supported delegates attending the conference.

The Alzheimer Society of Canada applauds the publication of these guidelines for primary care physicians. The guidelines are a valuable resource to assist physicians in their work with individuals who have Alzheimer Disease and their caregivers.

At present there are over 250 000 seniors with dementia in Canada.[1] Since dementia occurs predominately in seniors, the aging of our society[2] indicates that these disorders will affect an increasing number of Canadians. By the year 2031, there will be an estimated 778 000 seniors with dementia in Canada.[1] The present and increasing burden of suffering that dementing disorders impose on patients, their caregivers and the health care system, makes recommendations for the assessment and management of these conditions timely and important.

In 1989, the Canadian Consensus Conference on the Assessment of Dementia (CCCAD) developed guidelines for the evaluation of people with suspected dementia.[3,4] Although these have remained relevant, a wealth of new information has increased our understanding of dementing disorders. We now recognize that there are many forms of dementing illnesses, which can usually be distinguished and can have different therapies and prognoses. Better ways of treating the complications of dementia, managing caregiver stress and enhancing cognitive function have become available. Many physicians and others are unaware of these new developments. Clear recommendations, if implemented, could improve the care of people with dementia in Canada. Given that the majority of medical care for these patients is provided by primary care physicians, recommendations should support these physicians in the assessment and management of their patients.

The goals of the Canadian Consensus Conference on Dementia were as follows:

1. To develop consensus statements on which to base clinical practice guidelines for primary care physicians for the recognition, assessment and management of dementing disorders.
2. To base these recommendations on the best available evidence, and widely disseminate them to primary care physicians.
3. To evaluate the impact of these recommendations and guidelines, based on these statements.

In this paper we intend to explain the methods we used and provide a summary of the consensus statements agreed to.

Methods

Consensus development process

A Steering Committee was formed (co-chaired by SG and CP) with representatives from the disciplines of Family Medicine, Neurology, Preventive Health Care, Geriatric Medicine and Psychiatry.

The Canadian Medical Association's clinical practice guidelines were used.[5] Rather than developing detailed guidelines, the Committee chose to develop consensus statements upon which guidelines (which are often context specific) could be based. Topics were chosen for their relevance to primary care physicians. For each topic, a lead author for a background paper was selected. The authors were responsible for: (a) a literature search; (b) critical review of articles; and (c) preparation of a draft background document. These were circulated to the Steering Committee for initial feedback and then to all conference participants with their feedback directed to the authors.

The conference was held on Feb. 27 and 28, 1998, in Montreal. Thirty-four participants attended. For each topic, the lead authors provided a brief overview and summary of recommendations. A period of discussion followed, after which the recommendations were either voted on, or the authors were asked to reformulate recommendations in light of the discussion. This reformulation usually involved rewording or clarification rather than any substantive change. Reformulated recommendations were later voted on.

Each conference participant (except for the industry observers) voted on the recommendations. The question posed was, "Does the evidence support the recommendation?" Abstentions were counted as votes against the recommendation. Consensus was defined as greater than 80% of conference participants voting for the recommendation; partial consensus was defined as between 60% and 80%; and no consensus was defined as less than 60%.

In preparing background papers, authors were instructed to use the rules of evidence developed by the Canadian Task Force on the Periodic Health Examination.[6] Criteria used to grade the levels of evidence are shown in Table 1.

Each background paper concluded with recommendations graded as shown in Table 2.

Ideally, "A" or "E" recommendations were supported by Level 1 evidence. The paucity of Level 1 evidence in the field of dementia resulted in recommendations frequently being based upon less rigorous evidence. A "C" recommendation did not imply that the manoeuvre was useless or harmful; there was simply insufficient evidence to make a stronger recommendation. For each recommendation, the grading and strength of supporting evidence was given.

Table 1: Criteria for assigning levels of evidence

Level	Criteria
1	Evidence obtained from at least 1 properly randomized controlled trial.
2	Evidence obtained from well-designed controlled trials without randomization.
	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
	Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments are included in this category.
3	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Conference participants were chosen on the basis of the following criteria: expertise in dementia or a related area; reputation for being able to deliver high quality work in a timely manner; reputation as opinion leaders in the field; and willingness to consider alternative perspectives with an open, yet critical mind.

To deal with any potential conflict of interest the following procedures were adopted:

- The process for formulating recommendations was outlined in detail before the conference.
- The entire process was transparent, with each vote counted by 2 individuals and recorded.
- Each conference participant completed a questionnaire outlining previous involvement with pharmaceutical companies, using the form developed by the National Auxiliary Publications Service.[7]

After the conference, recommendations were collated and circulated to conference participants to ensure that the final recommendations reflected the evidence and conference discussion. Only minor changes to wording, solely to clarify recommendations, were allowed at this point. Endorsement was requested from sponsoring societies through their designated representatives.

Diagnosis and natural history of dementia

Dementia is diagnosed when acquired cognitive deficits are sufficient to interfere with social or occupational functioning in a person without depression or clouding of consciousness.[8] This syndrome is usually progressive when due to neurodegenerative (primary) or vascular causes, but is occasionally reversible.

Once dementia has been diagnosed, the specific cause can often be recognized by the following clinical profiles of common dementing disorders:

- Alzheimer's disease (AD) is characterized by gradual onset, continuing decline of memory and at least 1 additional cognitive domain, not explained by other neurologic or systemic disorders.[9] The most common cause of dementia in Canada, AD accounts for about 60% of cases.[1]

Table 2: Grades of recommendations

Grade	Criteria
A	There is good evidence to support this manoeuvre.
B	There is fair evidence to support this manoeuvre.
C	There is insufficient evidence to recommend for or against this manoeuvre, but recommendations may be made on other grounds.
D	There is fair evidence to recommend against this procedure.
E	There is good evidence to recommend against this procedure.

- Vascular dementia (VaD) exists as a number of syndromes typically associated with cerebrovascular disease. These are generally characterized by abrupt onset, stepwise decline, impaired executive function, gait disorder and emotional lability, with clinical or neuroimaging evidence of cerebrovascular disease.[10] A temporal relationship between a vascular insult and cognitive change should be sought. VaD and AD frequently coexist — a condition called mixed dementia.[11]
- Frontotemporal dementia (FTD) is characterized by an insidious onset and slow progression of behavioral changes such as loss of social awareness, disinhibition, mental rigidity, inflexibility, hyperorality, perseverative behaviour, distractibility, loss of insight, and declining hygienic standards; prominent language changes frequently occur with reduction in verbal output.[12]
- Dementia with Lewy bodies is a progressive cognitive decline with fluctuating symptoms, recurrent visual hallucinations and spontaneous extrapyramidal signs. The diagnosis is supported by repeated falls, hypersensitivity to neuroleptics, delusions, nonvisual hallucinations and syncope or transient losses of consciousness.[13]

Assessment of dementia

Although some aspects of cognitive performance (especially timed activities) may deteriorate with advancing age,[14] dementia is usually suspected when cognitive losses are associated with declining function in occupational, social or day-to-day functioning. If a person has only subjective complaints without objective impairments or family confirmation of decline, further investigation for dementia is not warranted. Follow-up studies have shown that depression or anxiety is more likely to be the cause.[15,16] If objective evidence of memory loss or decline in other areas of cognition is uncovered by mental status testing, function in terms of daily activities should be assessed. When there is evidence of a decline in function, either from caregivers' description or objective testing, further investigation and close follow-up are indicated.

A structured clinical approach will help to establish the presence of dementia and enable the physician to distinguish underlying causes, including the presence of reversible conditions that may aggravate or even cause cognitive decline.[17,18] Substance abuse, adverse drug effects, depression, metabolic disorders and systemic illnesses are among the most common of these.[19,20] The history should describe onset, duration and evolution of symptoms, and precipitating factors such as stroke. Delirium must be ruled out.[21] The presence of depression, delusions, hallucinations, personality changes and other behavioural abnormalities, such as apathy or agitation, should be sought. A family history of dementing disorders is important. Collateral history from a caregiver is essential. Careful history (including collateral information), physical examination (including a search for

focal neurological finds and evidence of systemic disease) and mental status testing, remain the cornerstones of diagnosis.[19] Serial observation at intervals of 3 to 6 months may be necessary to confirm the progressive nature of the problem, make a diagnosis of dementia and establish prognosis.[22]

Recommendation

1. Dementia is a clinical diagnosis requiring detailed history and physical examination, including office-based psychometric tests (e.g., the Mini Mental State Examination [MMSE])[23,24] as well as scales that look at functional autonomy, particularly for instrumental tasks (e.g., the Functional Assessment Questionnaire [FAQ]).[25,26] Serial assessments over time may be necessary to establish and confirm a diagnosis. [Grade B, Level 3, consensus[3,27,28]]

Basic laboratory tests

Extensive investigations for potential reversibility are no longer justified unless there are features in the presentation that would suggest an alternative diagnosis such as delirium or a particular reversible cause.[3,29–31] Only a few basic tests are suggested for general use (see recommendation 2). Additional investigations are determined by the results of the history, physical examination and initial investigations (Table 3). For example, a serum vitamin B_{12} level is indicated if proprioceptive loss, peripheral neuropathy or a macrocytic anemia accompany cognitive decline.

Recommendation

2. For most patients who have a clinical presentation consistent with AD with typical cognitive symptoms or presentation, only the following basic set of laboratory tests should be ordered: complete blood count; and measurement of thyroid stimulating hormone, serum electrolytes, serum calcium and serum glucose levels. [Grade B, Level 3, consensus[3,30]]

Table 3: Optional additional tests that may be helpful to diagnose specific causes of dementia

Measurement of
Ammonia
Blood gases
Drug levels
Erythrocyte sedimentation rate
Folic acid
Heavy metal levels
Serum cortisol
Serum lipids
Urea nitrogen/creatinine
Vitamin B_{12}
Water soluble vitamins
Carotid Doppler studies
Chest radiography
Electrocardiography
Electroencephalography
Lumbar puncture
Mammography
Serologic tests for syphilis
Tests for the human immunodeficiency virus

Neuroimaging in dementia

Neuroimaging (most commonly computed tomography [CT]) has a role in detecting certain causes of dementia such as VaD, tumour, normal pressure hydrocephalus or subdural hematoma; it is less effective in distinguishing AD or other cortical dementias from normal aging. Exaggerated cerebral atrophy may be present in advanced AD. Patchy white matter lucencies occur in up to 12% of cognitively intact older patients, and are of uncertain significance.[32] In primary care settings, some have stated that CT could be limited to atypical cases,[3,29,31] but others have recommended routine scanning.[28] A recent retrospective study, examined the utility of the CCCAD criteria in 200 consecutive memory clinic patients. Application of these criteria would have reduced the number of scans done by nearly two thirds, without changing clinical outcomes.[31] Our recommendation, therefore, limits CT to people who meet the criteria listed. Magnetic resonance imaging (MRI) currently offers no advantage over CT in most cases of dementia.

Recommendation

3. A cranial CT scan is recommended if 1 or more of the following criteria are present:
   a. age less than 60 years
   b. rapid (e.g., over 1 to 2 months) unexplained decline in cognition or function
   c. "short" duration of dementia (less than 2 years)
   d. recent and significant head trauma
   e. unexplained neurologic symptoms (e.g., new onset of severe headache or seizures)
   f. history of cancer (especially in sites and types that metastasize to the brain)
   g. use of anticoagulants or history of a bleeding disorder
   h. history of urinary incontinence and gait disorder early in the course of dementia (as may be found in normal pressure hydrocephalus)
   i. any new localizing sign (e.g., hemiparesis or a Babinski reflex)
   j. unusual or atypical cognitive symptoms or presentation (e.g., progressive aphasia)
   k. gait disturbance [Grade B, Level 2-ii, consensus[3,29,31]]

Ancillary tests

Many ancillary tests are being investigated for their use-

fulness in diagnosing specific dementias, distinguishing subtypes within major categories, determining likelihood of responding to therapy or assessing the risk that a dementing disorder will develop, or both. These investigations,* are not appropriate for the primary care setting until more evidence of clinical usefulness is available.

Recommendation

4. A growing number of ancillary tests are available as tertiary care clinical investigations or experimental studies. There is insufficient evidence to suggest that family physicians should use these tests routinely.* [Grade C, Level 3, consensus]

Referral of patients with dementia

The initial clinical assessment of memory complaints usually takes place in the primary care setting. Given the difficulties in allocating sufficient time for an informant interview and cognitive assessment of the patient, the use of nonmedical personnel or multiple office visits may be necessary. In some cases, it will be desired or necessary to refer the patient. Identification of "typical" AD has become less a diagnosis by exclusion and more a diagnosis based upon its characteristic features (i.e., insidious onset, progressive decline over 7 to 10 years, gradual loss of cognitive and functional abilities). Patients who do not follow this "typical" pattern (e.g., those who manifest early behavioural changes or delusions, fluctuating course, early motor changes) may be considered for referral.

Guidelines for referral established at the CCCAD remain appropriate.[3] The choice of consultant will depend upon the specific reason for referral, availability and preference. In addition to physicians (e.g., neurologists, geriatricians, psychiatrists), referral to support organizations (e.g., the Alzheimer Society of Canada) and health care professionals with expertise in cognitive and functional assessment (e.g., occupational therapists, clinical psychologists) may be necessary. Referral may be made to community-based (e.g., home care) and institution-based (e.g., day programs, long-term care facilities) continuing care agencies. Referral to a social worker can be helpful for caregiver support, advice for available services and future planning. Multidisciplinary dementia clinics, where available, provide a valuable local source of expertise.[33]

Recommendation

5. Most patients with dementia can be assessed and managed adequately by their primary care physicians. However, there are several reasons to consider referral to a geriatrician, geriatric psychiatrist, neurologist or other professional:
   a. continuing uncertainty about the diagnosis after initial assessment and follow-up
   b. request by the patient or the family for another opinion
   c. the presence of significant depression, especially if there is no response to treatment
   d. treatment problems or failure with new specific medications for AD
   e. the need for additional help in patient management (e.g., behavioural problems) or caregiver support
   f. the need to involve other health care professionals, voluntary agencies such as the Alzheimer Society of Canada, or other local service providers
   g. when genetic counselling is indicated
   h. when research studies into diagnosis or treatment are being carried out [Grade B, Level 3, consensus[3]]

Screening and case finding

Screening and case finding are appropriate when a condition is common and carries a high burden of suffering — both of these criteria are present in dementia. To be effective, there must be evidence that early identification changes the natural history in a beneficial way without negative effects such as labelling. Resources for screening and case finding should not detract from those allocated to other beneficial manoeuvres.[34]

People who demonstrate acquired cognitive deficits that do not meet the criteria for a diagnosis of dementia have been described as having "cognitive impairment, not demented" (CIND).[35] Currently there is insufficient evidence to recommend for or against identification of CIND; this awaits a clearer definition of the natural history of CIND. Recent evidence suggests that annually 5% to 6% of survivors with CIND progress to dementia (Dr. Ian McDowell, Principal Investigator, Canadian Study of Health and Aging: personal communication, February 1998).

Relatives and caregivers can accurately identify cognitive decline and their concerns must always be taken seriously.[36,37] People who see their primary care physicians frequently, are more likely to have their cognitive deficits identified.[38] Short mental status questionnaires are insufficiently sensitive or specific for use in screening. For example, Folstein's MMSE,[23,24] the most commonly used short test of cognitive function, has an average sensitivity of 83%

*Examples of ancillary tests for the diagnosis of dementia include: brain imaging (e.g., MRI hippocampal volumes, functional imaging [positron emission tomography, single photon emission computed tomography, MRI]); cognitive assessments (e.g., reaction time measures, semantic priming and computer algorithms); neurophysiologic tests (e.g., electroencephalography [EEG] with power spectral analysis, sleep EEG, measurement of cognitive evoked potentials [P300]); and genetic and neurochemical tests (e.g., blood apolipoprotein E [apoE] genotyping, measurement of τ- and b-amyloid fragments in the cerebrospinal fluid).

and an average specificity of 82% for detecting dementia.[39] If this test were applied to a population of 65- to 74-year-old people, the false positive rate (i.e., risk of falsely labelling a person as demented) would be 93%.[40] Enquiring about function, especially in instrumental activities of daily living (e.g., managing finances, use of the telephone, driving) is particularly useful in assessing patients with signs of possible dementia.[41]

Recommendations

6. There is insufficient evidence to recommend for or against screening for cognitive impairment in the absence of symptoms of dementia. [Grade C, Level 2-ii, consensus[40,42,43]]
7. There is insufficient evidence for or against screening or case-finding for dementia with short mental status questionnaires in unselected older people. [Grade C, Level 2-ii, consensus[40,42,43]]
8. Given the burden of dementia for older people and their caregivers, it is important for the family physician to maintain a high index of suspicion for dementia and to follow up concerns about, and observations of, functional decline and memory loss. [Grade B, Level 2-ii, consensus[41,44]]
9. Memory complaints should be evaluated and the patient followed up to assess progression. [Grade B, Level 2-ii, consensus[3,22]]
10. When caregivers or informants describe cognitive decline in an individual, these observations should be taken very seriously; cognitive assessment and careful follow-up are indicated. [Grade A, Level 2-ii, consensus[36,37]]

Genetics of dementia

First-degree relatives of AD patients have a two- to fourfold increase in their personal risk for the disease.[45,46] In a small number of families there is autosomal-dominant transmission for AD manifesting in middle age.[45] Almost all Down's syndrome patients over the age of 40 years have neuropathological changes typical of AD.[47] The apoE gene on chromosome 19 has 3 alleles — 2, 3 and 4. In the general population, the presence of apoE4 genotype is associated with an increased risk of AD. For example, a population-based prospective study of people over the age 75 years revealed a relative risk for AD of 3.24 (95% confidence interval, 1.67 to 6.25) in those possessing apoE4.[48] However, the sensitivity (approximately 50%) and specificity (approximately 75%) for the presence of the apoE4 genotype in diagnosing AD is insufficiently high to guide diagnosis or accurately quantify genetic risk.[48,49] The place of genetic testing and genetic risk assessment remains unclear.

Resources available for advice include genetic clinics and the Alzheimer Society of Canada. The consequences of genetic testing must be carefully considered since significant harm can result from inadequate counselling.[50]

Recommendations

11. Screening asymptomatic people for genetic risk factors such as apoE4 is not recommended at this time. [Grade D, Level 3, consensus[50]]
12. There is insufficient evidence at this time to suggest that family physicians should use ancillary tests such as apoE genotyping for the diagnosis of dementia in symptomatic patients. [Grade C, Level 3, consensus[50]]
13. Attention should be paid to changes in functional abilities in middle-aged people with Down's syndrome (trisomy 21), because they are at a high risk for AD. [Grade B, Level 2-ii, consensus[47]]
14. Asymptomatic people presenting to the family physician with concerns regarding inheritance of AD can be referred to a genetic clinic if the family history is suggestive of autosomal dominant inheritance. If the family history is not supportive of such inheritance (indeterminate or negative), the family physician should refer the patient to community resources such as the Alzheimer Society of Canada or a genetic clinic only if the physician or the asymptomatic patient, or both, require further reassurance or assistance. [Grade B, Level 3, consensus]
15. If a person who has a diagnosis of AD presents to the family physician with concerns about family members, these relatives should be encouraged to consult with their own family physicians. [Grade B, Level 3, consensus]
16. Consider collecting a blood sample for provincial DNA banking (where available) when the diagnosis of AD is made before the patient reaches the age of 60 years. Consider encouraging an advance directive indicating their willingness to agree to brain banking. [Grade B, Level 3, consensus]

Prevention of dementia

As the etiologic factors for dementing disorders become more clearly identified, prevention may become a reality. If the onset of dementia could be delayed by 5 years, the population prevalence could be reduced by one half. If delayed by 10 years, prevalence could decline by 75%.[51] For VaD, prevention is already potentially possible by treatment of stroke risk factors such as the use of antihypertensives,[52] HMG (3-hydroxy-3-methylglutaryl) coenzyme A reductase inhibitors,[53,54] and anticoagulants for atrial fibrillation.[55] By reducing the incidence of stroke, such measures may decrease the incidence of VaD, although this is yet to be proven.[56] The timely correction of metabolic disturbances associated with dementia (e.g., vitamin B_{12} deficiency, alcohol abuse) can be reasonably expected to reduce the inci-

dence of subsequent dementia. Although there is evidence from case-control and cohort studies that postmenopausal hormone replacement therapy may reduce the incidence of AD,[57] it is premature to recommend estrogens solely for this purpose. Because hormone replacement therapy may be recommended for other reasons, all potential risks and benefits including the prevention of AD, should be discussed with postmenopausal women.[58] Similarly, whereas case-control and cohort evidence suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with a reduced incidence of AD, it is premature to recommend them for this purpose.[59] Large prospective randomized controlled trials of estrogens, antioxidants and NSAIDs are currently under way, or are being planned.

Epidemiologic studies have shown an association between AD and a lack of formal education.[60] Improved basic education can be viewed as having a potential role in reducing the incidence of AD, in addition to other societal benefits. Head injuries have been suggested to increase the subsequent incidence of AD.[60,61] Encouraging the use of seatbelts and bicycle helmets could have a role in the primary prevention of dementia.

Recommendations

17. When clinical conditions that can lead to cognitive impairment are uncovered by clinical and laboratory assessment, appropriate corrective treatment should be instituted (e.g., thyroid or vitamin B_{12} replacement, alcohol abstinence programs, etc.). By effectively treating vascular risk factors such as arterial hypertension, hypercholesterolemia, diabetes mellitus and smoking, and by using prophylactic anticoagulation for chronic atrial fibrillation, the risk of dementia may be reduced. The decision to treat transient ischemic attacks and stroke by secondary prevention measures (as above), and by use of anticoagulants, antiplatelets and carotid endarterectomy (as appropriate), may likewise lower the risk of vascular dementia. [Grade B, Level 3, consensus[52–55]]
18. Physicians should be aware of genetic risk factors for AD and follow the recommendations under genetic screening. Evidence suggesting that substandard education (less than 6 years) or 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 seat belts when driving and helmets for cycling or other sports). [Grade B, Level 3, consensus[50,60,61]]
19. The use of NSAIDs cannot be recommended for the treatment or prevention of AD on the basis of available evidence, but if required for arthritis or other conditions they may afford some protection against the development of AD. [Grade C, Level 2-ii, consensus[59]]
20. Physicians should provide counselling on the risks and benefits of estrogen therapy in peri- or postmenopausal women. Although current evidence does not support the use of estrogen specifically for the prevention of AD, the reduced risk associated with long-term estrogen use in epidemiologic studies may provide an additional potential benefit to consider when weighing the pros and cons of estrogen therapy. [Grade B, Level 2-ii, consensus[57,58]]

Ethical issues in dementia

Loss of insight, declining capacity to make reasonable decisions and risk to others must be carefully balanced against preservation of autonomy. Recognizing the scope of relevant ethical issues, the conference participants chose to focus on 2 areas: disclosure of diagnosis and driving. Other important issues that were not dealt with include: participation in research, decision-making — respecting individual choice, quality of life, behaviour control, use of restraints, advance directives and end-of-life decisions.

Several publications have looked at these difficult issues. For further information the reader is directed to *Tough Issues*, published by the Alzheimer Society of Canada[62] and recent reviews by Fisk and associates[63] and Cohen.[64]

Disclosure of diagnosis

The case for informing patients of their diagnosis rests upon the patients' right-to-know (principle of autonomy). Knowledge of the diagnosis can allow for future planning (e.g., advance directives, power of attorney, planning for future living arrangements). Disclosure allows for consent to treatment and participation in research. It also facilitates the dialogue between patient and caregiver, avoiding the conspiracy of silence that might otherwise exist. Arguments against disclosure include: the risk of depression and, in rare instances, suicide; concern about diagnostic uncertainty; and the lack of effective disease-modifying treatments. Most seniors and caregivers of AD patients state that they would wish to be told the diagnosis.[65] Although each case should be weighed on its own merits, it is considered ethically preferable to inform persons with dementia of their diagnosis.[65]

Recommendation

21. Although each case should be considered individually, in general the diagnosis of a dementing condition should be disclosed to the patient and family. This process should include a discussion of prognosis, diagnostic uncertainty, advance planning, treatment options, support groups and future plans. Exceptions to disclosing prognosis to the patient could be severe de-

mentia where understanding of the diagnosis is unlikely, phobia about the diagnosis or severe depression. [Grade B, Level 3, consensus[65]]

Driving and dementia

The risk of motor vehicle collisions and fatal injury increases with the duration and severity of dementia.[66] Reporting concerns about driving to provincial transport ministries is mandatory in many, but not all, provinces. It is difficult for a physician to assess accurately a patient's driving competence in the office setting.[67] The exception is when the patient is so severely demented that an increased driving risk is obvious. Performance-based evaluations of driving competence are preferable for accurate assessment, especially in uncertain cases.[67,68] The physician should ask about driving problems, accidents or infractions, and look for significant deficits in visuospatial abilities, attention and judgement. A combination of lesser degrees of impairment may be equally hazardous. Also to be considered are other conditions that may affect the patient's level of consciousness or abilities (e.g., syncope, hypoglycemia, seizures, transient ischemic attacks) as well as medications that can affect cognition. Long half-life benzodiazepines substantially increase the risk of motor vehicle collision in older patients.[69]

A description of how the patient actually drives should be sought from observers. Asking about behaviour (e.g., anger) and ability to perform daily functions (e.g., does the patient get lost) are potentially useful for assessing driving risk. Even if the risk is considered acceptable, it is recommended that each case be reviewed periodically (to be determined by the patient's rate of decline or onset of new symptoms). Physicians who have concerns regarding a patient's capacity to drive should communicate their concern to the patient and caregiver and suggest an evaluation of driving competency.

Recommendations

22. While caring for patients with cognitive impairment, physicians should consider risks associated with driving. Focused medical assessments (including specific details in the medical history and physical examination) are recommended in addition to the general medical evaluation. [Grade B, Level 3, consensus[67]]
23. Physicians should be aware that driving difficulties may indicate other cognitive/functional problems that need to be addressed. [Grade B, Level 3, consensus[67]]
24. Physicians should encourage patients with AD and their caregivers to plan early for eventual cessation of driving privileges and provide continuing support for those who lose their capacity to drive. [Grade B, Level 3, consensus[67]]
25. Primary care physicians should notify licensing bodies of concern regarding competence to drive, even in those provinces that have not legislated mandatory reporting by physicians, unless the patient gives up driving voluntarily. [Grade A, Level 3, consensus[67]]
26. Physicians should advocate strongly for the establishment and access to affordable, validated performance-based driving assessments. [Grade B, Level 3, consensus[67,68]]

Caregiving in dementia

Caregivers have multiple roles in caring for people with dementia. Their reports are often as reliable as objective measures of cognitive decline, and may alert health care professionals to the presence of dementia.[70] Caregivers play a vital role in providing direct care for patients with dementia. Physicians rely on caregivers to monitor changing status and symptoms and need to include them in treatment plans. Absence of a caregiver(s) is a major predictor of earlier institutionalization of people with dementia. Higher perceived caregiver burden also leads to earlier institutionalization.

Up to 50% of caregivers experience significant psychiatric symptoms during the course of their caregiving.[71] Despite these negative consequences, many caregivers also report a sense of satisfaction with their role, particularly a sense of accomplishment in keeping their loved ones at home. Support for caregivers is offered by agencies such as the Alzheimer Society of Canada, specialized dementia services, support groups and community services providing education and case management. A program of counselling and support has been shown to delay institution admission.[72] Partnerships between primary care physicians and caregivers are strongly recommended to help families cope with the care of people with dementia. The family physician's role includes: establishing and conveying the diagnosis; management of behavioural disorders related to dementia; assistance with advance planning; assessing and treating caregivers for depression and other illnesses; and facilitating referral to appropriate services for additional assistance.[64]

Recommendations

27. Acknowledge the important role played by the caregiver in dementia care; work with caregivers and families on an ongoing basis from the time of diagnosis of dementia until the death of the patient; schedule regular appointments for patients and caregivers together and alone. [Grade B, Level 3, consensus[64]]
28. Educate patients and families about the disease and how to cope with its manifestations. This includes appropriate modifications to the home environment and learning to communicate and interact with the patient with dementia. [Grade B, Level 3, consensus[64]]
29. Evaluate caregiver coping strategies and encourage caregivers to care for themselves using health promo-

tion and stress reduction strategies. [Grade B, Level 3, consensus[64]]

30. Assess the caregiver's social support system and help caregivers rally support for themselves from appropriate family members and friends. [Grade B, Level 3, consensus[64]]
31. Enquire about caregiver burden, and psychiatric and health problems by regular meetings with caregivers, asking specific questions about their health and caregiver strain; offer treatment for these problems (individual psychotherapy or medications as indicated) or refer to appropriate specialists or services. [Grade B, Level 3, consensus[64]]
32. Refer caregivers to appropriate community services for dementia care (e.g., daycare, respite, local Alzheimer Society) realizing that it may take encouragement and time for these services to be used; if available, refer patients to specialized dementia services that offer comprehensive treatment programs. [Grade B, Level 3, consensus[64]]
33. Discuss legal and financial issues and obtain appropriate help for caregivers and families if required. [Grade B, Level 3, consensus[64]]

Cultural issues in dementia

In a multicultural society such as Canada, physicians need to be aware that the concept of dementia is essentially a Western one. In many cultures this diagnostic label does not even exist.[73] In making diagnoses, cultural sensitivity must be observed. One must avoid over-reliance on mental status instruments that may not be valid in other cultural groups. Standard cognitive testing measures frequently contain items that are biased for educational attainments or ethnicity.[74,75] It can be extremely difficult to assess patients whose language of communication is different from that of the examiner. Different cultural or ethnic groups may have differing proportions of the various causes of dementia; for example, VaD is the most common type of dementia in Japan, but when Japanese men migrate to Hawaii they appear to be more susceptible to the development of AD.[76] Decisions about management may be affected by cultural differences, for example, in willingness to seek institutional care.

Recommendations

34. Family physicians need to be aware of the cultural impact on families' recognition and acceptance of dementia in a family member, and that more in-depth discussion about symptoms and the meaning of aging may be required. [Grade B, Level 3, consensus[73]]
35. Physicians should recognize that measures of cognitive abilities (e.g., MMSE) will often overestimate cognitive impairment in many cultural and linguistic groups. [Grade B, Level 3, consensus[74,75]]
36. The care and management of patients from specific cultural groups should take into account the risk of isolation, the importance of culturally appropriate services and special issues that arise in providing caregiver support. [Grade B, Level 3, consensus[73]]

Depression and dementia

Depressive symptoms occur frequently in people with AD. One study found at least 1 depressive symptom in 63% of people with AD.[77] Prevalence estimates for major depressive disorder in people with dementia varies between 6% and 20%.[78,79] It has been suggested that major depressive disorder becomes less common as dementia advances and insight is lost;[80] this, however, is controversial. Other depressive syndromes that occur in dementia include chronic dysthymia, grieving and bipolar affective disorders. It may, however, be difficult to distinguish depression from personality changes such as apathy and passivity which are commonly found in AD and FTD, or emotional lability which is most commonly associated with VaD.

Much has been written about distinguishing dementia from depression, but these syndromes often coexist.[77–79,81] Many symptoms such as sleep disturbance, anorexia, irritable behaviour, anergy and social withdrawal may occur in both dementia and depression. When symptoms suggest depression, a trial of antidepressants can be considered. In dementia, response to antidepressant therapy is less predictable.[80,82] There is, unfortunately, a paucity of randomized controlled trials to guide the prescribing physician.[83]

Anticholinergic side effects from many antidepressants (particularly the tricyclic drugs) limit their usefulness in AD since cognitive deficits may worsen on these medications.[80,84] Moclobemide, selective serotonin reuptake inhibitors, trazodone, nefazodone and venlafaxine, are considered reasonable choices since they have minimal anticholinergic effects.[83] Trazodone may cause hypotension in high doses. If tricyclics are used, nortriptyline is preferred if sedation is required, whereas desipramine is preferred if sedation is not desired.[85] An antidepressant trial should last at least 2 to 3 months and be continued if the patient is responding. Continued use of medication must be re-evaluated regularly. Depressive illness coincident with dementia should be treated before starting a cognitive enhancer.

Recommendations

37. As depressive syndromes are frequent in patients with dementia, physicians should consider diagnosing depression when presented with the subacute development (e.g., weeks, rather than months or years) of symptoms characteristic of depression such as behavioural symptoms, weight and sleep changes, sadness, crying, suicidal statements or excessive guilt. [Grade B, Level 3, consensus[85,86]]
38. Depressive illness should be treated and when refrac-

tory the patient should be referred to a specialist.* [Grade B, Level 3, consensus[85,86]]

39. Depressive symptoms that are not part of a major affective disorder, severe dysthymia or severe emotional lability, should initially be treated nonpharmacologically. [Grade B, Level 3, consensus[85]]
40. In patients suffering from disturbing emotional lability or pathological laughing and crying, consider a trial of an antidepressant or mood stabilizer. [Grade B, Level 3, consensus[85,86]]

Management of behavioural disturbances in dementia

Behavioural and psychological signs and symptoms of dementia are common, serious problems that impair the quality of life for both patient and caregiver. At some point during the course of the illness, 90% of patients have behavioural problems.[87] These are particularly common in long-term care institutions. Although behavioural manifestations tend to occur later in patients with AD or VaD, they occur more frequently and earlier in the course of FTD[12] and Lewy body dementias.[13]

Assessment should include a review of potential triggers (e.g., pain, intercurrent illness, medications). Behaviours should be carefully documented. It is important to look for precipitants such as physical treatments, bathing, mealtimes, company or loneliness. Consequences of the behaviours should also be recorded. The act of observing and documenting these behavioural symptoms and signs can, in itself, reduce the number of incidents by learning to recognize, anticipate and avoid provocation.[88]

Nonpharmacologic interventions are generally tried first and may involve environmental modifications (e.g., therapy with light, music, pets or activity) and specific behavioural techniques.[89] There is surprisingly little evidence from randomized controlled trials that psychotropic medications are effective in demented patients. Neuroleptic agents appear modestly effective.[90,91] Traditional neuroleptic agents have a high incidence of extrapyramidal side effects including Parkinsonism and tardive dyskinesia. Newer agents (atypical neuroleptics such as risperidone,[92] olanzepine[93] and quetiapine[94]) may offer advantages. A recent large randomized controlled trial showed that risperidone (1 mg daily) was effective and well tolerated.[95] Results of several other trials will be available shortly. Neuroleptics with marked anticholinergic effects such as chlorpromazine and thioridazine should be avoided. Several antidepressants, such as trazodone[96–98] and the selective serotonin reuptake inhibitors, have been recommended but trials are generally small or inconclusive. Benzodiazepines should be used cautiously, in low doses, and on an "as required" basis. No medication will control wandering, which is best managed with behavioural and environmental modifications. In view of the sensitivity of demented patients to psychotropic agents, the old adage "start low and go slow" should be observed. After instituting or changing a medication, an appropriate period of observation should ensue before changing the therapeutic approach again. This period will usually be of several weeks' duration.

Recommendations

41. Serious behavioural and psychological disturbances are commonly found in people with dementia. Family doctors should ask caregivers about such disturbances and regularly assess their patients. Evaluation to rule out treatable or contributory causes should be done with new onset of agitation, aggression, psychotic behaviour, sleep disturbance or wandering. Environmental (e.g., changes in light or sound stimulation level) and behavioural modifications should be attempted first, often with advice from the Alzheimer Society of Canada and specialists. [Grade B, Level 1, consensus[88,89]]
42. If medications are required for the symptomatic control of agitation, aggression or psychotic behaviour, consider low doses of neuroleptic drugs, a serotonin reuptake inhibitor or trazodone. [Grade B, Level 1, partial consensus 77%[90–98]]
43. For sleep disturbances, consider trazodone. [Grade B, Level 2-ii, partial consensus 63%[96]]
44. After successful control of symptoms with pharmacotherapy, regularly evaluate the need for continuing treatment and consider withdrawal of medication with close monitoring for emerging symptoms. [Grade B, Level 3, consensus[85]]

Pharmacologic therapy in dementia

Despite the introduction of pharmacologic agents for dementia, the mainstay of management continues to be education and support for caregivers, and treatment of complications. Cognitive-enhancing agents have been primarily developed for AD. Although the authors of the background paper reviewed a large number of agents, recommendations were offered only for agents that are currently easily available. In making these recommendations, the goals of antidementia therapy were carefully reviewed.

Guidelines for initiating and monitoring the effect of anti-dementia drugs were based upon the expert opinion of the London (UK) Alzheimer's Disease Treatment Working Group.[99] For individual drugs, a systematic review of English language articles was carried out to identify all randomized controlled trials. This included a review of articles retrieved from a MEDLINE search (1986 to present) and

*Preferably a geropsychiatrist, if available.

contact with experts in the field of behavioural neurology and cognitive enhancement. Forty-one articles were considered for review, 27 of which were of acceptable methodologic quality. Efficacy trials of drugs for dementia had to include at least 1 measure of cognitive function and at least 1 global measure. Drugs available for use in Canada as of March 1998 were donepezil, vitamin E and *Ginkgo biloba*.

Donepezil is approved for the symptomatic treatment of mild to moderate probable AD. In 3 randomized controlled trials, donepezil has shown improvements in both cognitive performance and global functioning when compared to placebo.[100–102] The benefits are usually modest (an average improvement of 2 points on the MMSE) and may not be apparent for 3 months after starting the medication; however, clinically useful improvement does occur in some patients.

Two randomized controlled trials of *Ginkgo biloba* have been published in the English language literature.[103,104] In each of these studies, a standardized *Ginkgo* preparation (EgB761) was used. In the first study, 222 outpatients with mild to moderate AD were randomized to receive placebo or 240 mg/d of EgB761.[103] The primary outcome measure was the therapeutic responder rate, defined as a change in cognitive scale score of at least 1 standard deviation from the baseline on at least 2 of the 3 outcome measures. Twenty-eight percent of the *Ginkgo* group and 10% of the placebo group responded, although there was a large (30%) dropout rate. Therapeutic response rate is not a standard way of assessing response in North America. In the second study, 120 mg/d of EgB761 was compared with placebo in 327 patients with AD or multi-infarct dementia.[104] Only 50% of the *Ginkgo* group and 38% of the placebo group completed the study. Of those in the *Ginkgo* group completing the 52-weeks of treatment, a modest but statistically significant improvement was recorded in cognitive performance and in a rating scale provided by relatives. The high dropout rate and lack of standardized preparations led the reviewers to conclude that there was insufficient evidence either for or against this drug.

Although there are theoretical reasons to believe that vitamin E may be beneficial in AD, only 1 randomized controlled trial of vitamin E has been published.[105] Vitamin E (2000 IU daily) was compared to selegiline (10 mg daily) in a double-blind placebo-controlled randomized multicentre trial involving 341 patients with moderate AD.[105] The duration of treatment was 2 years and the primary outcome measure was the time to the occurrence of any of the following: death, institutionalization, loss of the ability to perform basic activities of daily living or severe dementia (clinical dementia rating of 3). The primary analysis revealed no difference between either of the treatment groups and placebo. However, despite random allocation, the baseline score on the MMSE was higher in the placebo group than in the other 3 groups; this variable is well known to be highly predictive of outcome. When the results were reanalysed to include the baseline MMSE scores as covariate, significant delays in time to the primary outcome were increased (selegiline median time 655 days; vitamin E 670 days; combination therapy 585 days; placebo 440 days). It is unclear why combination therapy appeared less effective, and selegiline itself appears to offer no advantages over the less expensive vitamin E.[105] As such, the reviewers dealt only with vitamin E. It was felt that there was insufficient evidence to make a recommendation for or against this agent. A dissenting opinion was written.

Although cure would be the ideal goal, currently available agents do not allow for this possibility. Monitoring of the response to medications should include the use of standardized instruments such as the MMSE[23,24] and FAQ,[25,26] at regular intervals. Reasonable treatment goals include the following:

- halting or slowing the course of the disease with respect to measurable cognitive and functional decline leading to institutionalization
- improvement in memory and other cognitive functions
- maintenance or improvement in self-care abilities
- improvement in behavioural abnormalities; improvement in mood, contentedness and quality of life of the patient and caregiver.

Recommendations

45. Guidelines for anti-dementia drugs include the following:
    a. It is recommended that primary care physicians be instructed through continuing medical education on the administration and interpretation of measures of functional activities and cognitive abilities.
    b. After treatment has been started, patients should be reassessed regularly, such as every 3 months.
    c. Records should be kept such that stabilization, improvement or persisting deterioration in patients treated with an anti-dementia drug will be determinable and will indicate whether to continue or discontinue the drug.
    d. Caregivers should be asked to keep a written record of personal impressions and historical data on the performance of the patient in daily life.
    e. When the primary care physician is unable to perform such assessments, referral to a specialist is advised.
    f. Primary care physicians should be able to communicate appropriate information concerning dementia, including realistic treatment expectations to their patients and their families. [Grade B, Level 3, consensus[3,85,99]]
46. Use of donepezil.
    a. Donepezil is currently (as of March 1998) the only approved drug available in Canada for the treatment of mild to moderate AD. Statistically significant differences in favour of donepezil were found in cogni-

tive tasks and on the Clinician's Interview Based Assessment of Change; however, the long-term clinical benefit remains unclear. At present there is no evidence to support the use of this drug in preventing AD or in the treatment of more severe stages.

b. A trial course of donepezil can be prescribed to informed and willing patients with mild to moderate dementia due to probable AD, in the absence of contraindications. [Grade B, Level 1, consensus[101–103]]

47. Use of vitamin E (please see dissenting opinion in Appendix A). There is currently (as of March 1998) insufficient evidence to recommend the use of vitamin E for the treatment or prevention of AD. At the doses evaluated in clinical trials there were side effects in some patients. The benefit of low dose vitamin E has not been evaluated. [Grade C, Level 1, consensus[105]]
48. Use of *Ginkgo biloba*. There is currently (as of March 1998) insufficient evidence to recommend the use of *Ginkgo biloba* for the treatment or prevention of AD. There is great variability between different *Ginkgo* preparations. [Grade C, Level 1, consensus[103,104]]

Validation

Four other sets of clinical practice guidelines have been published recently.[27,85,86,106] Although all of these guidelines were aimed at an American audience, recommendations were broadly similar. In detail, however, a number of discrepancies were present, originating partly from the different audiences targeted for these documents. The following organizations have received and endorsed the recommendations of this paper: Alzheimer Society of Canada; Canadian Academy of Geriatric Psychiatry, Canadian Neurological Society; Canadian Society of Geriatric Medicine; College of Family Physicians of Canada; Consortium of Canadian Centres for Clinical Cognitive Research; Société québécoise de gériatrie. Conference participants report that slides of the recommendations have been well received at continuing medical education presentations.

Discussion

Guidelines for complex interventions are hard to build.[107] Dementia is an extremely complex field. The epidemiology of this syndrome is beginning to be understood. Current agreement on diagnoses, even among experts with specific diagnostic criteria, is far from perfect.[108] There are no treatments that are clearly effective in the majority of cases. Finally, complications of dementing illnesses are legion and difficult to manage.

For these and other reasons, guidelines for dementia care based upon sound evidence are hard to produce. To develop consensus statements, we reviewed all the evidence that could be gathered using a comprehensive search strategy. We used a ranking of levels of evidence that is well established and widely emulated.[6] Wherever possible, we based our recommendations on the best evidence available. Where evidence was lacking, often a "C" recommendation was given; this does not recommend for or against the manoeuvre but simply states that there is insufficient evidence to make a decision on evidence alone. Levels of evidence and strength of recommendations were incorporated into each background paper, although at consensus, the strength of recommendations was modified in some cases.

For those in the field, it was no surprise that there were very few studies that fulfilled the criteria for Level 1 evidence. We elected to adopt the best available evidence approach, combining the conclusions of other consensus groups with the expert opinion of our group, to supplement those areas where Level 1 evidence was lacking but where clinical direction appeared important.

The organizing committee also decided to produce consensus statements rather than true clinical practice guidelines. This was primarily in response to the concern that primary care in Canada is so diverse that universal guidelines are not practical and would not be applicable in every setting. It was felt instead that groups of physicians could formulate appropriate guidelines from the consensus statements (i.e., ones that would be more applicable to their particular setting).

Some of the recommendations are more vague than prescriptive. This resulted from the necessity to reach consensus among a diverse group of professionals, which included primary care and specialist physicians, as well as those from other disciplines. We attempted to distill the available evidence and wisdom into statements helpful to primary care physicians. Indeed, 7 out of the 34 participants were primary care physicians and every attempt was made to keep the focus of the recommendations on primary care. Rapid evolution of the field will result in new developments and recommendations. The preceding recommendations represent the best available advice as of the time of the conference (February 1998).

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Society representatives: Alzheimer Society of Canada, Linda LeDuc; Canadian Academy of Geriatric Psychiatry, Carole Cohen; Canadian Neurological Society, Andrew Kertesz; Canadian Society of Geriatric Medicine, Peter McCracken; College of Family Physicians of Canada, Steven Wetmore; Consortium of Canadian Centres for Clinical Cognitive Research, David Hogan; Société Québécoise de Gériatrie, Guy Lacombe. All of these societies endorsed the recommendations.

Invited speaker: A.M. Clarfield, Division of Geriatrics, Ministry of Health, State of Israel.

Coordinator: L. Edwards, Canadian Congress of Neurological Sciences, Calgary.

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Appendix A: Dissenting opinion on vitamin E

David B. Hogan, MD; Sandra E. Black, MD

Recommendation proposed: There is currently (as of March 1998) fair evidence to support the use of vitamin E in high doses (2000 IU daily) for the treatment of Alzheimer's disease of moderate severity. [Level 1 evidence]

Justification: Agents that protect against oxidative damage may slow the progression of Alzheimer's disease. A double-blind placebo-controlled randomized trial in patients with Alzheimer's disease of moderate severity, showed that a-tocopherol (vitamin E, 2000 IU daily) led to a statistically significant delay in the time to 1 of 4 primary outcomes (death, institutionalization, loss of ability to perform basic activities of daily living, progression to severe dementia) if the baseline Mini-Mental State Examination score was included as a covariate.[1] This delay was approximately 230 days (nearly 8 months). There was no statistically significant difference in the frequency of adverse effects in those who received vitamin E (compared to those subjects receiving placebo) after adjustment for multiple comparisons. Vitamin E is safe, with few reported cases of toxicity at dosages less than 3000 IU daily.[2] Vitamin E supplementation may also decrease the risk of cancer[3,4] and cardiovascular disease.[5,6] It may also improve immune function in the elderly.[7] Vitamin E has been shown to slow the progression of Alzheimer's disease at a dose that is safe for humans. Furthermore, there is the potential for additional health benefits with its use.

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