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Management of mild to moderate Alzheimer's disease and dementia

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Abstract The authors were charged with making a series of evidence-based recommendations that would provide concrete advice on all aspects of the management of mild to moderate stages of dementia and Alzheimer's disease (AD). The recommendations were primarily targeted to primary care physicians practicing in Canada. The assigned topic area did not include either the assessment of a patient with suspected dementia or the prevention of AD and other dementias. An extensive examination of the available literature was conducted. Explicit criteria for grading the strength of recommendations and the level of evidence supporting them were used. The 28 evidence-based recommendations agreed on are presented in this article.

Keywords: Dementia; Alzheimer's disease; Vascular dementia; Mild-to Moderate; Disease management

1. Introduction

This article deals with the management of Alzheimer's disease (AD) and other forms of dementia. The working group was asked to produce a summary of the available evidence on this topic. On the basis of this review we were to develop a series of recommendations that would provide concrete advice on all aspects of therapy along with suggestions for future developments. The primary target audience for these recommendations would be primary care physicians.

The definition of mild to moderate AD and dementia was left up to the authors of the articles reviewed. Typically they defined it as a patient meeting criteria for a diagnosis of AD and/or dementia who had a Mini-Mental State Examination (MMSE) score between 10–11 and 24–26 (inclusive). This would translate to a Global Deterioration Scale stage of 4-6 and/or a Clinical Dementia Rating score of 1–2.

In this document we will not deal with the prevention of dementia and AD. Also, other than for AD we will make few recommendations for the management of specific types of dementia (eg, dementia with Lewy bodies [DLB]). We will not address the issue of the cost-effectiveness of the various interventions described for patients with mild to moderate AD and dementia. A fiercely debated issue at this time is whether any of the available medications for mild to moderate AD are cost-effective. Our assigned topic area overlapped with the severe dementia working group because a number of the studies we examined dealt with moderate to severe stages of the condition. We would advise the reader to review the background article of this working group as well.

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2. Methods

Our working group was charged with the responsibility of addressing the management of mild to moderate AD and dementia. The chair (D.H.) and the initial members of the working group (P.B., C.C., M.H., L.T.) were selected by the Steering Committee of the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (3rd CCCDTD). In a series of teleconferences the assigned task was divided into a number of subsections, with delegation of lead responsibility to members of the working group. To ensure that we had the range of required talent and expertise, additional members of the working group were recruited (A.C., B.C., D.F., and K.L.). The involved subsection leads identified, discussed, and resolved in mutually acceptable manner areas of potential overlap. During our teleconferences we clarified how we would approach the task and dealt collectively with any concerns expressed by working group members. Minutes were kept of these teleconferences and circulated to all members of the working group and the Chair of the 3rd CCCDTD Steering Committee.

The initial literature searches were conducted by an information specialist hired by the 3rd CCCDTD. PubMed and Embase databases were used. The strategy and major keywords used in the searches were "dementia" OR "Alzheimer's disease" AND "mild" OR "moderate" AND "therapy" OR "treatment." Secondary search terms included (listed alphabetically) "affective disorder," "agitation," "antidepressants," "anti-inflammatory drugs," "antioxidants," "anxiety," "anxiolytics" OR "tranquilizers," "behaviour," "cholinesterase inhibitors," "care-giver," "counseling," "depression," "disinhibition," "discontinue," "education," "environment," "ginkgo," "hormones," "hypnotics" OR "sleep medications," "maintain," "memantine," "metabolic enhancers," "neurotrophic agents," "nootropics," "rehabilitation," "selective serotonin reuptake inhibitors" OR "sleep." The search was limited to articles written in English, dealing with human research, and published since January 1, 1996.

A total of 1,615 articles were identified. Six hundred sixty-one of the articles were eliminated after examination of the title. The titles, authors, and abstracts of the remaining 954 were distributed to all working group members. Each was responsible for selecting articles for detailed review by their subsection, abstracting data from the selected articles, synthesizing the available information, and developing draft recommendations. Full texts of articles selected by working group members were provided by the information specialist. On the request of working group members, additional searches were conducted by the information specialist. The search strategies for them were developed in consultation with the individuals making the request. Working group members were also encouraged to use their own files and to search the reference lists of selected articles for additional relevant articles. Working group members were told that although they could use articles that summarize the research literature (eg, meta-analyses, systematic reviews, consensus statements, clinical practice guidelines), there would be some areas in which they would have to perform a primary review of the pertinent literature. They were also asked to focus their energies on what they thought were the key areas within their subsections and to draft recommendations that would be both important and feasible for a primary care physician.

The draft recommendations developed by working group members and a first draft of the background article were distributed by the Chair to all working group members for review, discussion, and modification. After this process the background article with recommendations was submitted to the Steering Committee for posting on the Web page of the 3rd CCCDTD. Feedback received was discussed by the working group, and final modifications were made to the recommendations before their presentation at the consensus meeting on March 10, 2006. All of the recommendations presented in this article achieved consensus (80% plus approval by participants of the 3rd CCCDTD).

The quality of the literature (levels of evidence) was graded by using the following system adapted from Canadian Task Force on Preventive Health Care [1]:

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

The strength of the recommendations (Grade of Recommendation) was graded by using the following system adapted from the Canadian Task Force on Preventive Health Care [1,2]:

A: There is good evidence to support this maneuver.
B: There is fair evidence to support this maneuver.
C: The existing published evidence is either conflicting or insufficient and does not allow one to recommend for or against this maneuver; however, a recommendation might be made on other grounds.
D: There is fair evidence to recommend against this maneuver.
E: There is good evidence to recommend against this maneuver.

Our recommendations were based on the best available evidence. We preferentially used rigorously done system-

atic reviews of the current literature. When a primary examination of the literature was done, we sought to base our conclusions on statistically and clinically significant findings from high quality RCTs.

The conclusions of the 1998 Canadian Consensus Conference on Dementia (CCCD) that were considered relevant to our assigned area and were still supported by the members of the working group are also included in this document [1].

3. Results: Management of mild to moderate Alzheimer's disease and dementia

3.1. General measures

A number of the conclusions reached at the CCCD [1] were believed to be both relevant to our assigned topic area and received the support of the members of the working group after minor modifications. Three are presented below, and others will be appear later in the document.

3.2. Recommendation 1

Most patients with dementia can be assessed and managed adequately by their primary care physicians. However, to assist them in meeting the needs of patients and their caregivers, it is recommended that (1) all patients with dementia and their families who consent be referred to the local chapter of the Alzheimer Society (eg, First Link program where available); and (2) primary care physicians should be aware of the resources available for the care of those with dementia in their community (eg, support groups, adult day programs) and to make appropriate referrals to them (Grade B, Level III).

3.3. Recommendation 2

The referral/consultation process is essential to the delivery of high quality health care. In the care of a patient with mild to moderate dementia, reasons to consider referral to a geriatrician, geriatric psychiatrist, neurologist, or other health care professional (eg, neuropsychologist, nurse, nurse practitioner, occupational therapist, physical therapist, psychologist, social worker) with the appropriate knowledge and expertise in dementia care would include (1) continuing uncertainty about the diagnosis after initial assessment and follow-up; (2) request by the patient or the family for another opinion; (3) presence of significant depression, especially if there is no response to treatment; (4) treatment problems or failure with specific medications for AD; (5) need for additional help in patient management (eg, behavioral problems, functional impairments) or caregiver support; (6) genetic counseling when indicated; and (7) if the patient and/or family express interest in either diagnostic or therapeutic research studies that are being carried out by the recipient of the consult request (Grade B, Level III).

3.4. Recommendation 3

The care and management of patients with dementia from specific cultural groups should take into account the risk of isolation, the importance of culturally appropriate services, and issues that arise in providing caregiver support (Grade B, Level III).

The presence of a preexisting dementia is the risk factor most strongly associated with the development of delirium in older hospitalized patients [3]. A multicomponent intervention to prevent delirium (ie, orienting communication, therapeutic activities, sleep enhancement strategies, exercise and mobilization, provision of vision and hearing aids, oral repletion of dehydration) has been shown to decrease the likelihood of delirium developing in older hospitalized patients at increased risk [4]. Once it occurs, the management of delirium in a patient with dementia remains empirical, with no evidence from recent studies to support changes from current practices [5].

Comorbidities are both common and costly in patients with AD and dementia [6,7]. Appropriate therapy of their comorbidities is an important component of the care provided to these patients. There is evidence that patients with dementia are less likely to be offered recommended therapy for other conditions [8]. Also, poor control of comorbidities might accelerate the rate of progression in AD. With diabetes as an example, hyperglycemia itself can induce cognitive changes by disrupting glucose metabolism with the formation of abnormal glycosylation products and the development of microvascular changes [9]. Hyperinsulinemia is a risk factor for accelerated cognitive decline [10]. Insulin increases the release of beta-amyloid and interferes with its degradation by competing for the insulin-degrading enzyme that metabolizes both insulin and beta-amyloid in the central nervous system [11]. Optimal diabetic management might slow down the rate of further decline in patients with existing AD, but this requires confirmation [12]. Community-based studies have shown that the presence of comorbidities predicts a higher mortality rate in patients with AD [13–15]. The presence of AD and dementia will affect the management of other chronic conditions. A unique feature of the care of a demented patient is reduced reliance on patient self-care and a concomitant increase in the effort to provide caregiver support and education.

3.5. Recommendation 4: Recommendations with regards to the general medical care of a patient with mild to moderate dementia

A. Patients with mild to moderate dementia when hospitalized should be identified as being at increased risk for delirium. They should be offered multicomponent interventions including orienting communication, therapeutic activities, sleep enhancement strategies, exercise and mobilization, provision of vision

and hearing aids, and/or oral repletion of dehydration to decrease their risk of developing delirium (Grade B, Level II-1).

B. Comorbidities of patients with mild to moderate AD should be appropriately managed (Grade B, Level III).

C. The management of other chronic medical conditions might have to be modified in the setting of a dementia. In general there should be less reliance on patient self-care and a concomitant increase in the role played by caregivers (Grade B, Level III).

Ensuring medication adherence can be a significant challenge in the care of an individual with dementia because cognitive factors limit the ability of patients to self-medicate [16]. Caregivers might have to become involved in medication management. The use of compliance aids would be another option. For example, computer telephony systems might improve medication adherence [17].

Studies have shown that older adults with probable dementia are more likely to be taking anticholinergics than matched controls [18]. A partial listing of medications with anticholinergic activity is given in Table 1. Use of medications with anticholinergic effects can worsen the cognitive status of individuals with AD and dementia [19–23]. Older persons taking anticholinergic medications can manifest significant deficits in cognitive functioning and be classified as having mild cognitive impairment [24]. Although some drugs (eg, amitriptyline, benztropine) are well-known for their anticholinergic effects, numerous other medications possess mild anticholinergic properties. By themselves these latter agents are unlikely to lead to significant clinical symptoms, but the additive effects of multiple anticholinergic medications taken simultaneously might result in adverse effects. Another concern with their use is that they might blunt the effects of cholinesterase inhibitors because anticholinergics directly oppose the therapeutic effect of these medications. The concurrent use of anticholinergics and cholinesterase inhibitors is reportedly common [25]. A small cohort study found that concomitant therapy with anticholinergics was associated with worse outcomes in a group of demented individuals being treated with donepezil [26]. Another small study looked at cognitive and behavioral status both on and off incontinence medications that had anticholinergic effects. The subjects exhibited better performance on specific measures of cognition and behavior when off these medications. A significant, inverse relationship was found between mental status and anticholinergic level [27].

3.6. Recommendation 5: Recommendations about the use of medications in the setting of a mild to moderate dementia

A. Determination of how medications are being consumed and identification of any problems/concerns with medication management, including poor adherence, should be done on all patients with mild to moderate dementia. If problems are detected, in particular with adherence, the use of compliance aids or the assumption of medication management by another party will be necessary. The effectiveness of any alterations in medication management will have to be assessed (Grade B, Level III).

B. Even when the patient is safely self-managing their medications, there should be planning for the involvement of a third party in the management of medications for all patients with a progressive dementia because this will eventually become necessary in nearly all (Grade B, Level III).

C. The use of medications with anticholinergic effects should be minimized in persons with AD (Grade D, Level III).

The presence of dementia does not in itself mean that patients lack capacity to make decisions about themselves and their estate. AD and other neurodegenerative dementias are progressive conditions, however, that at some point will likely rob patients of their mental capacity to consent to treatment, consent to participate in a research study, look after their estate, and/or make decisions about other aspects of their life. Questions about capacity are likely to occur during the mild and moderate stages of AD.

3.7. Recommendation 6: Ethicolegal recommendations

A. Although each case should be considered individually, in general the diagnosis of dementia should be disclosed to the patient and family. This process should include a discussion of prognosis, diagnostic uncertainty, advance planning, driving issues, treatment options, support groups, and future plans (Grade B, Level III).

B. Primary care physicians should be aware of the pertinent laws in their jurisdiction about informed consent, the assessment of capacity, the identification of a surrogate decision maker, and the responsibilities of physicians in these matters (Grade B, Level III).

C. While patients with AD retain capacity, they should be encouraged to update their will and to enact both an advance directive and an enduring power of attorney (Grade B, Level III).

4. Nonpharmacologic interventions for cognitive and functional limitations

4.1. Cognitive training/cognitive rehabilitation

Cognitive training is defined as guided practice on a set of standard tasks designed to reflect specific cognitive function such as memory or attention. Cognitive rehabilitation is an individualized approach to helping people with cognitive im-

Table 1
Select medications with anticholinergic activity [18,280,281]

Antiarrhythmic
Disopyramide
Antidiarrheal
Diphenoxylate/atropine
Antiemetics/antivertigo
Cyclizine
Dimenhydrinate
Meclizine
Scopolamine
Trimethobenzamide
Antihistamines, either single or combination products containing
Azatadine
Brompheniramine
Carbinoxamine
Chlorpheniramine
Clemastine
Cyproheptadine
Dexbrompheniramine
Dexchlorpheniramine
Dimenhydrinate
Diphenhydramine
Doxylamine
Hydroxyzine
Phenindamine
Promethazine
Trimeprazine
Triprolidine
Antiparkinsonian
Benztropine
Biperiden
Ethopropazine
Orphenadrine
Procyclidine
Trihexyphenidyl
Antipsychotics
Chloropromazine
Clozapine
Flupenthixol
Fluphenazine
Loxapine
Mesoridazine
Methotrimeprazine
Olanzapine
Pericyazine
Pimozide
Prochlorperazine
Promazine
Promethazine
Thioflupromazine
Thioproperazine
Thioridazine
Thiothixene
Zuclopenthioxol
Bronchodilators
Atropine
Ipratropium
Gastrointestinal/genitourinary antispasmodics, either single or combination products containing
Belladonna alkaloids
Clidinium bromide
Dicyclomine
Dicycloverine
Flavoxate
Glycopyrrolate
Hyoscine butylbromide
Hyoscyamine
Methscopolamine bromide
Oxybutynin
Pinaverium bromide
Propantheline
Tolterodine
Muscle relaxants
Cyclobenzaprine
Orphenadrine
Opioid
Meperidine
Tricyclic antidepressants
Amitriptyline
Amoxapine
Clomipramine
Doxepin
Imipramine
Nortriptyline
Protriptyline
Trimipramine

pairment during which the person and family member determine personally relevant goals and then devise strategies for addressing them to improve function in everyday contexts.

Three small-sample RCTs examined the effect of cognitive training on memory tasks and functional performance in persons with dementia also taking cholinesterase inhibitors [28–30]. The results suggest that performance on instrumental activities of daily living (IADL) were modestly enhanced. Overall there were no significant differences in functional performance between the groups at the end of the study period or on follow-up. The modest improvements seen on specific memory tasks were not sustained or generalizable to other tasks.

The only systematic review of cognitive training concluded that because of a limited number of small-sample RCTs and their equivocal results, it was not possible to draw any firm conclusions about the effectiveness of these interventions on cognitive skills [31]. The data suggest that there was a training effect on the specific skills being trained (splinter skills) but little or no generalization to other cognitive abilities or to functional performance.

There was some evidence that an errorless learning paradigm and/or consistent practice of usual daily activities (procedural memory training) worked in a cognitive rehabilitation program to improve functional performance [32–35]. There were gains in functional performance that were maintained during a period of 2 years. However, none of the studies were RCTs.

4.2. Environment

There is one high quality RCT, some pilot projects, and two systematic reviews of the literature examining the im-

pact of environmental interventions on functional performance. The RCT examining the effectiveness of a home-environmental intervention was conducted to examine, among other things, its effect on the daily functioning of persons with dementia living at home. The program consisted of individualized environmental modifications (consistency, structured) and aides (bath seats, visual cues). The results indicated a modest but statistically significant effect on IADL 3 and 6months after intervention [36], with trends still present at 12 months [37].

Two systematic reviews of environmental impact on functional performance were undertaken. Day et al [38] reported that discrete individualized design features such as organization of space, simplicity, and structure that promoted orientation, problem-solving, memory, and mobility had positive impacts on functional performance. A review of six RCTs that met inclusion criteria [39] suggested that environmental modification in the form of assistive devices, aides, and adaptations together with individualized occupational therapy impacted positively on functional performance of persons with cognitive impairment still living at home.

4.3. Exercise

An RCT of 153 persons [40] examined whether a 3-month home-based exercise program together with strategies for caregivers to manage behavior improved functional independence in those with mild to moderate AD. The results indicated that the exercise group had significant increases on measures of physical functioning and ADL. This trend persisted at 1 year after intervention. A systematic review of the literature supports the notion that repetitive, consistent training of tasks by using procedural memory improves motor tasks and functional performance [41]. A meta-analysis of 2,020 subjects in 30 trials to determine whether exercises are beneficial for people with mild to moderate dementia suggested that exercise programs increased strength, fitness, functional performance (ie, ADL, IADL), cognitive function, and positive behavior [42].

4.4. Occupational therapy

One experimental study compared a structured occupational therapy program of caregiver strategies, environmental modifications, and community-based assistance to caregivers receiving a written report [43]. They found that for persons with moderate dementia, self-care improvements noted after intervention were maintained at 3 months. However, a systematic review [39] concluded that there is insufficient evidence about the effectiveness of individualized occupational therapy programs, and further research was required.

4.5. Other therapies

One small RCT (14 subjects) reported that transcutaneous electrical nerve simulation (TENS) appeared to have a statistically beneficial effect on ADL that was present 6 weeks after intervention [44]. A systematic review of TENS suggests that it produced short-term improvements in specific neuropsychological tests, but that the effectiveness of this intervention was stage-dependent, did not appear to impact functional performance, and was not maintained beyond 3 weeks [45]. A systematic review of psychosocial interventions for persons with mild or moderate dementia [46] reported that reality orientation was not effective in improving functional performance.

4.6. Recommendation 7: Recommendations for nonpharmacologic interventions for the management of the cognitive and functional limitations arising from mild to moderate AD

The available research on nonpharmacologic interventions for functional performance in persons with mild or moderate dementia is limited. There are few well-designed studies on which to base any firm conclusions. There is promise for individualized exercise programs, individualized environmental modifications, and individualized practice of ADL and IADL tasks. Future research, however, is required to provide the evidence needed to reach solid conclusions about the effectiveness of these interventions.

A. There is insufficient research evidence to come to any firm conclusions about the effectiveness of cognitive training/cognitive rehabilitation in improving and/or maintaining cognitive and/or functional performance in persons with mild or moderate dementia (Grade C, Level 1).
B. Further research is required to be able to conclude that cognitive training/cognitive rehabilitation is effective in improving cognitive and/or functional performance in persons with mild or moderate dementia (Grade B, Level II-1).
C. Although there is some indication of a beneficial impact on IADL and ADL, there is insufficient evidence to make firm conclusions about the effectiveness of environmental interventions in promoting functional performance in persons with mild or moderate dementia (Grade C, Level 1).
D. There is good evidence to indicate that individualized exercise programs have an impact on functional performance in persons with mild or moderate dementia (Grade A, Level 1).
E. For other nonpharmacologic therapeutic interventions there is insufficient evidence to allow any conclusions being made about their efficacy in improving or maintaining functional performance in persons with mild or moderate dementia (Grade C, Level 1).

5. Pharmacotherapy for cognitive and functional impairments

5.1. Retained general recommendations for the pharmacotherapy of dementia initially proposed by the CCCD [1] (with minor amendments)

5.1.1. Recommendation 8

Primary care physicians should be able to administer and interpret brief measures of functional activities and cognitive abilities or refer to health care professionals with the required knowledge and expertise (Grade B, Level III).

5.1.2. Recommendation 9

After treatment has been started, patients should be reassessed regularly by the appropriate health care professional involved in their care (Grade B, Level III).

5.1.3. Recommendation 10

Records should be kept such that stabilization, improvement, or persisting deterioration in treated patients will be determinable (Grade B, Level III).

5.1.4. Recommendation 11

In monitoring the response to therapy of patients with dementia, the input of caregivers (where available) should be sought. They can provide information on the patient's cognition, behavior, and social and daily functioning (Grade B, Level III).

5.1.5. Recommendation 12

If the attending primary care physician is unable to perform the assessments required to gauge response to therapy, referral to another health care professional with knowledge and expertise in dementia care (eg, other physician, nurse, occupational therapist) or a service (eg, memory clinic) who is willing to perform such assessments is advised (Grade B, Level III).

5.1.6. Recommendation 13

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 III).

Most clinicians view the cholinesterase inhibitors as first-line treatment for mild to moderate stages of AD [47]. There are three cholinesterase inhibitors available in Canada: donepezil, galantamine, and rivastigmine. Although rivastigmine and galantamine have additional modes of action, they all inhibit the breakdown of acetylcholine by blocking the enzyme acetylcholinesterase.

Cochrane reviews of each of the agents are available [48–50] as well as other meta-analyses [51–53] and qualitative systematic reviews [54–57]. Cognitive, functional, and global outcomes have been measured in these trials. The primary cognitive test in most studies has been the cognitive section of the Alzheimer's Disease Assessment Scale (ADAS-Cog). This instrument consists of 11 individual items (spoken language, comprehension of spoken language, recall of test instructions, word finding, following commands, naming objects, construction, ideational praxis, orientation, word recall, and word recognition) and is scored out of 70 (higher scores indicate greater impairment). MMSE scores are also often reported as a secondary cognitive outcome. Activities of daily living have been evaluated with a variety of instruments such as the Progressive Deterioration Scale (PDS), the Disability Assessment for Dementia (DAD), and the Bristol Activities of Daily Living Scale (BADLS). Global assessment has usually been done with the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC-Plus). Patients are assessed at baseline. At subsequent assessments they are graded on a 1 to 7 scale relative to this baseline assessment, with one indicating very much improved, four no change, and seven very much worse. The RCTs of these agents have shown consistent, albeit modest, benefits of treatment in cognition, activities of daily living, and global clinical state. Systematic reviews including those with severe dementia find similar results to those including only trials of those with mild to moderate impairment. The methodologic limitations of the published studies (eg, reporting more than one outcome without statistical correction for multiple comparisons, absence of final outcome measures on subjects who had withdrawn) were specifically noted in a systematic review of the cholinesterase inhibitors. Because of the modest benefits seen and the methodologic limitations of the studies, the authors questioned the utility of these agents [57]. Other commentators have concluded, however, that the likely effect of the methodologic concerns does not invalidate the findings of the studies reviewed and that these agents are modestly efficacious for the treatment of mild to moderate AD.

Comparison of the relative efficacy and tolerability of the cholinesterase inhibitors across clinical trials is not appropriate because of differences in the baseline characteristics of the subjects, the efficacy assessments done, and how subjects were assessed for adverse effects. The available trials that directly compared one cholinesterase inhibitor to another have methodologic limitations and/or show no significant differences in their primary outcome measures [47,58,59].

The most common side effects encountered with the cholinesterase inhibitors in the RCTs of these agents were gastrointestinal (eg, anorexia, nausea, vomiting, diarrhea) [47–50,60]. They are more likely to occur at the commencement of therapy or when the dose of the agent is increased. These side effects are dose-related and tend to be transient. Gastrointestinal side effects in the RCTs were more common with rivastigmine. Slower titration and ensuring rivastigmine is taken with food appear to decrease the risk of gastrointestinal side effects. Weight loss did occur during the RCTs of all three agents, but a follow-up of patients with AD treated with cholinesterase inhibitors found that there was not an increased risk for long-term weight loss (compared with patients with AD not receiving a cholinesterase inhibitor) and might in fact be a protective factor [61].

A variety of other adverse effects can occur. Dizziness has been reported with all three agents. If disabling, dose reduction would be a reasonable initial approach. Syncope, while rare, has been associated with the use of these agents. In a small descriptive study, noninvasive evaluation successfully identified the probable cause of syncope in most patients with AD treated with donepezil [62]. Therapeutic options would include stopping the agent or pacemaker implantation [63]. Donepezil has been associated with sleep disturbances, vivid dreams/nightmares, and hypnopompic hallucinations [60]. The Cochrane meta-analysis of donepezil confirmed a dose-related increased odds ratio for insomnia [47]. Rivastigmine and galantamine are less likely to cause sleep disturbances. Management options for this problem would include changing the timing and/or dose of donepezil or switching to another cholinesterase inhibitor.

A prescribing cascade involves the misinterpretation of an adverse reaction to one drug followed by the prescription of potentially inappropriate second drug to deal with this adverse effect. The use of cholinesterase inhibitors is associated with an increased risk of receiving an anticholinergic drug to manage urinary incontinence [64]. The use of an anticholinergic drug in this setting might represent a clinically important prescribing cascade. Another potential example of this would be the higher use of hypnotics in patients with AD treated with donepezil [65].

A number of studies have shown that it is possible to switch from one cholinesterase inhibitor to another [66–72]. Generally in these studies patients abruptly discontinued the first cholinesterase inhibitor and started taking the second agent the following day at the usual starting dose followed by up-titration at the usual rate for the new agent. Unfortunately, these studies do not tell us when we should switch. Commonly cited reasons for switching include unsatisfactory response to the first agent, intolerable side effects to the first agent, and request of the patient and/or caregiver. Switching from donepezil to memantine was well-tolerated in a study sponsored by Lundbeck, whether it was done abruptly (donepezil discontinued abruptly with memantine up-titrated to 20 mg/d during a period of 3 weeks) or gradually (donepezil dropped from 10 mg/d to 5 mg/d for 2 weeks before stopping with memantine up-titrated to 20 mg/d during a period of 3 weeks) [73]. Please note that switching from one cholinesterase inhibitor to another cholinesterase inhibitor or memantine can lead to deterioration in the status of a patient. Patients and families should be informed of this possibility before a switch is made.

5.2. Recommendation 14: Recommendations regarding the use of cholinesterase inhibitors

A. All three cholinesterase inhibitors available in Canada are modestly efficacious for mild to moderate AD. They are all viable treatment options for most patients with mild to moderate AD (Grade A, Level I).
B. Although all three cholinesterase inhibitors available in Canada have efficacy for mild to moderate AD, equivalency has not been established in direct comparisons. Selection of which agent to be used will be based on adverse effect profile, ease of use, familiarity, and beliefs about the importance of the differences between the agents in their pharmacokinetics and other mechanisms of action (Grade B, Level I).
C. All physicians prescribing these agents should be aware of the contraindications and precautions with the use of cholinesterase inhibitors (Grade B, Level III).
D. If adverse effects occur with a cholinesterase inhibitor, the agent should either be discontinued (if the side effects are judged to be disabling and/or dangerous), or the dose of the agent should be decreased, with an option to retry the higher dose after 2 to 4 weeks if the lower dose is tolerated (if the side effects are judged to be minor in severity) (Grade B, Level III).
E. If nausea and/or vomiting occur with the use of a cholinesterase inhibitor, review how the medication is being taken (eg, dose, frequency, with or without food, evidence of an unintentional overdose) and consider modifying the prescription (eg, lower dose), responsibility for administration (eg, caregiver taking over from the patient), the directions given to the patient (eg, with food), or stopping the agent. Although antiemetics can be used for nausea and/or vomiting, a number of them (eg, dimenhydrinate, prochlorperazine) have anticholinergic properties that can lead to adverse cognitive effects (Grade B, Level III).
F. Clinicians should consider the possible contributing role of cholinesterase inhibitors in new-onset or worsening medical presentations and the potential risk of co-prescribing cholinesterase inhibitors and other drugs to patients with dementia (Grade B, Level II-2).
G. Patients can be switched from one cholinesterase inhibitor to another. A decision to make a switch is based on the judgment of the prescribing physician and the patient (or their proxy) about the relative benefits and risks of making a change in the patient's pharmacotherapy (Grade B, Level III).
H. Patients can be switched from a cholinesterase inhibitor to memantine (note: see recommendation 15B). The decision of when to make a switch is based on the judgment of the prescribing physician and the patient (or their proxy) (Grade B, Level III).

Memantine is a low to moderate affinity, uncompetitive antagonist to glutamate N-methyl-D-aspartate (NMDA) receptors and might prevent excitatory neurotoxicity in dementia. Published studies show a small beneficial effect of memantine in moderate to severe AD [74]. It has not been

shown to be effective for mild stages of AD. Although the one published study showed efficacy on cognitive, behavioral, and global outcomes, two additional unpublished studies of memantine failed to show statistically significant benefits for patients with mild AD [74,75].

The NMDA receptor antagonist memantine and the cholinesterase inhibitors have different mechanisms of action. It seems reasonable to assume that an additive effect might be achieved from combination therapy. One RCT did show additional benefit when memantine was added to chronic donepezil therapy in patients with moderate to severe AD [76]. An unpublished study of memantine failed to show any statistically significant benefit when it was given to participants with mild to moderate AD who were on a stable dose of a cholinesterase inhibitor [75].

5.3. Recommendation 15: Recommendations regarding the use of memantine

A. Memantine is an option for patients with moderate to severe stages of AD (Grade B, Level I). Its use in mild stages of AD is not recommended (Grade D, Level I).
B. Combination therapy of a cholinesterase inhibitor and memantine is rational (because the medications have different mechanisms of action), appears to be safe, and might lead to additional benefits for patients with moderate to severe AD. This would be an option for patients with AD of a moderate severity (Grade B, Level I).

An area of clinical uncertainty is when to stop a cholinesterase inhibitor (or any other agent being given for AD). There is general acceptance that these decisions should be individualized and based on the balance between benefits and harm for the patient. This has become particularly contentious as a result of studies suggesting that interrupting therapy for prolonged periods of time (eg, 6 weeks) can result in the loss of treatment benefits that cannot be recaptured [77].

5.4. Recommendation 16: Recommendations about when medications for the treatment of cognitive and functional manifestations of AD should be discontinued

A. The patient and/or their proxy decision maker decide to stop;
B. The patient refuses to take the medication;
C. The patient is sufficiently nonadherent with the medication that continued prescription of it would be useless, and it is not possible to establish a system for the administration of the medication to rectify the problem;
D. There is no response to therapy after a reasonable trial;
E. The patient experiences intolerable side effects;
F. The comorbidities of the patient make continued use of the agent either unacceptably risky or futile (eg, terminally ill); or
G. The patient's dementia progresses to a stage where there is no significant benefit from continued therapy (Grade B, Level III).

5.5. Recommendation 17

After stopping therapy for AD, patients should be carefully monitored, and if there is evidence of a significant decline in their cognitive status, functional abilities, or the development/worsening of behavioral challenges, consideration should be given to reinstating the therapy (Grade B, Level III).

Both basic and clinical studies have examined whether antioxidants might be beneficial for individuals with AD [78,79]. It remains unclear whether reactive oxidative species are a cause or are a consequence of AD pathology. A number of studies have examined the natural antioxidants found in foods, vitamins E and C, and carotenes. In vitro studies have shown that vitamin E can decrease both amyloid-induced lipid peroxidation and oxidative stress while suppressing the inflammatory signaling cascade [79,80]. Vitamin C can block the creation of nitrosamines through the reduction of nitrates and might also affect catecholamine synthesis. Carotenes can modify lipid peroxidation [80]. Cohort studies examining the relationship between antioxidant intake and the likelihood of subsequent dementia have shown equivocal results [81–83]. Uncertainty persists as to the optimal agent, timing, duration, dosage, and mode of intake [79]. There has been one high quality RCT that examined the utility of high dose vitamin E (2,000 IU/d) in subjects with moderate AD [84]. Although this study suggested benefit, a recent RCT for subjects with mild cognitive impairment found none [85]. An older Cochrane review concluded there was insufficient evidence of efficacy of vitamin E in the treatment of AD to justify its use [86]. Recent reports of a higher mortality rate among those treated with high doses of vitamin E (400+ IU/d) supplementation have cast even further doubt on the advisability of using this antioxidant [87]. Treatment with idebenone, a synthetic analog of coenzyme Q10 that is an antioxidant, did not slow cognitive decline in a 52-week RCT of 536 subjects with AD [88].

A number of studies have examined the potential role of vitamin supplementation. Homocysteine levels can increase with a deficiency of any of vitamins B_6, B_{12}, and/or folic acid [89]. In the Framingham study the incidence of both cerebrovascular disease and AD was increased if homocysteine levels were greater than 14 μmol/ L [90]. Other studies, however, have failed to support the association between higher homocysteine levels and AD [91,92]. Individuals with lower levels of folate and/or vitamin B_{12} have been found to have a higher risk of developing dementia in some

[93] but not all studies [94]. Several trials of vitamin B_{12} for AD have shown inconsistent results [95,96]. Cochrane reviews for vitamins B_1 (for AD), B_6 (for cognition), B_{12} (for cognition), and folic acid (for cognition and dementia) have been done. No conclusions could be drawn from the B_1 studies examined [97]. No methodically adequate B_6 trials that involved people with dementia were found [98]. Two studies of people with dementia and low serum B_{12} levels were examined, but no statistically significant evidence of cognitive benefits with B_{12} supplementation was found [99]. No benefits on any measure of cognition or mood from folic acid with or without vitamin B_{12} supplementation were seen in patients with a dementia [100]. Although more studies are needed, the routine administration of any of these vitamins to individuals with a dementia who do not have a documented deficiency state cannot be endorsed at the present time.

Ginkgo biloba is an ancient Chinese herbal preparation that is commonly used for the treatment of cognitive impairment and dementia. Ginkgo is one of the five top prescribed products in Germany, and in North America it is the top-selling herbal remedy [101]. A review of the published studies of ginkgo concluded there was a small but statistically significant benefit seen with ginkgo compared with the placebo arm. Although the typical benefit seen was consistently less than that obtained with the cholinesterase inhibitors, ginkgo was better tolerated [102]. A Cochrane review of Ginkgo biloba for cognitive impairment and dementia concluded that the agent appeared both safe and promising. Concerns were expressed, however, about the methods used in a number of the earlier trials. The more methodologically sound trials showed inconsistent results [103]. Fifteen published case reports have described a temporal association between use of ginkgo and a bleeding event [104]. In 13 of the case reports other identified risk factors for bleeding were present. Patients using ginkgo, particularly those with known bleeding risks (eg, concurrent use of warfarin or antithrombotics), should be counseled about a possible increase in bleeding risk.

A number of lines of evidence suggest that there are increased levels of inflammatory mediators (eg, interleukins 1 and 6, tumor necrosis factor, complement) in the brains of those with AD [105,106]. Microglia cells are activated around amyloid plaques [107]. There is epidemiologic evidence that patients on anti-inflammatory agents have a reduced incidence of AD [108,109]. The RCTs that use anti-inflammatory drugs (eg, naproxen) as therapy for AD, however, have been unsuccessful to date [110]. Initial trials with nonsteroidal anti-inflammatory drugs (NSAIDs) were plagued with high dropout rates [111]. A systematic review concluded that indomethacin cannot be recommended for the treatment of mild to moderate AD [112]. Selective cyclooxygenase 2 inhibitors were better tolerated, but the trials of both rofecoxib and celecoxib were negative [111,113]. There are mechanisms other than cyclooxygenase inhibition that might contribute to the potential benefits of NSAIDs in the prevention or management of AD. Some (ie, sulindac, indomethacin, flurbiprofen. ibuprofen) but not all NSAIDs have been found to affect beta-amyloid deposition and metabolism. It is possible that the negative NSAID trials to date might have occurred because the wrong NSAID was tested. For example, no RCTs have been completed that used ibuprofen [114]. A study of prednisone (20 mg for 1 month and then 10 mg for 1 year) in 132 patients failed to show any significant benefit [115]. An RCT of hydroxychloroquine was also negative [116].

The large RCTs of inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme (ie, "statins") have had primary cardiovascular outcomes, although some of the studies have included secondary cognitive outcomes. The MRC/BHF Heart Protection Trial of simvastatin found no beneficial impact with active treatment on the likelihood of either cognitive decline or being diagnosed with a dementia [117]. The PROSPER trial of pravastatin also could not detect any cognitive benefit with active therapy [118]. On the other hand, a 12-month placebo-controlled pilot trial of atorvastatin 60 mg in 71 patients with mild to moderate AD showed statistically significant improvement on the ADAS-Cog at 6 months and a positive trend at 12 months [119]. Additional trials are ongoing.

Estrogens have a number of potentially beneficial effects for women with dementia. A Cochrane review examined the effect of hormone replacement therapy on cognition in women with a dementia. Five double-blind RCTs that included 210 women were evaluated in detail. Short-lived and clinically insignificant positive effects with conjugated equine estrogens (CEEs) were found on the MMSE (CEE, 0.625 mg/d only), Trail-Making Test-B (CEE, 0.625 mg/d only), and digit span backwards (CEE, 1.25 mg/d only). Cued delayed recall of a word list was positively affected after 2 months of transdermal diestradiol. Control subjects did significantly better on delayed recall (1 month), finger tapping (12 months), and on the Clinical Dementia Rating scale. The positive effects seen were believed to be possibly from random effects caused by multiple analyses. After correction for multiple testing only the short-term effect of transdermal estrogen remained statistically significant [120].

Androgens (the primary androgen is testosterone; it can be metabolized to the more potent androgen, dihydrotestosterone) can influence brain function directly through interactions with androgen receptors or indirectly through estradiol (testosterone is converted to estradiol by aromatase) [121]. In vitro and animal studies indicate that androgen depletion is associated with higher brain levels of beta-amyloid, hyperphosphorylation of tau protein, and decreased neuronal survival after exposure to a toxin [121–123]. Studies of healthy older men suggest that therapy with testosterone has a weak and inconsistent association with better visuospatial and memory scores on testing [122].

Some but not all studies have shown an association between reduced testosterone levels and a diagnosis of AD [124]. Two small intervention studies that included subjects with AD have been done. In one study 10 hypogonadal nursing home patients with AD were randomized to either intramuscular testosterone enanthate 200 mg every 2 weeks or placebo [125]. Unblinded assessments at 3, 6, and 9 months showed improvements on the ADAS-Cog, MMSE, and the Clock Drawing Test. One patient became aggressive and developed hypersexual behaviour. No other problems were noted. The second study was a randomized, double-blind, placebo-controlled 6-week trial that examined the effects of weekly intramuscular injections of 100 mg of testosterone enanthate on subjects with mild cognitive impairment or AD (a total of 15 subjects with AD were enrolled) [126]. Improvements in spatial memory/ability and verbal memory were seen with testosterone therapy. No adverse effects were encountered. Both groups of researchers believed that additional studies were required.

A large number of other agents with diverse mechanisms of action have been tested as potential therapies for AD. A partial listing (in alphabetical order) of these agents would include acetyl-L-carnitine; active or passive beta-amyloid immunization; Alzhemed; aniracetam; BMY21,502; besipiridine; cerebrolysin; clioquinol; cytidinediphosphocholine (CDP-choline); D-cycloserine; DGAVP; dehydroepiandrosterone; doxycycline and rifampin; erythropoietin; extract of *Melissa officinalis*; garlic; gamma-secretase inhibitor; growth hormone releasing hormone; huperzine A; hydergine; ispronicline; lethicin; lithium carbonate; melatonin; milacemide; neramexane; nicergoline; nicotine; nimodipine; paclitaxel; phosphatidyl serine; physostigmine; piracetam; propentofylline; rosiglitazone; selegiline; velnacrine; and vinpocetine. The studies of these agents have been either negative or inconclusive. None have been approved for the treatment of AD in Canada.

5.6. Recommendation 18: Recommendations with regard to supplements, herbal preparations, and other medications for the cognitive and functional manifestations of AD and dementia

A. High-dose (ie, 400+ IU/day) vitamin E supplementation is not recommended for the treatment of AD (Grade E, Level I).
B. The use of the synthetic antioxidant idebenone is not recommended for the treatment of AD (Grade E, Level I).
C. The administration of vitamin B_1, B_6, B_{12}, and/or folic acid supplements to persons with AD who are not deficient in these vitamins is not recommended (Grade D, Level III).
D. There is insufficient evidence to allow for a recommendation either for or against the use of ginkgo biloba in the treatment of dementia. Further methodologically sound trials are required (Grade C, Level I).
E. The use of an anti-inflammatory drug is not recommended for the treatment of the cognitive, functional, or behavioral manifestations of a dementia (Grade D, Level I).
F. The use of a HMG-CoA reductase enzyme inhibitor is not recommended for the treatment of the cognitive, functional, or behavioral manifestations of a dementia (Grade D, Level III).
G. Hormone replacement therapy (estrogens combined with a progestagen) or estrogen replacement therapy (estrogen alone) is not recommended for the cognitive impairments of women with AD (Grade D, Level I).
H. There is insufficient evidence to recommend the use of androgens (eg, testosterone) to treat AD in men (Grade C, Level I).
I. There is negative, inconclusive, or conflicting evidence for a number of other agents proposed as potential therapies for the cognitive and behavioral manifestations of AD. Their use cannot be recommended at this time (Grade C or D, Levels I to III, varies between agents).

6. Nonpharmacologic and pharmacologic therapy of behavioral and mood disturbances

Neuropsychiatric symptoms of dementia, also known as behavioral and psychological symptoms of dementia (BPSD), occur in the majority of people with dementia over the course of the disease [127]. Disease severity affects the prevalence of psychiatric symptoms. Major depression occurs more often in mild to moderate cognitive impairment, whereas most other symptoms are considered more common with greater dementia severity [128,129]. However, noncognitive behavioral symptoms do not correlate well with each other. In some longitudinal studies they have not shown progressive worsening with time but have appeared episodically [130]. In mild AD, some symptoms are common. For example, Lopez et al [129] found that of those with mild AD, 60% had anxiety, 55% had lack of energy, 50.5% had anhedonia, 49% had agitation, 39% had irritability, and 25.5% had delusions or hallucinations. In early dementia psychotic symptoms (especially visual hallucinations) are relatively uncommon with AD, but they occur more frequently with DLB.

The typical rating scales used for psychiatric disorders become progressively more difficult to use as the severity of dementia increases. For example, whereas in mild AD instruments such as the Geriatric Depression Scale [131] might still be valid in screening for depression, by the later stages psychometric factors such as internal consistency worsen [132], necessitating the use of alternate instruments. Instruments available for rating behavioral and mood symp-

toms in more advanced dementia are addressed in more detail in the section on severe dementia.

6.1. Recommendation 19

Assessment of patients with mild to moderate AD should include measures of behavior and other neuropsychiatric symptoms (Grade B, Level III).

6.2. Recommendation 20

The management of BPSD should include a careful documentation of behaviors and identification of target symptoms, a search for potential triggers or precipitants, recording of the consequences of the behavior, an evaluation to rule out treatable or contributory causes, and consideration of the safety of the patient, their caregiver, and others in their environment (Grade B, Level III).

Few data are available for the nonpharmacologic treatment of depression in dementia. One controlled study [133] suggests that behavioral treatments, including those emphasizing pleasant events (for the patient) and those emphasizing caregiver problem solving, might decrease depressive symptoms in this group. A Cochrane review [134] examined high quality trials of antidepressants for depressive disorders in patients with dementia. Eight studies met their stringent inclusion criteria. The mean MMSE score before treatment in the studies ranged between 15 and 23. The authors concluded there was only weak support for the efficacy of antidepressants in treating depression in patients with dementia, but they noted that only two studies used selective serotonin reuptake inhibitors (SSRIs) and sample sizes were small.

Although the treatment of depression in demented people might not improve cognition [135], there is good evidence that it might improve the quality of life of patients and their caregivers [136]. Therefore, most review articles [137] strongly recommend treatment of depression in people with AD. Antidepressants with significant anticholinergic activity (eg, tertiary amine tricyclics such as amitriptyline, imipramine, trimipramine, and doxepin) are likely to worsen cognition [138] and should generally be avoided. The SSRIs generally have less anticholinergic activity (note: paroxetine has significantly more anticholinergic activity than other SSRIs) [139], although they do have other side effects that are of concern in frail older people (ie, gastrointestinal symptoms, weight loss, sleep problems, and hyponatremia) [140]. They have been associated with falls and hip fractures [141], possibly related to mechanisms that differ from those causing falls in tricyclics [142]. The choice of a specific antidepressant therefore has to consider both its particular advantages and potential adverse effects, individualizing the choice for each patient. Once a decision has been made to use an antidepressant, of the classes of agents currently available, SSRIs would be appropriate for first-line treatment of depression in patients with AD. Other classes of nontricyclic antidepressants might also be appropriate for first-line treatment of depression [143]. Although data are sparse, electroconvulsive treatment can be useful for patients with depression who have not responded to antidepressants or who cannot tolerate pharmacotherapy [144].

6.3. Recommendation 21: Recommendations with regard to the management of depressive symptoms in the setting of mild to moderate dementia

A. Because depressive syndromes are frequent in patients with dementia, physicians should consider diagnosing depression when patients present with the subacute development (eg, weeks, rather than months or years) of symptoms characteristic of depression such as behavioral symptoms, weight and sleep changes, sadness, crying, suicidal statements, or excessive guilt (Grade B, Level III).
B. Depressive symptoms that are not part of a major affective disorder, severe dysthmia, or severe emotional lability should initially be treated nonpharmacologically (Grade B, Level III).
C. If the patient had an inadequate response to the nonpharmacologic interventions or has a major affective disorder, severe dysthymia, or severe emotional lability, a trial of an antidepressant should be considered (Grade B. Level III).
D. If an antidepressant is prescribed to a person with AD, the preferred choice would be an agent with minimal anticholinergic activity, such as an SSRI (Grade B, Level III).

The prevalence of sleep disturbance and complaints is high in older persons including those with dementia. Normal age-associated changes in sleep include less deep sleep and less rapid eye movement (REM) sleep and worse sleep efficiency (defined as the amount of time sleeping over the amount of time spent in bed). The major sleep difficulty encountered in older individuals is a decreased ability to maintain sleep. A variety of factors such as medical and psychiatric illnesses, changes in the timing and consolidation of sleep (from changes in the endogenous circadian rhythm), medications, the presence of other sleep disorders (eg, periodic limb movements in sleep [PLMS], REM sleep behavior disorder [RBD], sleep-disordered breathing), environmental factors (eg, noise and light), and poor sleep habits can all contribute to a decline in the quantity and/or quality of sleep [145]. Sleep disturbances can affect up to 44% of community-dwelling persons with dementia [146]. For family caregivers, nocturnal disturbances such as being awakened at night by care recipients wandering or getting out of bed repeatedly are disturbing aspects of care and a major risk factor for institutionalization [147].

McCurry et al [148,149] evaluated the effectiveness of the Nighttime Insomnia Treatment and Education for Alzheimer Disease (NITE-AD) program in improving sleep.

Caregivers in the treatment group received specific recommendations about setting up and implementing a sleep program for their care recipient and training in behavior management skills. Care recipients were also instructed to walk daily and increase daytime light exposure with the use of a light box. Control subjects received general dementia education and caregiver support. After 2 months of treatment, care recipients exhibited significantly greater reductions in number of nighttime awakenings, total time awake at night, and depression. At 6-month follow-up, treatment gains were maintained, and additional significant improvements in duration of night awakenings emerged. Clinicians who recommend these interventions should be aware that many caregivers need active assistance with setting up and implementing a sleep program. Simply providing caregivers with education is often insufficient. A strength of this study is the combination of approaches (sleep program, walking, and bright light) that individually might influence behavioral problems.

Although the treatment of insomnia in the older patients with the newer sedative hypnotics has been shown to be effective and safe [145], a recent and very comprehensive meta-analysis has found that the magnitude of effect was small, and that the increased risk of adverse effects was of concern [150]. These adverse effects include ataxia, memory loss, and falls, as well as impairment in driving ability. There is also a risk of dependency and accidental overuse. There are no randomized clinical trials of sedative hypnotic medications for sleep disturbance in AD [151], but these agents are widely clinically used. Their short-term use can be justified in situations in which sleep disturbance is particularly problematic. The pharmacotherapy of specific sleep disturbances such as PLMS and restless legs syndrome are supported by a greater evidence base and might include other pharmacologic interventions such as dopamine agonists.

RBD is manifested by vivid, often frightening dreams during REM sleep but without atonia. Patients "act out their dreams" with vocalization, flailing of their limbs, and/or moving around the bed. The history of RBD is obtained from the patient's bed partner. RBD is frequently associated with synucleinopathies including Parkinson's disease and DLB. It is considered a suggestive feature of DLB [152]. REM sleep reportedly has a cholinergic basis [153]. Although this is an area requiring further study, treatment options for RBD in the setting of DLB would include a clonazepam, cholinesterase inhibitor, melatonin, and quetiapine [152,154–157].

6.4. Recommendation 22: Recommendations with regard to sleep problems in the setting of a mild to moderate dementia

A. Patients with AD experiencing sleep problems should first undergo a careful assessment for medical illnesses (including pain), psychiatric illnesses (especially depression), potentially contributing medications, environmental factors, and/or poor sleep habits (eg, daytime naps) that might be adversely affecting sleep. Any identified secondary cause should be managed (Grade B, Level III).
B. The presence of an RBD in the setting of a dementia would be suggestive of DLB and related conditions. Treatment options would include clonazepam (Grade B, Level II-2).
C. Nonpharmacologic approaches to sleep disturbances can be effective for patients with AD, but a combination of these approaches will likely be required (Grade B, Level I).
D. When considered clinically necessary, pharmacologic interventions for insomnia, including short- to intermediate-acting benzodiazepines and related agents, can be used at the lowest effective doses and for the shortest possible time (Grade B, Level III).

Several systematic reviews of approaches that address behavioral problems associated with dementia also have been conducted [158–161], with the most comprehensive review conducted by Livingston et al [162]. Specific types of psychosocial education for caregivers about managing behavioral and psychological symptoms were effective treatments whose benefits lasted for months. Music therapy, Snoezelen, and possibly sensory stimulation were beneficial during the treatment session but had no long-term effects [162].

Several Cochrane Reviews have examined the effect of a variety of interventions in managing the symptoms of dementia. They concluded that although some of the interventions studied look promising, they remain unproven. All of the following Cochrane Reviews included subjects with moderate to severe dementia and who resided in long-term care facilities. A review of reminiscence therapy included four trials that revealed significant improvement in cognition and mood 4 to 6 weeks after the treatment [163]. A review of validation therapy included three studies that demonstrated no significant differences between validation and social contact or between validation and usual therapy [164]. Five trials were included in a review on bright light therapy [165]. This review revealed insufficient evidence of the effectiveness of bright light in managing sleep, behavior, cognitive, or mood disturbances associated with dementia. A review to assess whether music therapy can diminish behavioral and cognitive problems or improve social and emotional functioning included five trials. However, there was insufficient evidence to draw any useful conclusions [166]. A review that assessed the efficacy of aroma therapy as an intervention for persons with dementia concluded that the one small trial provided insufficient evidence [167]. A review of Snoezelen (multi-sensory stimulation) included two trials that demonstrated some short-term benefits in promoting adaptive behaviors during and immediately after

participation in the sessions. However, the carryover and longer-term effects of Snoezelen were not evident [168]. A review of the effectiveness of a range of massage and touch therapies offered to persons with dementia is currently being conducted [169].

The lack of demonstrated effectiveness in all of these reviews does not mean that the interventions are ineffective, but rather that there is a lack of sufficient evidence to demonstrate effectiveness. More experimental studies with larger samples and improved quality are needed to further examine the efficacy of these interventions with different types and severity of dementia. Combining subjects with a variety of dementias and at various stages of their illness does not contribute to our understanding of the efficacy of these interventions.

Most trials of cholinesterase inhibitors have been done on those with a mild to moderate severity of their dementia. Many of these trials have included caregiver-rated scales that measure behavioral and psychiatric symptoms such as the Neuropsychiatric Inventory (NPI) [170], the Cornell Depression Rating Scale [171], the Behavioral Rating Scale for Dementia [172], the noncognitive subscale of the ADAS [173], the Behavioral Pathology in Alzheimer's Disease Rating Scale [174], the Gottries-Brane-Steen scale (GBS) [175], and the Cohen-Mansfield Agitation Inventory [176].

Trinh et al [177] performed a meta-analysis that examined the efficacy of cholinesterase inhibitors in the treatment of the neuropsychiatric symptoms and the functional impairments that arise with AD. They reviewed 29 parallel group or crossover randomized, double-blind, placebo-controlled trials of patients with mild to moderate probable AD. Patients randomized to cholinesterase inhibitors improved on average 1.72 points on the NPI and 0.03 points on the ADAS-noncog compared with those on placebo. There were no significant differences between the various cholinesterase inhibitors. The authors concluded that there was a modest improvement of neuropsychiatric symptoms with the use of cholinesterase inhibitors.

Cummings et al [178] used a caregiver mailout survey to compare 84 patients taking donepezil with 248 patients not on it. They found that those taking donepezil were significantly less likely to be threatening, destroy property, and talk loudly. Although the treatment groups were not randomly assigned, supportive evidence for donepezil having a positive effect on difficult behaviors was the decreased rate of use of sedatives in those on the agent. Winblad et al [179] studied 286 patients with mild to moderate AD by using the GBS scale (which includes various behavioral and emotional items) and the NPI. There were nonsignificant improvements on the emotional/behavioral items of the GBS and on the NPI seen in those patients receiving donepezil compared with those allocated to the placebo group. Holmes et al [180] examined the efficacy of donepezil in the treatment of neuropsychiatric symptoms in AD by using the NPI. After an initial open trial of donepezil, 134 patients were randomized to either placebo or 10 mg of donepezil and assessed at further intervals. Patients randomized to donepezil after the open-label segment had significantly more improvement on the NPI as well as on the NPI-distress measure compared with the placebo group. Discordant results were obtained in the AD2000 study [181]. In this randomized, placebo-controlled, double-blind trial the effects of donepezil on 565 community-residing patients with mild to moderate AD were studied. The NPI was used. The study design was complicated, and as a result, its outcomes are difficult to evaluate. Although the authors concluded that there was no significant improvement on any of their cognitive, functional, or psychiatric measures, it is unclear what conclusions can be drawn from this study. A Cochrane review [49] of donepezil for AD evaluated the available data on the effects of treatment on behavior (as measured by the NPI). The authors concluded that there was a significant benefit seen with donepezil. Compared with the placebo arm, there was a mean difference of 6.20 at 6 weeks and 3.2 at 24 weeks favoring active therapy on the intent to treat (ITT)–last observation carried forward (LOCF) analysis. An article by Seltzer et al [182] was not included in the Cochrane review because they used an apathy scale [183] as their behavioral measure. This trial was a double-blind, 24-week, placebo-controlled study of donepezil in 153 patients with early AD. The active treatment group scored better on the apathy scale, although this was not statistically significant.

Rösler al [184] used the CIBIC-Plus to measure the effects of rivastigmine treatment compared with placebo in 98 patients with mild to moderate AD. This was a 26-week randomized, placebo-controlled trial followed by an open-label extension period. A variety of behavioral and psychiatric measures derived from the CIBIC-Plus showed significant improvements with rivastigmine compared with placebo. Finkel [185] published a meta-analysis of three 6-month, placebo-controlled trials of rivastigmine in mild to moderate AD. He found that patients on rivastigmine with neuropsychiatric symptoms at baseline exhibited significant improvements with paranoid and delusional thoughts as well as in aggression. Patients who did not have significant neuropsychiatric symptoms at study entry were less likely to see their emergence if treated with rivastigimine, but this was not statistically significant for hallucinations.

Herrmann et al [186] performed a post hoc analysis of pooled data from three large trials (2,033 subjects) of galantamine treatment for mild to moderate AD. They found that compared with those on placebo, treatment with galantamine was associated with a better total NPI score and better scores on specific NPI items that included agitation/aggression, anxiety, disinhibition, and aberrant motor behavior. Similar beneficial results were found in a priori defined symptom clusters 1 (delusions, hallucinations), 3 (disinhibition, elation, aberrant motor behavior), and 4 (hallucinations, anxiety, apathy, aberrant motor behavior). The

authors believed that the cluster of hallucinations, anxiety, apathy, and aberrant motor behaviors might represent a specific group of cholinergic-responsive behavioral symptoms. A Cochrane review of galantamine for AD and mild cognitive impairment examined 10 trials with a total of 6,805 subjects [50]. Treatment effects on the NPI were reported at 3 months in one trial and at 6 months in three trials. There was no statistically significant treatment effect at 3 months for the 24 to 32 mg per day dosage (OC and ITT), but at 6 months there was a significant treatment effect (OC and ITT) for 16 mg per day.

Areosa Sastre et al [187] performed a Cochrane review of the use of memantine for dementia. They identified only one reported trial for mild to moderate AD [188]. In this trial, NPI scores at 24 weeks were significantly better (3.5 points) if the patients received memantine compared with those allocated to the placebo arm. However, there were two completed but unpublished studies that examined subjects with mild to moderate AD. Their specific behavioral results are not available for detailed evaluation. This makes it difficult to make any conclusions at this time.

RCT data on the effects of cholinesterase inhibitors and memantine on the BPSD come principally from secondary outcome measures of trials primarily designed to measure cognitive and global outcomes in subjects with a low frequency and severity of BPSD. With few exceptions, these studies were not designed to look at BPSD as the primary outcome. The available data have to be interpreted with this in mind. The benefits seen in the studies done to date might not apply to patient populations with more severe baseline neuropsychiatric abnormalities.

Antipsychotics, antidepressants, anticonvulsants, and other medications have also been used for the treatment of neuropsychiatric symptoms of dementia. However, most of the trials of these agents have been conducted in more severely impaired populations (see section on severe AD for information and recommendations on specific agents).

Patients with psychotic features and a mild dementia might be prescribed an antipsychotic. Patients with DLB exhibit an abnormal sensitivity to antipsychotics, and they should be avoided if possible [152]. The presence of visual hallucinations and visuospatial/constructional dysfunction (eg., problems copying the intersecting pentagons on the MMSE) early in the course of the dementia would be suggestive of DLB [189]. In this autopsy-confirmed study, the positive predictive value for DLB was 83% for visual hallucinations, whereas the lack of visuospatial impairment had the best negative predictive value (90%). Treatment options for visual hallucinations in the setting of DLB would include cholinesterase inhibitors and/or a cautious trial of an atypical neuroleptic [152]. Of the available atypical neuroleptics, quetiapine would appear to be an attractive choice, but controlled trials are needed [152,157].

6.5. Recommendation 23: Recommendations with regard to the management of BPSD in the setting of a mild to moderate dementia

A. Nonpharmacologic treatment of BPSD should be considered first. Nonpharmacologic interventions are often used in combination with pharmacotherapy (Grade C, Level I).
B. Although there is insufficient evidence regarding the effectiveness of the interventions to strongly advocate for their routine use in the management of BPSD, some persons with dementia might benefit from the following: music, Snoezelen (multi-sensory stimulation), bright light therapy, reminiscence therapy, validation therapy, aroma therapy, and massage and touch therapy (Grade C, Level II-3).
C. Pharmacotherapy for BPSD should be initiated only after consideration, and usually a trial where appropriate, of nonpharmacologic interventions (Grade B, Level III).
D. The presence of visual hallucinations in the setting of mild dementia would suggest that the patient has DLB. Patients with DLB are abnormally sensitive to antipsychotics. If pharmacotherapy is required for the visual hallucinations, a cholinesterase inhibitor should be tried first if possible. If acute symptom control is required or the cholinesterase inhibitor is ineffective, a cautious trial of an atypical antipsychotic (eg, very low dose quetiapine) can be attempted (Grade B, Level II-2).
E. Medications for BPSD should normally be initiated at a low starting dose and then subsequently titrated carefully on the basis of the patient's response and the presence of adverse effects (Grade B, Level III).
F. There should be periodic attempts to taper and withdraw medications after a period of 3 months of behavioral stability (Grade B, Level III).
G. Patients who have mild to moderate AD and neuropsychiatric symptoms can be considered for a trial of a cholinesterase inhibitor and/or memantine for these symptoms (Grade B, Level III).
H. Treatment of BPSD with cholinesterase inhibitors or memantine should persist until clinical benefits can no longer be demonstrated (Grade B, Level III).

Behavioral disturbances have been reported to occur in 63% of community-dwelling persons with dementia [190]. These disturbances increase distress for those with dementia, increase the strain for caregivers, and might be potentially dangerous for the care recipient, caregivers, and others. Those with behavioral disturbances enter long-term care facilities nearly 2 years earlier than those without [191]. Dementia-related behavioral disturbances that most frequently occur in the home setting are wandering, general restlessness, agitation, and uncooperativeness [192].

In 1994, the Canadian Study on Health and Aging (CSHA) [193] reported that half of those diagnosed with dementia live in the community and are cared for by family and friends who must deal with the long-term and disabling behavioral problems associated with the care recipient's dementia. In 2000, the proportion of persons with dementia who live at home had risen to 80% [194]. Although community services have been shown to be useful in prolonging independence and quality of life of those with dementia, the CSHA revealed that community services are underutilized. Sixty-nine percent of spouse caregivers and 46% of caregivers who were sons or daughters used no services, and only 3% to 5% of caregivers used three or more services [195]. Only 38% of Canadians with dementia received home care services in 2000/2001 [196]. Several barriers to using home care services have been identified: cultural and ethnic factors, a reluctance to use formal services until absolutely necessary, a perception that caregiving is a familial responsibility, acknowledging their family member has dementia and they are unable to manage, lack of awareness, acceptability and accessibility of services (eg, distance especially in rural areas, costs, inadequate training of service providers), and challenges in service delivery (care often needed 24 hours a day) [197–199].

Although community-based programs have primarily focused on caregivers [200], in this section we will highlight community-based programs and interventions that aim to manage the behavioral disturbances associated with mild to moderate dementia. Interventions that are of benefit to caregivers are described elsewhere. Included studies in this review had to meet the following criteria: (1) the majority of subjects were diagnosed with AD or related dementia, (2) the majority of subjects were classified as having mild to moderate dementia (defined as MMSE score of $\geqslant$10 or a Global Deterioration Scale score of 3 to 5 [201], and (3) the sample size was at least 10. The term *caregivers* refers to unpaid caregivers who are usually family or friends of the care recipient and who provide support and assistance in the activities of daily living and instrumental activities.

Case management involves an assessment of client and caregiver needs and the development, implementation, and monitoring of a care plan that can maintain a client safely in the community. The care plan typically involves the arrangement and coordination of a number of in-home and community-based services such as housekeeping, personal care, and respite services to supplement care already received from family and friends. Case management activity has been shown to be reactive and focused on dealing with the consequences of the behavioral problems rather than addressing the management of the behavior [192]. A demonstration project randomly assigned individuals with dementia and their caregivers to a treatment group that received community-care services (eg, homemaking, personal care, companion services, and adult day care) and case management or to a control group that received regular medical care [202,203]. The study investigated whether increased access to community care and case management led to a reduction in health care use and expenditures. Only a tendency toward reduced health care expenditures was observed in the treatment group. Case management did not result in increased access to health care or to the prevention of conditions that might increase expenditures. Perhaps case manager involvement produces short-term increases in expenditures, and a longer time period (greater than 3 years) is required to demonstrate the benefits. The demonstration study was also not designed to promote collaboration between the case manager and other health care practitioners in identifying and managing high-risk people. Further research is necessary to demonstrate and evaluate the role of case managers in managing behavioral problems of community-dwelling persons with dementia.

Adult day care programs provide supervised, structured activities for the care recipients during the day, enabling their caregivers to rest or tend to other responsibilities. Several studies have evaluated the effect on behavior problems of persons with dementia. One study demonstrated that behavioral difficulties such as wandering, agitation, and anger were not found to predict use of adult day care programs [204]. Several studies revealed that combined family support (patient and family supported by one professional staff member) while participating in an adult day care program was more effective in decreasing behavior problems (including inactivity and nonsocial behaviour), improving mood, improving caregiver's level of confidence, and delayed nursing home placement when compared with those who received psychogeriatric day care only. The support offered to caregivers included informational, practical, emotional, and social support [205–207].

Support groups for caregivers are widespread in health and voluntary organizations. However, the majority of experimental studies have been unable to demonstrate any significant effect in decreasing caregiver burden and stress or on patient behavioral and psychological symptoms [208–210]. Hébert et al [211] addressed some of the limitations of these previous studies by offering the group program during a longer period (15 two-hour weekly sessions), incorporating a specific theoretical framework, and focusing on the management of behavioral problems and the reactions they created. This experimental study demonstrated a 14% decrease in reactions to the behavioral problems of the care receivers compared with a 5% decrease in the control group. The frequency of behavioral problems also decreased. Focusing on immediate, tangible outcomes that are expected to change as a result of the intervention (such as behavioral problems) rather than more long-term, global outcomes (such as preventing institutionalization and enhancing well-being) are important lessons learned from this study.

More expensive home-based programs have also demonstrated a significant effect in managing the disturbing behaviors associated with dementia. In a Finnish study

Eloniemi-Sulkava et al [212] compared a 2-year program that consisted of systematic, comprehensive support by a dementia family care coordinator (nurse) with conventional care. The coordinator addressed health problems of the care recipient and caregiver, behavioral and psychological symptoms of the care recipient including restlessness, anger, delusions, aggression, and depression, and caregiver stress and burden. Educational courses were offered annually. The support of the coordinator deferred placement in long-term institutionalized care, especially for persons with severe dementia. The authors recommend that the intervention be targeted especially at persons with behavioral problems that threaten their ability to continue to remain in their home.

A less intensive psychoeducational intervention, based on the Progressively Lowered Stress Threshold Model [213], was offered in home during two 2-hour sessions to teach caregivers how to manage behavioral problems (eg, structured routine, environment modifications, decreased environmental stimuli) [214]. This study was conducted in five states in the United States. The intervention had a positive impact during a period of 12 months on the frequency of and response to problem behaviors among spousal caregivers, and nonspousal caregivers reported a reduction in the frequency of memory/behavioral problems. An experimental study conducted in Taiwan demonstrated that a two-session in-home caregiver training program and telephone consultations every 2 weeks for 3 months decreased physically nonaggressive behavior, verbally aggressive and nonaggressive behavior (but not physical aggression), and improved caregivers' self-efficacy for managing these behaviors. The subjects' level of severity of dementia is not reported [215]. Other similar behavioral intervention studies [216] have not been able to demonstrate a significant effect in managing disturbing behaviors, possibly as a result of their small sample sizes and short duration of the programs.

The remaining retrieved community-based studies did not meet our inclusion criteria because the sample sizes were less than 10 [217,218], or the subjects' MMSE scores were less than 10 [219].

6.6. Recommendation 24: Recommendations concerning community-based programs for the management of behavioral disturbances

For the following community-based programs for the management of behavioral disturbances, there is limited high quality evidence regarding effectiveness. The recommendations are based on one to two RCTs for each program.

A. Adult day care (greater involvement of the caregiver might decrease problem behaviors in the care recipient) (Grade B, Level II-2).
B. Support groups that focus on the management of behavioral problems and extend for a period of several months (Grade B, Level I).
C. In-home systematic, comprehensive support by a health care provider with advanced training in dementia care during an extended period (ie, couple of years) (Grade B, Level I).
D. In-home psychoeducational intervention that teaches caregivers how to manage behavioral problems (Grade B, Level I).

7. Driving

In North America, driving a motor vehicle is an important aspect of modern culture that has almost become an activity of daily living. The ability to drive is often needed to maintain independent mobility [220]. It is also an expression of autonomy and independence and contributes to many important aspects of a person's quality of life, including maintenance of family/social ties and participation in recreational activities. For all individuals, including those with physical, mental, or functional disabilities, the ability to drive permits the continuation of independent living.

Loss of driver licensure for an older person can have a direct health impact, with increases in depressive symptomatology [221]. Increased loneliness, social isolation, and stress on family and friends have been linked to the loss of the ability to drive in older persons [222–225], with this impact tending to be greater for those in rural areas [226]. Even for those in urban areas, public transportation systems do not adequately replace the mobility and freedom of operating one's own motor vehicle [227]. Older drivers often feel angry and frustrated with those who deem them unfit to drive, straining personal and professional relationships [228]. However, as much as it is desirable to promote personal independence, the safety implications of driving from an individual and societal perspective require careful consideration.

Given that many forms of dementia are progressive in nature, and unlike other medical conditions, persons with dementia often lack the insight to curtail their driving exposure in the face of an increased crash risk, some authors have advocated for the suspension of driving privileges in all persons who are diagnosed with dementia [229]. However, some studies have shown that some older persons in the early stage of dementia are able to safely operate a motor vehicle [230,231]. Research and public policy have been primarily focused on cognitive and visuoperceptual deficits as they relate to driving [232–235]. Cognitive deficits affecting driving include memory impairment, poor sequencing skills, impaired insight and judgment, apraxia, and slowed processing time [236–243]. Visuoperceptual deficits are an important subset of cognitive skills directly related to driving ability [244–246].

7.1. Dementia and driving risk

Table 2 summarizes controlled studies that have examined driving risk in patients with dementia. A total of 25

Table 2
Summary of controlled studies determining motor vehicle crash risk in persons with dementia [229–232,282–302]

Study (Author, Date)	Methodology	Outcome Measure Used	Main Findings
Waller et al [300], 1993	Case control: 99 AD patients; 495 unmatched controls	State driving record	No difference in crash rates
Cooper et al [284], 1993	Case control: 165 dementia patients; 165 age-, sex matched	State driving record	Dementia patients 2× more likely to have had a crash
Tuokko et al [298], 1995	Case control: 249 AD patients; 249 age-, sex matched controls	State driving record	AD patients 2.5× more likely to have had a crash
Trobe et al [230], 1996	Case control: 143 AD patients; 715 age-, sex matched controls	State driving record	No difference in crash rates
Carr et al [231], 2000	Case control: 63 AD patients; 58 unmatched controls	State driving record	No difference in crash rates
Drachman et al [287], 1993	Case control: 130 dementia patients; 112 unmatched controls	Caregiver reported crashes	Dementia patients 2.5× more likely to have had a crash
Friedland et al [229], 1988	Case control: 30 AD patients; 20 age-matched controls	Caregiver reported crash past 5 y	AD patients 8× more likely to have had a crash
Zuin et al [302], 2002	Case control: 56 dementia patients; 31 unmatched controls	Caregiver reported crashes	More frequent crashes in dementia patients ($P = .12$)
Ott et al [294], 2003	Case control: 27 mild dementia patients; 40 unmatched controls	Caregiver reported driving ability	More frequent crashes in dementia patients
Hunt [291], 1989	Case control: 12 questionable dementia patients; 14 mild dementia patients 13 age matched controls	On road performance	More mild dementia patients failed test ($P < .05$)
Hunt [292], 1993	Case control: 12 very mild dementia patients; 13 mild dementia patients; 13 unmatched controls	On road performance	5/13 mild failed test; all controls and very mild passed
Rebok et al [295], 1994	Case control: 10 AD patients; 12 unmatched controls	On road performance	Worse performance in AD patients
Fitten et al [232], 1995	Case control: 25 mild dementia patients; 24 age-matched controls	On road performance	Worse performance in dementia patients
Cushman [286], 1996	Case control: 32 early AD patients; 91 unmatched controls	On road performance	More AD patients failed test
Hunt et al [293], 1997	Case control: 36 very mild AD patients; 29 mild AD patients; 58 unmatched controls	On road performance	Worse performance in AD patients
Wald [299], 1998	Case control: 112 dementia patients; 50 unmatched controls	On road performance	Worse performance in dementia patients
Duchek et al [288], 1998	Case control: 49 very mild AD patients; 29 mild AD patients: 58 unmatched controls	On road performance	Worse performance in AD patients
Bieliauskas et al [282], 1998	Case control: 9 AD patients; 9 age matched controls	On road performance	More driving errors in AD patients
Duchek et al [289], 2003	Case control: 21 very mild AD patients; 29 mild AD patients; 58 unmatched controls	On road performance	More rapid decline in driving skills in dementia patients
Whelihan [301], 2005	Case control: 23 mild dementia patients; 23 age-matched controls	On road performance	Worse performance in dementia patients
Harvey [290], 1995	Case control: 13 dementia patients; 125 unmatched controls	Driving simulator performance	Worse performance in dementia patients
Rizzo et al [296], 1997	Case control: 21 AD patients; 18 unmatched controls	Driving simulator performance	Higher crash rate in AD patients ($P = .02$)
Cox et al [285], 1998	Case control: 29 AD patients; 21 age-matched controls	Driving simulator performance	Worse performance in AD patients
Rizzo et al [297], 2001	Case control: 18 AD patients; 12 unmatched controls	Driving simulator performance	Higher crash rate in AD patients ($P < .05$)
Carr et al [283], 1998	Case control: 70 dementia patients; 667 unmatched controls	Traffic sign recognition test	Worse performance in dementia patients

studies were identified, all using a case-control design. Increased driving risk for patients with dementia was found in two of five studies with state driving records as their outcome, four of four with caregiver report of collisions/driving ability, ten of ten with on-road driving performance, four of four with driving simulator performance, and one of one with the ability to recognize traffic signs. Similar results were found for studies that examined patients with AD only. All studies that used a form of driver performance (on-road or driving simulator performance) as their outcome measure found that drivers with dementia performed worse than control subjects. However, when using state crash records,

the most objective and arguably the most relevant measure of driving risk, increased driving risk for patients with dementia was not consistently found. Collision rates as recorded on state driving records might be a relatively insensitive measure of driving risk and thus have limited ability to detect differences in outcomes between drivers with and without dementia. However, crash rates might be the most important outcome measures because they are the events of most concern to society, placing individual drivers at most risk. It is possible that as the driving skills of patients with dementia deteriorate, patients, their families, and health professionals undertake measures to restrict driving exposure, thus reducing crash risk. No studies were found examining the driving performance of persons with mild cognitive impairment.

7.2. Magnitude of driving risk

It is difficult to precisely estimate the magnitude of driving risk for persons with dementia. Of the two of five studies that found a positive association between crashes recorded on the state driving record and dementia, persons with dementia had a 2 to 2.5 times increased risk. However, factors such as severity of dementia and level of driving exposure were not factored into these estimates. The latter is important because persons with dementia drive fewer miles per year compared with age- and sex-matched controls. When tested on road and in driving simulators, it is very clear that persons with dementia are poorer drivers compared with those with normal cognition. This poorer performance might not translate into consistently higher collision rates per miles driven because of self, family, or authority imposed driving restriction.

7.3. Cognitive functions and driving

Numerous studies have examined the association of specific neuropsychological tests and driving risk [247]. Brief tests of general cognitive functioning such as the MMSE [248] have shown an inconsistent relationship with driving risk. Similar results were also found for studies specifically examining tests of attention and concentration, visuospatial skills, memory, executive functioning, and language. In each of these domains, there were a few studies finding positive associations between specific tests and driving risk, but these results have not been confirmed in other studies. There is no single brief cognitive test that has sufficient validity, reliability, sensitivity, and/or specificity to be considered a robust tool in identifying older drivers with dementia who are cognitively unfit to drive or need further testing. Further research is necessary to determine whether a combination of brief tests can meet this goal.

7.4. Assessment and follow-up

In many provinces and territories, physicians and other clinicians are legally mandated to report drivers whom they believe have medical conditions that might/will impact on their ability to drive to their respective Ministries of Transportation. Given that not all drivers with dementia (especially those with mild dementia) have higher crash rates than drivers without dementia, a diagnosis of dementia is not sufficient in itself to lead to automatic revocation of the driver's licenses. Rather, as recommended by a number of organizations and groups [249,250], determination of the functional driving abilities at the individual level is the fairest and most appropriate method of assessing fitness to drive in persons with mild dementia.

Given that many causes of dementia are progressive in nature, most persons with dementia will eventually need to give up driving. To lessen the impact of transition to nondriving, planning for this inevitability should take place as soon as the diagnosis of dementia is made. This planning could include the development of alternative transportation options and participation in driver cessation support groups. For those with a progressive dementia initially deemed safe to drive, progressive deterioration in driving skills can be expected. Studies show that persons with mild dementia who are initially deemed safe to drive are often found to be unsafe 6 to 12 months later [251,252].

7.5. Compensation methods

Potential methods of compensating for the decreased driver performance and increased crash risk in drivers with dementia include the following.

7.5.1. Retraining/education programs

No studies were found assessing the efficacy of retraining/education programs on improving the driving performance in persons with dementia. Because persons with dementia have underlying progressive memory and cognitive deficits and often difficulties with insight and judgment, attempts to upgrade their driving skills is not a reasonable option.

7.5.2. Use of co-pilots

No studies were found assessing the efficacy of having other persons accompany drivers with dementia with respect to reducing their driving risk. Because many crashes occur in a split second without time to give instructions to drivers, this method of compensation would seem to be ineffective.

7.5.3. Use of on-board navigation and crash warning systems

No studies were found that assessed the efficacy of these systems on improving the driving risk in persons with dementia. Because the information processing of most persons with dementia is impaired, these technologies are unlikely to compensate for the driving deficiencies that drivers with dementia demonstrate.

7.5.4. Restricted licensing

Although some studies have shown that, in general, restricted licenses reduce crash rates, no studies were found that specifically examined whether the granting of restricted or conditional licensing to drivers with dementia reduces their driving risk. Although many drivers with dementia perform adequately in routine predicable situations, they do not perform as well in situations that are less predictable, precisely the time when many crashes occur. Therefore, it is unlikely that the use of restricted/conditional licenses significantly reduces crash risk in persons with dementia.

7.6. Recommendation 25: Recommendations with regard to driving a motor vehicle and individuals with a mild to moderate dementia

A. Clinicians should counsel persons with a progressive dementia (and their families) that giving up driving will be an inevitable consequence of their disease. Strategies to ease this transition should occur early in the clinical course of the disease (Grade B, Level II-2).
B. No single brief cognitive test (eg, MMSE) or combination of brief cognitive tests has sufficient sensitivity or specificity to be used as a sole determinant of driving ability. Abnormalities on cognitive tests such as the MMSE, clock drawing, and Trails B should result in further in-depth testing of driving ability (Grade B, Level III).
C. Driving is contraindicated in persons who, for cognitive reasons, have an inability to independently perform multiple instrumental activities of daily living (eg, medication management, banking, shopping, telephone use, cooking) or any of the basic activities of daily living (eg, toileting, dressing) (Grade B, Level III).
D. The driving ability of persons with earlier stages of dementia should be tested on an individual basis (Grade B, Level III).
E. A health professional–based comprehensive off-road and on-road driving evaluation is the fairest method of individual testing (Grade B, Level III).
F. In places where comprehensive off-road and on-road driving evaluations are not available, clinicians must rely on their own judgment (Grade B, Level III).
G. For persons deemed safe to drive, reassessment of their ability to drive should take place every 6 to 12 months or sooner if indicated (Grade B, Level III).
H. Compensatory strategies are not appropriate for those deemed unsafe to drive (Grade B, Level III).

8. Support of caregivers

In Canada about half of the individuals with dementia reside in the community, and more than 90% are cared for by family and friends [193,195]. Previous research has characterized the negative consequences of dementia caregiving or caregiver burden. Depression and anxiety are of particular concern. All individuals caring for someone with a chronic illness have been found to have increased rates of psychiatric morbidity, but those caring for someone with dementia are even more at risk, with rates reportedly as high as 50% [253].

The primary theoretical model explaining the specific effects of this burden is the stress/health model that explains how the stress of caregiving is translated into psychiatric and physical morbidity [254]. Factors associated with significant caregiver burden and/or stress have been well-described. These include factors related to the dementia patient and those related to the caregiver themselves. Problem behaviors of the dementia patient such as depression and aggression are the most important predictors of caregiver burden. Less predictive of burden is the amount of assistance with ADL provided to the patient by the caregiver. Important caregiver factors that have been found to be associated with caregiver burden include female gender, low income, low life satisfaction, poor self-esteem and self-assessed competence, and lack of social support. Limited research has been done to understand the positive aspects of caregiving. These might be of particular importance because caregivers who could identify at least one positive aspect of caregiving are less likely to report burden or depression [255]. A thorough understanding of the negative and positive aspects of caregiving is important not only to reduce caregiver burden but also to reduce potentially negative outcomes for individuals with dementia. For example, caregiving burden has been shown to be a risk factor for nursing home placement [256].

Many intervention studies have been designed to reduce caregiver burden and delay the negative outcomes of burden such as nursing home placement. These interventions target patient and caregiver factors that have been associated with burden. These interventions include those designed to reduce the behavioral and psychological problems of the dementia patient or the amount of assistance needed by the demented patient. They also include strategies aimed primarily at the caregiver to increase their knowledge about the disease, provide additional resources and supports, reduce anxiety and depression, or alter caregiver behavior.

Interventions have been delivered in a variety of modalities either singly or in combination. Intervention formats include those that are group based, individually based, technology based (telephone or computer), or service configurations [257]. Broadly speaking, the interventions focus on education, psychotherapy, or provision of services. Education can include providing information about dementia or skills training to change the caregivers' interaction with the dementia patient. Psychotherapy can include psychological support for the caregiver, assistance to develop their social support network, and self-care strategies. Services might include access to respite care, day care, or a case manager.

The most clinically relevant effects of these interventions have been reductions in rates of caregiver depression and delays in nursing home placement, although some might argue that prolonging community care might not always be a desirable outcome. Other positive effects include caregiver satisfaction with services, improved self-appraisal of caregiver coping skills and knowledge, and improved relationships with the care recipients. Common features of successful interventions include (1) a continuing relationship between the caregiver and helper over time, (2) a variety of flexible interventions offered that can meet the varied needs of caregivers, (3) psycho-education or skills training that teaches caregivers to change their interactions with patients with dementia, and (4) involvement of the caregiver and patient in the intervention. Interventions that appear unsuccessful include short educational programs that only enhance knowledge about dementia, support groups alone, and service configurations such as case management or brief interventions that do not include long-term contact with the caregiver [161,254,256–258]. A Cochrane review on respite care for people with dementia and their caregivers found no evidence of either benefit or adverse effects from the use of respite services. The authors believed their results should be treated with caution because they might reflect the dearth of high quality studies rather than any true lack of benefit [259].

There is often a major discrepancy between the elaborate programs that the literature tells us are effective and what is locally available. Although these latter services might not decrease caregiver burden, they can improve caregiver satisfaction. Long-term involvement with these programs tends to be more beneficial.

The studies examined were often limited by small sample sizes, short follow-up times, and the many caregiver and patient outcomes that were studied. The heterogeneity of the caregiver experience is clearly a factor limiting the effectiveness of these interventions or the generalizability of many studies. Targeting caregivers who meet specific criteria such as scoring above a certain level for measures of depression might improve outcomes in the future. Schultz and Martire [254] recommended the assessment of caregiver risk in five domains. Interventions can then be targeted to those areas identified as problematic for individual caregivers. The risk areas are safety, self-care and preventative health behaviors, caregiver support (informational, instrumental, and emotional), depression and distress, and problem behaviors of care recipients.

A number of the RCTs of drug therapy for mild to moderate AD have included caregiver burden as a secondary outcome measure. A recent systematic review of the effect of cholinesterase inhibitors on burden and active time use of caregivers of persons with AD concluded that they had a small beneficial effect on both [260].

There have been a few guidelines and position statements on dementia care published since the CCCD. The American Academy of Neurology (AAN) published guidelines in 2001 that included two recommendations of relevance for family caregivers [261]. One recommendation was that short-term programs directed toward educating caregivers about AD be offered to improve caregiver satisfaction. In addition, the AAN recommended that intensive long-term education and support services (when available) be offered to caregivers to delay time to nursing home placement. Listed as practice options (evidence supported by expert opinion, case series, and studies with historical controls only) were use of computer networks to provide education and support to caregivers, telephone support programs, and respite services including adult day care.

The American Association of Geriatric Psychiatry issued a statement on family caregivers of dementia patients in 2001 [262]. It emphasized the importance of caregivers in the treatment of patients with dementia and recommended that caregiver counseling be a reimbursable covered service. The American Medical Association has also encouraged a physician/caregiver/patient partnership in dementia care. They have advocated that physicians monitor caregiver functioning and have developed Web-based materials and information to assist physicians in addressing caregiver needs [263]. A caregiver self-assessment tool is available to assist in identifying caregivers at risk of adverse health outcomes. Caregivers who report high levels of distress in completing this questionnaire are encouraged to get a check-up from their physician, obtain respite from caregiving, and consider joining a support group. Physicians caring for these caregivers are encouraged to discuss the need for counseling and other interventions and to refer them to available community services.

Financial hardships can be encountered in caring for a person with dementia at home. Government plans might provide a degree of financial relief. For example, in Canada most patients with a dementia would be eligible for a disability tax credit. Physicians and other qualified practitioners can alert caregivers of this potential tax benefit and can help them in making an application by filling out Part B of the Disability Tax Credit Certificate (Form T2201, available at www.cra.gc.ca/forms). For details of this program please refer to *Information Concerning People With Disabilities* (guide RC4064) or visit the Canada Revenue Agency Web site (www.cra.gc.ca/disability).

8.1. Recommendation 26: Recommendations with regard to caregivers

A. The clinician should acknowledge the important role played by the caregiver in dementia care. The clinician should work with caregivers and families on an ongoing basis and schedule regular appointments for patients and caregivers together and alone (Grade B, Level III).

B. The clinician should inquire about caregiver information and support needs, provide education to patients and families about dementia, and assist in recruiting other family members and formal community services to share the caregiving role. If available, refer patients to specialized dementia services (eg, Alzheimer Society, community-based dementia programs, memory clinics) that offer comprehensive treatment programs including caregiver support, education, and training (Grade A, Level 1).
C. The clinician should inquire about caregiver health (both physical and psychiatric), offer treatment for these problems (including individual psychotherapy or medications as indicated), and refer to appropriate specialists (Grade B, Level III).
D. The clinician should enquire about problem behaviors of the dementia patient and the effect these behaviours are having on the caregiver. If these are causing significant caregiver distress, refer the caregiver and patient to specialized dementia services that can offer treatment to the patient and assist the caregiver in modifying their interactions with the patient (Grade A, Level 1).
E. Pharmacotherapy for AD can decrease caregiver burden and the time required of caregivers to support the care recipient. It should be considered as a means to help support caregivers (Grade B, Level I).
F. Future studies of medications for the treatment of AD and dementia should examine the impact of these agents on caregiver burden and the time required to support the care recipient. There is a need to ensure consistency in the measurement of these outcomes (Grade B, Level III).

9. Training needs and system issues

To implement the recommendations for the management of the mild and moderate stages of AD, we need to ensure that clinicians are adequately trained, needed resources and services are available, and that we explore different models of care. Please note that the literature referenced below originates almost entirely outside Canada, and caution must be exercised in extrapolating the findings reported to our country.

Dementia presents unique challenges to the clinician [264]. Many health care providers remain uninformed about AD [265,266]. Specific educational needs among primary care physicians would include knowledge about local diagnostic and support services, development of assessment and communication skills, management of behavioral problems, and the coordination of support services [267]. A particular attitudinal barrier is the skepticism of many primary care practitioners about the effectiveness of interventions for AD [268].

Studies on the uptake of dementia guidelines by physicians have generally been disappointing, but the likelihood of this occurring does appear to be modifiable [269–271]. Guideline adherence is poor without specific interventions.

Common obstacles identified by Canadian physicians to meeting the health care needs of their community include inadequate time, inadequate remuneration, and lack of accessible community resources [272]. We were struck by the difference between what the literature tells us works and what is available in our communities. The availability of required community-based resources will be critical in improving the care provided to those with dementia and their families. There is some evidence that using in-home help services earlier might delay institutionalization [273].

The favored model for chronic disease management is the delivery of services by multidisciplinary teams who collaboratively educate, counsel, and empower patients with self-care techniques to manage their chronic diseases. Supported by customized treatment plans and the multidisciplinary team, patients are charged with undertaking necessary lifestyle and behavioral changes to manage their condition responsibly. Chronic disease management is dependent on the promotion of patient self-management and clinician adherence to evidence-based guidelines [274]. This approach would require modification if used for dementia. There would have to be reduced reliance on patient self-care and a concomitant increased effort on caregiver support and education. A chronic disease management approach, however, could address the need for comprehensive, evidence-based management of the person with dementia during the course of their illness. This could permit the efficient use of the entire continuum of resources including community-based and facility-based continuing care [275]. Studies suggest that a more systematic approach to the management of dementia can improve satisfaction levels and enhance adherence to guidelines [276]. Whether this approach for dementia improves patient outcomes, however, remains unknown at the present time.

Shared care models are being explored as a way to deal with chronic medical conditions. It can be defined as shared responsibility, enhanced information exchange, continuing medical education, and explicit clinical guidelines between specialty services and primary care practitioners [277]. Although it is being explored as a way to provide dementia care, obstacles to effective collaboration include therapeutic nihilism, risk reduction or avoidance, concerns about competency, and limited access to required resources [278]. Another barrier to shared care models for dementia is that a number of primary care physicians believe that dementia care should be dealt with by specialists and not themselves [267]. Reimbursement issues are another barrier to the delivery of high quality dementia care by physicians [279]. The complex, time-consuming aspects of dementia care are not adequately reimbursed by fee-for-service payments.

9.1. Recommendation 27: Recommendations with regards to education

A. All clinicians caring for patients with mild to moderate AD have to acquire the core knowledge and skills required to manage this condition (Grade B, Level III).
B. A multifaceted educational program should be implemented to promote adoption of the recommendations of the 3rd CCCDTD by practitioners (Grade B, Level I).

9.2. Recommendation 28: Recommendations with regards to the organization and funding of care for those with a dementia

A. Every community should examine the services locally available for the management of those with a dementia, assess their adequacy, and implement plans to deal with identified deficiencies (Grade C, Level III).
B. There is a need to modify the prevailing model of chronic disease management (ie, less reliance on promotion of patient self-management coupled with greater caregiver involvement) for dementia. The efficacy and efficiency of modified chronic disease management for dementia should be explored (Grade C, Level III).
C. Shared care models for the management of patients with mild to moderate AD and dementia should be developed and evaluated. This will require the acceptance of joint responsibility on the part of primary care practitioners and specialty services in delivering care to patients with dementia (Grade C, Level III).
D. Dementia care must be adequately funded and reimbursed. Inadequate remuneration should not be a barrier to the delivery of good dementia care (Grade C, Level III).

Author Disclosures

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