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Systematic Evidence Review
Number 20

Screening for Dementia

Prepared for:
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Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, the Evidence-based Practice Center at Oregon Health Sciences University systematically reviews the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help to further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/clinic/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the USPSTF in print and on the Web. These are available through the AHRQ Web site, through the National Guideline Clearinghouse (http://www.ngc.gov), and in print through the AHRQ Publications Clearinghouse (1-800-358-9295).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or e-mail uspstf@ahrq.gov.

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*The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, and chemoprevention--in the primary care setting. AHRQ convened the current USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services of a particular drug, device, test, treatment, or other clinical service.

Structured Abstract

Objective

To produce an evidence-based review to support recommendations from the US Preventive Services Task Force (USPSTF) concerning dementia syndrome screening in primary care settings.

Data Sources

We searched MEDLINE, PsycINFO, EMBASE, and the Cochrane Collaboration library from January 1994 to January 2001, with all searches limited to English language studies.

Study Selection

We developed an analytic framework comprising 9 key questions on dementia screening and treatment to be answered by systematic review. Next, we developed inclusion and exclusion criteria for each question. For questions of prevalence and accuracy of screening, we required cross-sectional or cohort studies in a primary care population with an acceptable reference standard test. For questions of treatment, we included randomized controlled studies (RCTs) of subjects with mild to moderate dementia. We included studies of 6 potential outcome domains: (a) cognitive, physical, and social function; (b) health care utilization rates; (c) behavioral symptoms of

dementia; (d) caregiver stress; (e) accidents and injuries; and (f) health-related quality of life.

Data Extraction

Two reviewers extracted data from included studies of fair to good quality for the preparation of evidence tables. We rated the quality of all selected studies using USPSTF methodology for study appraisal.

Data Synthesis

Key Question No. 1: Does screening for dementia in primary care settings affect any of the selected outcomes? We were unable to locate any RCTs or systematic reviews that addressed this question.

Key Question No. 2: What is the prevalence of undiagnosed dementia in primary care patients? Two studies in North American populations showed that 1.8% and 5.7% of persons older than age 65 have undiagnosed dementia; 2 studies in non-US populations reported prevalence rates of undiagnosed dementia of 3.2% and 12%.

Key Question No. 3: Does a reliable and valid screening test exist to detect dementia in primary care patients? Good evidence shows that the Folstein Mini-Mental State Examination (MMSE) has a sensitivity of 71% to 92% and specificity of 56% to 96% in primary care populations.

Key Question No. 4: Do pharmacological interventions improve any of the selected outcomes? The efficacy of pharmacological intervention varies with the etiology of dementia. We found no evidence of benefit from anti-inflammatory drugs, estrogen, nimodipine, or aspirin in the treatment of dementia. We found no RCTs of treatments for vitamin B_{12} deficiency, thyroid disease, neurosyphilis, normal pressure

hydrocephalus, or sleep apnea. Observational data show that no more than 1.5% of all cases of mild to moderate dementia are fully reversible. Multiple well-conducted RCTs show that for Alzheimer's disease, cholinesterase inhibitors improve cognitive and global function and delay functional decline by 3 to 5 months. One study shows that vitamin E and selegiline postpone functional loss by 7 months. Another study shows that gingko biloba produces a delay of approximately 3 months in cognitive decline. Some studies show that typical and atypical neuroleptics reduce agitated behaviors in patients with varied stages of dementia. One RCT found that clomipramine reduces depressive symptoms in early dementia. Another RCT found that sertraline reduced depressive symptoms in AD.

Key Question No. 5: Do nonpharmacologic interventions improve any of the selected outcomes? Only limited evidence supports the use of nonpharmacologic behavioral interventions in advanced dementia, but this type of treatment has not been studied in early dementia.

Key Question No. 6: Do caregiver interventions improve caregiver or patient outcomes? Five fair quality RCTs of intensive caregiver interventions found no direct benefit for either the patient or the caregiver. Two of these studies show a delay in nursing home placement of 11 to 19 months.

Key Question No. 7: What are the adverse effects of dementia screening? No study meeting our inclusion criteria addressed this question.

Key Question No. 8: What are the costs and cost-effectiveness of dementia screening? No study meeting our inclusion criteria addressed this question.

Key Question No. 9: What are the side effects of dementia therapy? In RCTs of dementia therapy, dropout rates because of adverse effects ranged from 0% for antidepressant therapy to 27% from gastrointestinal side effects of high-dose rivastigmine.

Conclusion

The prevalence and burden of the dementia syndrome are high after age 65. The majority of patients with early dementia are undiagnosed in primary care practices. A brief interview screen can detect dementia with reasonable accuracy. Pharmacologic and nonpharmacologic treatments show benefit on outcomes in mild to moderate Alzheimer's disease, but it is not clear how many subjects in these studies were detected by screening. Evidence for benefit of treatment for other etiologies of dementia syndrome is more limited than that for Alzheimer's disease.

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Chapter 1. Introduction

Background

Dementia is an acquired syndrome of decline in memory and at least one other cognitive domain such as language, visuo-spatial, or executive function sufficient to interfere with social or occupational functioning in an alert person.[1] Multiple diseases can cause the syndrome of dementia. The large majority of people with dementia have neurodegenerative disease or cerebrovascular ischemia as the underlying cause. Between 60% and 70% of people with the dementia syndrome have Alzheimer's disease; about 20% to 30% have vascular or mixed vascular and Alzheimer's disease causes. A smaller number have other causes such as Lewy body dementia, frontal dementia, Parkinson's disease, hypothyroidism, and vitamin B_{12} deficiency.[2,3]

To date, research has produced no effective approach for primary prevention of dementia. Chemoprevention has been advocated, but data on effectiveness are lacking. Although control of hypertension reduces the risk of cerebrovascular accidents, its role in reducing small vessel vascular dementia is less clear. The wealth of literature has been on screening for dementia with the hope of reducing its burden of suffering by earlier intervention.

Routine history and physical examinations do not readily diagnose dementia during clinic or physician visits. Multiple studies in the United States and abroad indicate low identification of dementia by primary care physicians.[4-11] More than 50% of patients with dementia have never been diagnosed by a physician.[12-14] This raises the

possibility that effective screening tests might be able to identify people with dementia at an early stage, thus allowing the possibility of earlier intervention.

No national organization recommends routine screening for dementia syndrome. The 1996 *Guide to Clinical Preventive Services* from the US Preventive Services Task Force (USPSTF) found insufficient evidence to make a recommendation either for or against screening.[15] Since that USPSTF review, however, several studies have been published concerning both pharmacologic and caregiver interventions. Given the new evidence and the large and growing importance of this condition, the RTI International-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) undertook this review for the use of the USPSTF in reconsidering its previous conclusions.

Burden of Suffering

The aging of the US population has been accompanied by a dramatic rise in the prevalence of the dementia syndrome. Several population-based studies indicate that 3% to 11% of persons over age 65 years and 25% to 47% of those over 85 have dementia.[16-21] In 1997, the number of people with Alzheimer's disease in the United States was estimated to be 2.32 million, more than 90% of whom were age 60 years and older.[22]

Alzheimer's disease is considered the 8th leading cause of death in persons over the age of 65 and is 11th overall in the United States.[23] Median survival estimates of people with dementia have been 5.0 to 9.3 years after diagnosis; a recent study found the median survival time, adjusting for date of onset, to be 3.3 years.[24] The annual societal cost of dementia is approximately $100 billion, from both health care and related costs and lost wages for patients and family caregivers.[9]

Dementia causes a high burden of suffering for patients and their families. For patients, it leads to cognitive and functional deterioration, behavioral complications, increased use of health and social services, complicated clinical management of other comorbid conditions, and increased risk for medical complications such as delirium, falls, motor vehicle crashes, incontinence, fractures, and infections.[25,26]

For family caregivers, dementia can lead to financial and emotional stress. Family members, usually elderly spouses, care for 66% to 75% of demented people at home.[27] The progressive nature of the dementia syndrome has especially negative effects on the caregiver; most studies have found higher levels of anxiety, depression, and use of psychotropic medications in caregivers compared with population controls.[28-33] One study reported that 80% of caregivers of dementia patients have chronic fatigue, depression, or anger.[34] Recent data have suggested that caregiver burden can be an important determinant of the severity and frequency of demented patients' behavioral problems and of the need to place patients in an institutional setting.[27,29,35-38]

Epidemiology

Associated Conditions

Experts disagree about definitions for cognitive impairment without dementia and the relationship of these conditions to the development of dementia. Observers have defined more benign conditions with terms such as "age-associated memory impairment" (AAMI), "age-related cognitive decline," and "mild cognitive disorder."[39] A study of patients diagnosed with memory impairment found that, after 3 years, 9.1% met Diagnostic and Statistical Manual III, Revised (DSM-IIIR) criteria for dementia, 7.4%

had worse cognitive functioning but did not have criteria for dementia, and 59.1% still met criteria for AAMI.[40] Almost 15% of these patients had improved functioning that no longer met AAMI criteria. "Mild cognitive impairment" (MCI) is a more severe condition that has a stronger association with the development of dementia. An estimated 10% to 15% of patients with MCI progress to dementia annually.[41]

Risk Factors

Age is the best studied and strongest risk factor for the dementia syndrome. The incidence rate among people ages 65 to 69 years is about 2.4 cases per 1,000 person-years, and incidence approximately doubles in each subsequent 5-year period.[42] A significant rise in the prevalence of dementia begins around age 75; rates of 1% to 3.5% in persons' ages 65 to 74 years jump to 6% to 15% in those ages 75 to 84 years.

The risk of Alzheimer's disease is related to family history. Individuals whose parents both had Alzheimer's disease have a 54% cumulative risk of developing this condition by age 80. This risk is about 1.5 times greater than the risk faced by those with 1 parent with Alzheimer's disease and nearly 5 times greater than for those with neither parent affected. First-degree relatives of patients with Alzheimer's disease have a cumulative lifetime risk of 39%, approximately twice the risk of Alzheimer's disease in the general population.[43]

Some genetic mutations have been associated with Alzheimer's disease. For example, about 20% to 30% of the general population and 45% to 60% of people with late-onset Alzheimer's disease have the apolipoprotein E-4 gene.[44] In a study of people with Down syndrome, 55% of individuals between 50 and 59 years and 75% of those 60 years of age and older had Alzheimer's disease.[45]

Cardiovascular risk factors are associated with vascular dementia. The presence of lacunar infarctions leading to symptomatic change is independently related to diastolic blood pressure, serum creatinine, tobacco smoking, carotid stenosis, male sex, and a history of diabetes.[46] A cross-sectional study found all indicators of atherosclerosis (vessel wall thickness, plaques of the carotid arteries, and the ratio of ankle-to-brachial systolic blood pressure) to be associated with all dementias, with odds ratios ranging from 1.3 to 1.9.[47]

Head trauma is also associated with Alzheimer's disease. A case-control study of Alzheimer's disease found the odds ratio of Alzheimer's disease to be 3.5 when comparing patients with previous head trauma to controls.[48]

Screening Tools

Most screening tests for dementia can be divided into cognitive tests of patients and functional assessments using both patients and other informants.[25] Newer strategies include testing for genetic mutations.

Cognitive tests, the primary screening approach that researchers have investigated, include the Mini-Mental Status Examination (MMSE), a widely used and studied test.[49] Several other cognitive tests that have been proposed are not relevant to the primary care setting, an environment that demands tests that are relatively brief, require minimal administration resources or training, and are reasonably accurate.[25] Among other available cognitive testing strategies, the Clock-Drawing Test (CDT), which can take less than 1 minute to administer, has the best potential for meeting these criteria.[50] The small number of methodologically sound studies regarding other clinically relevant cognitive tests limits our ability to evaluate them adequately.

Some informant-based functional tests, such as the Functional Activities Questionnaire (FAQ),[51] the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE),[52] and the Instrumental Activities of Daily Living (IADL) Questionnaire,[53] have also been tested. These instruments offer "everyday relevance," acceptability by subjects, adaptability to various types of patients, administrative ease, longitudinal perspective, and cross-cultural portability. The primary limitations of these tests are that not all patients have caregivers and that some functions (e.g., cognition) are not tested.[54] Most importantly, few methodologically sound studies regarding the accuracy of these questionnaires have been completed.

Testing for genetic mutations may be a potential advance in screening for people at risk of Alzheimer's disease. Investigations regarding genetic profiles associated with Alzheimer's disease have, however, provided limited population-based data regarding absolute dementia prevalence or risk among genotypic individuals. These tests also present weighty ethical issues with respect to their application to individual patients.[55]

Using cognitive tests, functional questionnaires, and genetic testing in the primary care setting poses substantial feasibility problems. This review will focus on the 2 tests of greatest potential near-term usefulness, the MMSE and the CDT.

Treatment Modalities

Early diagnosis and treatment are clearly relevant to the potentially reversible dementias (e.g., hypothyroidism, vitamin B_{12} deficiency); theoretically, treatment should begin early to be most helpful. The literature shows, however, that the probability of

discovering a truly reversible cause is less than 1.5%; thus, the magnitude of the possible benefits of screening depends heavily on the treatment of irreversible dementias.[56-62]

Treatment of irreversible dementia falls into 2 categories. Primary treatment attempts to halt or slow disease progression; secondary treatment deals with controlling the symptoms of the disease.

Primary treatment targets basic pathophysiologic mechanisms and seeks to affect the level of cognitive function (or its rate of decline) over time. For example, early detection of vascular dementia could lead to benefit through more aggressive control of such risk factors as atrial fibrillation, blood pressure, thrombotic tendencies, and dyslipidemia. For Alzheimer's disease, treatment with cholinesterase inhibitors and vitamin E do not reverse the disease process but may slow its progression.

Secondary or symptomatic treatment targets patients' psychiatric and behavioral symptoms and caregivers' stress and burden. Both types of treatment can affect health-related quality of life. Early detection of dementia may also induce some negative outcomes such as possible discrimination, inability to obtain life or health insurance, and, in extreme cases, suicide.[63,64]

In summary, the current management of dementia is not limited to improving patients' cognition. Rather, it also targets multiple outcomes, such as improving functional autonomy, decreasing institutionalization, decreasing behavioral problems related to dementia, limiting automobile crashes and accidental falls, and lowering caregiver stress.

Organization of this Systematic Evidence Review

Chapter 2 provides an overview of our methods for producing this systematic

evidence review. Chapter 3 presents the results of our literature search and synthesis organized by key questions. The results and limitations of the literature are discussed in Chapter 4 with attention to ramifications for future research. Tables accompanying the text can be found at the end of each chapter; references are at the end of the entire report. Appendix A contains acknowledgments; Appendix B contains the evidence tables developed from the literature synthesis; and Appendix C gives an overview of the scales used in dementia intervention trials, followed by a detailed description of a selected few.

Chapter 2. Methods

This chapter documents procedures that the RTI International-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) used to develop this report on screening for dementia. We first discuss the analytic framework and key questions developed at the beginning of the review. We then describe the inclusion and exclusion criteria for admissible evidence; our strategy for literature search, data extraction, and synthesis; and our approach to developing the final summary of the evidence.

Analytic Framework and Key Questions

The analytic framework (Figure 1) describes the relationship between screening and treating patients in a clinical setting and reduced suffering from dementia for either patients or caregivers. The arrows in the analytic framework represent steps in the chain of logic connecting screening with 6 defined sets of outcomes: patient function, use of health care, patient behavior, caregiver stress, accidents, and health-related quality of life (HRQOL). The superscripts refer to 9 key questions that guided our literature searches and synthesis of the evidence.

We examined 1 overarching question (Key Question No. 1, linking screening and the 6 categories of outcomes) and 8 additional questions pertaining to specific links in the analytic framework, including the prevalence of undiagnosed dementia, the accuracy of screening tests, the availability of effective treatment strategies, and the harms and costs of screening and early treatment.

Key Question No. 1: Does screening for dementia in older adults (>60 years) do any of the following:

- improve or worsen patients' cognitive, social, or physical function?
- increase or decrease hospitalizations, institutionalizations, or health care visits?
- prevent or precipitate behavioral problems?
- alleviate or worsen caregivers' stress and coping?
- prevent or precipitate accidents, such as accidental falls or automobile crashes?
- improve or worsen patients' health-related quality of life?

Key Question No. 2: What is the prevalence of undiagnosed dementia in primary care patients? What are the common causes of dementia in primary care patients?

Key Question No. 3: Is there a reliable and valid screening test to detect dementia in primary care populations?

Key Question No. 4: Do pharmacologic interventions of potentially reversible or irreversible dementia improve any of the 6 outcomes noted in Key Question No. 1? Such treatments include antiplatelet therapy for vascular dementia, cholinesterase inhibitors for Alzheimer's disease, thyroid treatment for hypothyroidism, and vitamin B_{12} for vitamin B_{12} deficiency.

Key Question No. 5: Do nonpharmacologic interventions, such as sensory, environmental, behavioral, or activity-directed programs, improve any of the 6 outcomes noted in Key Question No. 1?

Key Question No. 6: Do caregiver interventions improve any of the 6 outcomes noted in Key Question No. 1?

Key Question No. 7: What are the adverse effects of screening for dementia?

Key Question No. 8: What are the costs and cost-effectiveness of screening for dementia?

Key Question No. 9: What are the adverse effects of dementia therapy?

Inclusion/Exclusion Criteria for Admissible Evidence

The authors and Task Force liaisons developed inclusion and exclusion criteria for selecting evidence relevant to the key questions. Details can be found in Table 1. We first searched for evidence from randomized controlled trials (RCTs) for the efficacy of screening (Key Question No. 1). As we found no well-conducted RCT of screening, we then examined the evidence for Key Questions No. 2 through 9.

For Key Questions No. 2 and 3, we used systematic reviews, RCTs (Key Question No. 3 only), we accepted cross-sectional prevalence or prospective cohort studies that used an acceptable reference standard in a primary care population comparable to those typical in the United States. Key Questions No. 4 through 6 concerned the efficacy of various treatments (pharmacologic, nonpharmacologic, and caregiver, respectively). We included systematic reviews and required RCTs that included participants with mild to moderate dementia verified by an acceptable diagnostic test and that provided information on at least 1 of the 6 outcomes of interest; for studies of reversible dementia, we also included longitudinal studies.

Pharmacologic searches used specific drug names, restricting the pharmacotherapies to those that the Food and Drug Administration has approved, are available in the US market for off-label use, and are not investigational drugs.

For Key Questions No. 7 and 9, involving harms of screening and treatment, we again used systematic reviews. For screening, we also allowed prospective cohorts and cross-sectional prevalence studies; for therapy, we included RCTs and prospective cohort studies.

For Key Question 8, regarding the costs and cost-effectiveness of screening and early treatment, we searched for systematic reviews or studies of any research design (preferably RCTs and prospective cohort) that provided information about costs and for cost-effectiveness, cost-utility, and cost-benefit studies of screening.

Literature Search Strategy, Data Extraction, and Synthesis

We used our inclusion and exclusion criteria (Table 1) to develop search terms. In each case, we first searched for well-conducted systematic reviews, including any in the Cochrane Collaboration Database, relevant to the key question. When we found such reviews, we searched the MEDLINE, PsycINFO, and EMBASE databases for studies published since the date of the review. If we found no systematic review, we searched these databases for studies from January 1994 through January 2001. We accepted only studies in the English language concerning humans ages 60 years or older. All searches began with exploding the terms "dementia" and "Alzheimer's disease," then adding other terms as appropriate.

At least 2 authors independently reviewed the titles and abstracts of the articles identified in the searches and excluded those that did not meet eligibility criteria. If the reviewers disagreed, we carried the article in question forward to the next stage, in which

we reviewed the full article, and made a final decision about inclusion or exclusion. All senior authors reviewed articles of special interest. The second and third columns of Table 1 present the number of systematic reviews and articles we identified and examined; the final column presents the number of publications that met our inclusion criteria and were fully reviewed.

Several authors then abstracted data from included articles into predesigned evidence tables (see Appendix B). We also graded the articles using criteria developed by the USPSTF Methods Work Group.[65]

Development of the Final Systematic Evidence Review

During preparation of the evidence report, EPC staff collaborated through conference calls with 2 members of the US Preventive Service Task Force (USPSTF) who served as liaisons.

The authors presented an initial work plan including a provisional analytic framework and key questions to the Task Force in December 2000; we also presented interim reports on results of the literature search and early results of the synthesis of information in March 2001 and June 2001. Upon completion of the draft SER incorporating the review at the June 2001 USPSTF meeting, we conducted a broad-based external review of the draft. We took into account the comments of these reviewers in developing the final version of this SER, which was presented to the USPSTF in January 2002.

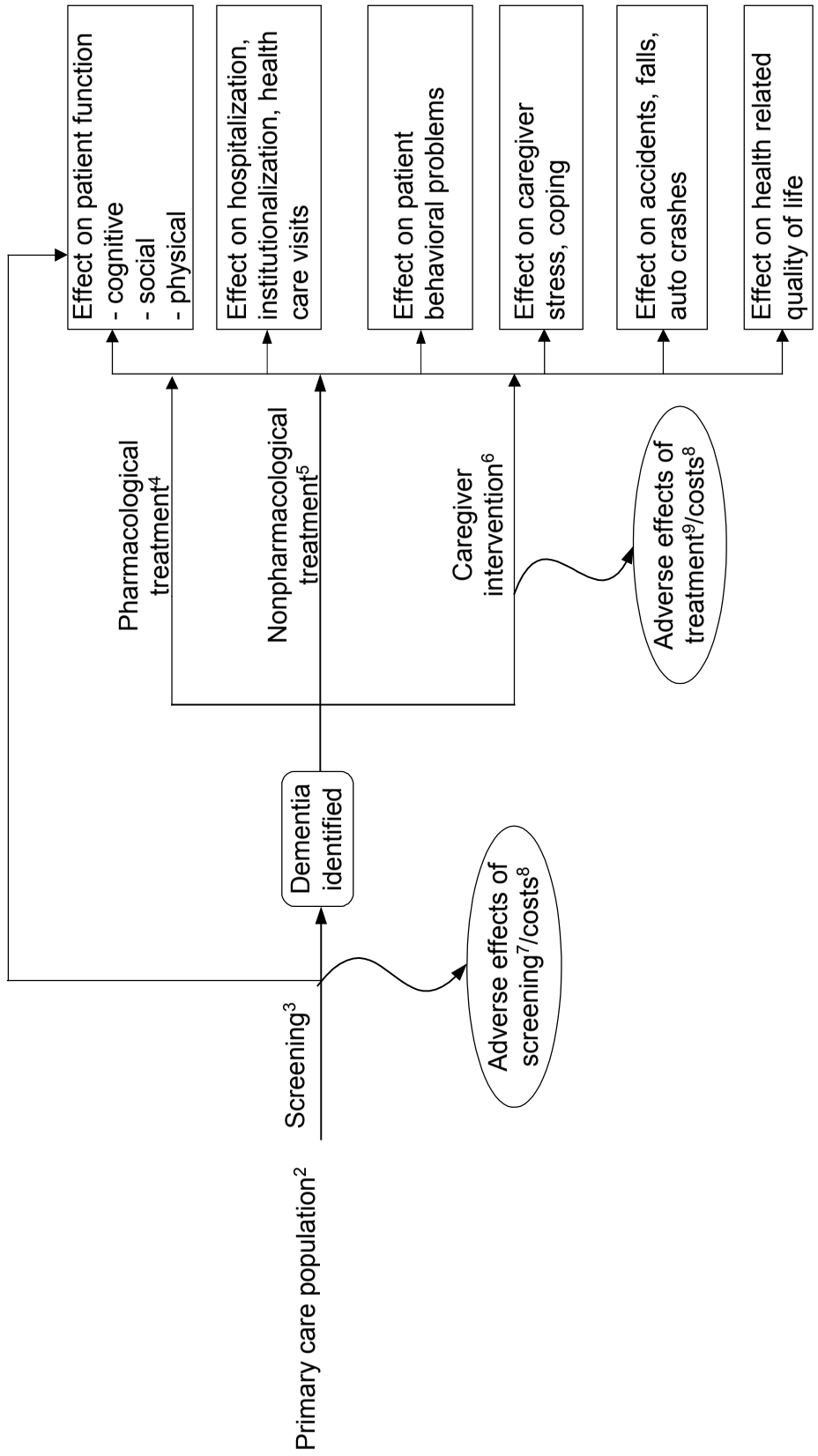

Figure 1. Screening for Dementia: Analytic Framework

Chapter 3. Results

Our presentation of results is arranged chiefly in accordance with the 9 key questions (KQ) introduced in Chapter 2 and Table 1. Specifically, we address the following issues: efficacy of screening in terms of 6 major outcomes (KQ No. 1); prevalence of undiagnosed dementia and common causes of this disease (KQ No. 2); reliability and validity of screening tests (KQ No. 3); efficacy of pharmacologic treatments of dementia (KQ No. 4); efficacy of nonpharmacological interventions (KQ No. 5); efficacy of caregiver interventions (KQ No. 6); adverse effects of screening (KQ No. 7); costs or cost-effectiveness of screening (KQ No. 8); and adverse effects of treatment (KQ No. 9). For KQ Nos. 4, 5 and 6 on therapies, we organize the discussion in terms of the 6 major health outcomes – functioning, health care utilization, behavioral problems, caregiver stress, adverse events, and quality of life – specified in the analytic framework (Figure 1).

Studies meeting our inclusion criteria that provide data for the sections that follow appear in one or more of the 12 evidence tables in Appendix B. Those tables contain abstracted information on the following topics:

- Prevalence of undiagnosed dementia (KQ 2)(Evidence Table 1);
- Effectiveness of screening tools (KQ 3) (Evidence Tables 2a, 2b);
- Treatment studies (KQ 4) (Evidence Table 3-9);
- Systematic reviews of the efficacy of nonpharmacologic interventions for behavioral problems related to dementia including sensory, environmental, behavioral, and activity-directed programs(KQ 5) (Evidence Table 10);
- Studies of the efficacy of various caregiver interventions (KQ 6) (Evidence Table 11); and
- Adverse effects of dementia therapy (KQ 9) (Evidence Table 12).

KEY QUESTION NO. 1: EFFICACY OF SCREENING

We were unable to locate any randomized controlled trial (RCT) or systematic review addressing the use of screening tools for dementia and the effects of screening on the outcomes of interest.

KEY QUESTION NO. 2: PREVALENCE OF UNDIAGNOSED DEMENTIA AND THE COMMON CAUSES OF DEMENTIA

Prevalence of Undiagnosed Dementia

Data for evaluating the yield of implementing a screening strategy for dementia in primary care settings are quite limited. To date, few studies have attempted to estimate the extent to which physicians simply do not recognize dementia syndrome.

We found 4 studies concerning the extent of undiagnosed dementia. Two were in European populations[12,66]1 in Canada,[13] and 1 in a predominantly Asian-American population.[14] Prevalence estimates from these studies are shown in Table 2; more detailed information can be found in Evidence Table 1 (Appendix B).

Eefsting et al. questioned rural Dutch general practitioners (GPs) as to the presence of dementia (defined by DSM-IIIR criteria) and cognitive impairment in each of their assigned patients who were 65 years or older.[66] The Dutch group compared these findings to data from a simultaneous community survey in which these same patients had been screened with the Mini-Mental State Examination (MMSE); they clinically evaluated patients with scores of less than 17 and a sample with scores between 18 and 27. The adjusted prevalence estimate of dementia among GP patients in the study was 5.2% (4.2% in men, 5.8% in women). Sensitivity for

diagnosis of dementia by GPs was only 39% (28 of 71 cases); specificity was 99.3% (275 of 277 cases). This sensitivity increased to 69% (50 of 71 cases) and the specificity decreased to 94% (260 of 277) when the definition of physician detection was expanded to any awareness of cognitive impairment. In short, GPs missed dementia in 3.2% of all primary care patients over age 65.

Olafsdottir et al. evaluated a random sample of patients greater than 70 years of age from a primary care center in Sweden.[12] Although 12% met Diagnostic and Statistical Manual Third Version, Revised (DSM-IIIR) criteria for dementia syndrome, they had no reference to cognitive impairment on their medical records.

A third study did not evaluate undiagnosed cases among primary care physicians but rather looked at the prevalence of "undetected" dementia (patients who had not visited their primary care physicians).[13] This study estimated that, among 252 cases of dementia in 9,008 community-dwelling people living in Canada, 64% of patients (161/252) with dementia either did not see their physicians for memory problems or the physician visit had not yet occurred. These data yield a 1.8% prevalence rate (161/9,008) of undetected dementia cases in elderly community-dwelling people.

Valcour et al. determined the rate of undiagnosed dementia in a cross-sectional study of 297 Asian-American patients ages 65 years and older who had been followed for at least 1 year by a private internal medicine practice.[14] Using strict diagnostic tools similar to DSM-IIIR criteria for dementia diagnosis, the investigators found 26 cases of dementia in the entire study population. Of these cases, 65% were undocumented and 67% were unrecognized at the time of the clinic visit. These data yield a prevalence of undiagnosed dementia of 5.7%.

Community-based Estimates of Dementia Prevalence

Even though studies of the prevalence of *undiagnosed* dementia are scarce, estimates of overall prevalence of dementia can provide supplemental information. Table 3 provides estimates of dementia prevalence among persons 65 years of age and older from 3 community-based cross-sectional studies published after 1994.[67-69]

Comparisons of estimates are hindered by the inconsistent classification of age groups. Nonetheless, the estimates vary widely even within comparable age groups. How much of this variation can be attributed to actual differences in the study populations and how much to methodological differences is not clear.

In a further review (data not shown in Table 3) Corrada et al. used a multivariable model to analyze methodological factors that determine variation in prevalence estimates of Alzheimer's disease.[70] Statistically significant factors included the inclusion of mild cases of dementia, adjustment for false negatives, random sampling versus entire population, mixed urban/rural community versus either population alone, use of computerized tomography scans, use of laboratory studies, and use of Hachinski Ischemic Score. These factors explained 76% of the model's variability.

Erkinjuntti et al. confirmed the importance of using standardized criteria for dementia diagnosis (data not shown).[71] Different criteria to determine cases of dementia led to substantial variability in prevalence estimates for the same study population. Their estimates ranged from 3.1% with International Classification of Disease-10 (ICD-10) criteria to 29.1% with DSM-III criteria.

Finally, the 1996 literature review for the US Preventive Services Task Force (USPSTF) had cited dementia prevalence estimates before 1994 of 0.8% to 1.6% for persons 65 to 74 years

of age, 7% to 8% for persons 75 to 84 years of age, and 18% to 32% for persons 85 years of age and older.[15] These study populations were primarily white.

Since that time, prevalence studies have expanded to determining rates within primarily nonwhite populations and have revealed somewhat higher rates. Estimates are erratic for African-Americans; estimated rates of dementia syndrome have fluctuated between 1.83% to 9.1% for persons 65 to 74 years of age, 6.7% to 19.9% for persons 75 to 84 years of age, and 11.9% to 58.6% for persons over 85. In Asian-Americans, the rates are more consistent (between 2 studies):[68,69] 1.4% to 2.1% for persons 70 to 74, 6.2% to 6.3% for persons 75 to 79, 12.7% to 12.9% for persons 80 to 84, and 29.7% to 33.4% for persons 85 to 89. Graves et al. found an even higher prevalence for Japanese-Americans older than 90 years of age (50.2% for 90 to 94; 74.3% for 95 and older).[69]

Common Causes of Dementia

Several pathological conditions cause the dementia syndrome. The 1996 USPSTF review reported that the proportion of dementia cases attributed to Alzheimer's disease was between 50% and 85%, with vascular (multi-infarct) dementia contributing an additional 10% to 20% of cases. Most of the recent studies conducted in different ethnic groups have confirmed these estimates, although they demonstrate that the prevalence of Alzheimer's disease and vascular dementia varies among different ethnic groups. The percentage of dementia cases due to Alzheimer's disease is lower in the Asian-American populations studied by Graves et al.[69] and White et al.;[68] conversely, the proportion of cases due to vascular dementia is higher.

Table 4 shows the estimated subtypes of dementia syndrome as reported by 4 studies conducted since 1994.[67,69,72,73] The high prevalence of Alzheimer's disease and vascular

dementia leads to a number of mixed cases (about 7% to 16% of all dementias). Approximately 5% to 17% of all people with the dementia syndrome have other types of dementia. The proportion of dementia cases that are truly reversible has been reported by 5 other studies to be less than 1.5%.[58-61,74]

Summary

The percentage of primary care patients over age 65 who have unrecognized dementia is between 2% and 12%. We estimate that one-half to two-thirds of cases of early dementia are not diagnosed by a routine history and physical examination. Considerable evidence shows that the prevalence of dementia increases with age; thus, the prevalence of missed dementia cases likely increases among older individuals.

In regard to the frequency of particular causes of dementia syndrome, Alzheimer's disease is a primary process for a majority of cases (about 60% of all dementias), but vascular dementia is the primary process for a significant proportion of cases (about 15%). The high prevalence of these etiologies leads to a number of mixed cases (7% to 16% of all dementias). Other etiologies account for 5% to 17% of all cases.

KEY QUESTION NO. 3: VALIDITY AND RELIABILITY OF SCREENING TESTS

Researchers and practitioners in this clinical area have traditionally divided screening tests into cognitive tests and functional assessment. Our search yielded 1 meta-analysis that evaluated both cognitive and functional screening tools (Evidence Table 2a).[75] We also reviewed 7 studies that evaluated cognitive screening tools,[76-82] 1 study that evaluated functional

screening tools,[83] and 1 study that was a comparison between cognitive and functional screening tools (Evidence Table 2b).[84]

Recent advances in genetic technology have revealed familial linkages for some Alzheimer's disease cases that may lead to genetic screening tests.[55] However, no studies evaluating genetic screening tests met our inclusion criteria or were of sufficient methodological quality to review here.

Cognitive Tests

Studies of screening tools for dementia have centered primarily on the MMSE. The Agency for Health Care Policy and Research (AHCPR) supported a systematic review and meta-analysis of studies (published primarily before 1994) that evaluated the MMSE for screening.[75] The AHCPR panel used mean effect size as the measure of effectiveness, as described by Hasselblad and Hedges.[85] The mean effect size for discrimination between patients with and without dementia was 1.78. This effect size corresponds to an equivalent sensitivity and specificity of 84% and a sensitivity of approximately 75%, for a fixed specificity of 90%.

Studies from 1994 to 2001 have had 2 usual orientations when evaluating the MMSE: primary investigations into its validity when adjusting for either cultural or educational factors (or both) and secondary investigations that compare the performance of newer screening tools to that of the MMSE. Table 5 compares the findings of 5 MMSE studies.[76,78,80,81,84] Three of these studies included cut-off levels on the basis of receiver-operator curve (ROC) analysis, and these are the usual values provided. Excluding the Wilder et al. study (evaluating specificity levels for 90% sensitivity), the MMSE sensitivity (71% to 92%) and specificity (77 % to 96%) fell into a moderate range and the percentage of falsely classified individuals (false negatives and false

positives as a percentage of the total number of tested individuals) ranged from 4% to 18%.[80] The primary factors determining the rate of false diagnoses are likely to be related to cut-off values and the overall percentage of individuals with dementia in each study. This percentage may not reflect the actual prevalence of dementia in these populations, however, because some studies evaluated only a sub- sample of those with negative screens.

To determine the validity of the MMSE for predicting the ultimate development of dementia, Braekhus et al. analyzed the use of MMSE with a prospective approach that excluded prevalent cases of dementia syndrome in a Norwegian population.[79] As reported in Table 6, the authors found that a likelihood ratio for predicting dementia syndrome in the next 3 to 6 years was 2.3 for an MMSE cutpoint of 25 and 3.45 for a cutpoint of 24. Because of the small sample size for each MMSE score and the low follow-up rates, the conclusion from this study is limited.

Folstein et al., in 1975, documented that the MMSE is a reliable instrument.[49] Two decades later, McDowell et al. provided additional reliability data (Table 7) that confirmed the earlier findings.[76]

In reviewing the current literature on the Clock-Drawing Test (CDT), Schulman reported that the mean for both sensitivity and specificity from various studies was 85%.[50] His review did not provide search terms or inclusion criteria; his quality appraisal called for only the presence of clearly defined methods and the presence of a comparator group. We examined all the individual studies ourselves, but none met our quality criteria for inclusion in this review. The primary weakness of most studies was that the investigators had not evaluated the CDT in either primary care or community-dwelling subjects.

Solomon et al. analyzed the use of the CDT as part of a larger battery of cognitive screening tests known as the 7-Minute Screen.[82] This tool also includes the Temporal

Orientation test, the Enhanced Cued Recall test, and the Verbal Fluency test. The study reported a mean administration time of 7 minutes and 18 seconds. Of subjects classified as having a high probability of dementia, 85% (11/13) had dementia diagnoses. The remaining 15% of subjects refused follow-up. Of the sample of subjects classified as having a low probability of dementia, 96% (25/26) did not have a diagnosis of dementia; the remaining subjects had cognitive impairment without dementia. These results indicate this screening tool may be more effective at detecting cases of dementia while having greater clinical utility than most cognitive tests. However, these conclusions are limited by the lack of any evaluation of the 7-Minute Screen in larger and more diverse primary care populations.

Screening tools must achieve a balance between comprehensiveness and clinical utility. Many of these cognitive and functional assessment tools were initially intended to be a component of a battery of tests in the full assessment of the presence of dementia. Some researchers have sought to transplant some items for applications oriented more to screening than to diagnosis. To accomplish this objective, a balance must exist that minimizes length and complexity of a test, maintains comprehensiveness of questions in evaluating total cognitive function, and does not compromise test accuracy.[25]

Costa et al., in the AHCPR review, evaluated 9 additional cognitive screening tests: the Blessed Orientation Memory Concentration Test (BOMC); the Blessed Information Memory Concentration (BIMC); the Short Test of Mental Status (STMS); the Modified Mini-Mental Status Exam (3MS); the Abbreviated Mental Test (AMT); the Chula Mental Test (CMT); the Mental State Questionnaire (MSQ); the Comprehensive Assessment and Referral Interview Cognitive Scale, Dementia Version (CARE-D); and the Short Portable Mental Status Questionnaire (SPMSQ).[75] Three other studies have examined at least 1 of these tests as well.[76-

[78] These tests were found to have a level of performance similar to that of the MMSE, as shown in Evidence Tables 2a and 2b.

In conclusion, of all studies that evaluate screening instruments for dementia, the proportion that meets acceptable methodological standards is low. However, a good degree of evidence is available on the MMSE. Administration within *asymptomatic* primary care or community populations, 4% to 21% of all screened individuals were falsely classified with positive or negative results. Valid data relevant to asymptomatic primary care populations for the CDT do not currently exist. Other instruments may have clinical utility, but the gaps in evidence as to whether these tests can screen elderly patients effectively for dementia diagnosis or progression are significant.

Functional Assessments

Some researchers have evaluated informant-based functional assessments as screening tests for dementia. Advantages of these assessments include everyday relevance, acceptability by subjects, adaptability to difficult-to-evaluate patients, administrative ease, longitudinal perspective, and cross-cultural portability. Primary limitations are that some patients have no caretakers and that some functions are not assessed.[54]

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is the most widely researched functional tool, providing most of the data that Jorm used in a meta-analysis comparing functional assessments with cognitive tests.[86] However, this meta-analysis failed to meet our quality standards because it did not state inclusion/exclusion criteria or any appraisal of the quality of the studies in the analysis.

Barberger-Gateau et al. examined the use of the instrumental activities of daily living (IADL) in multiple French populations as a predictor of the subsequent development of dementia over 3 and 5 years in multiple French populations (Evidence Table 2b).[87] Likelihood ratios, calculated as the ratio of the probability of the IADL score in those who develop dementia and the probability of the IADL score in those who do not develop dementia, are shown in Table 8. According to Stern and Mohs, the likelihood ratio for developing dementia among those with a positive IADL test was 2.58. The low absolute incidence made the IADL a relatively modest predictor of dementia development.[88]

Summary

Several cognitive and functional screening tests have been evaluated in a limited number of primary care populations. A few studies that evaluated screening instruments for dementia met our methodological standards. Of these, the MMSE is the best studied, clinically feasible screening tool. Whether the MMSE is a good screening tool in an elderly, community-based population depends on the prevalence of dementia in this population and the cut-off point of the MMSE that will determine if the screening result is said to be positive or negative. A positive result on this screening test requires further diagnostic tests to confirm the diagnosis.

KEY QUESTION NO. 4: EFFICACY OF PHARMACOLOGIC INTERVENTIONS

We looked at any randomized controlled trial that evaluated the efficacy of various pharmacologic therapies for potentially reversible, neurodegenerative, vascular, and other etiologies of dementia. Data are summarized in Evidence Tales 3-9.

Yield of Literature Searches

Reversible Dementia

Our search of the MEDLINE, PsycINFO, EMBASE, and Cochrane Collaboration databases yielded no RCT that evaluated treatment for dementia caused by depression, drug side effects, metabolic disorders, vitamin B_{12} deficiency, infectious disease, neoplasm, normal pressure hydrocephalus, or subdural hematoma. We then expanded our search to include longitudinal studies that followed cohorts of dementia syndrome patients who received treatment for the aforementioned diseases or other potentially reversible conditions. We define the terms "partially reversible" and "fully reversible" causes of dementia based on the availability of follow-up data on the clinical outcome of dementia patients after the treatment of the potential cause.

Our search from 1994 to the present yielded 1 meta-analysis[89] and 5 additional studies.[59-61,90,91] We included 1 other meta-analysis published before 1994 and that had been characterized as an important study.[62] Most of the studies included in these 2 meta-analyses did not meet our inclusion criteria and were considered to be methodologically poor by the USPSTF methodological appraisal method. After evaluation of all the studies in both reviews, we included 7 studies that met our inclusion criteria and were considered to be of at least fair quality.[57-61,74,92] All 7 included studies were longitudinal treatment trials conducted in patients drawn from specialty referral populations. These studies are summarized in Evidence Table 3.

Three of the 7 studies reported no case of fully reversed dementia among a total of 305 patients with dementia.[58-60] The remaining 4 studies reported 1% to 3% fully reversed cases among a total of 588 patients with dementia.[57,61,74,92] In the studies that reported a higher proportion of fully reversed dementia, more than 50% of reversed cases were caused by drug

toxicity.[57,61,92] It is likely that current diagnostic criteria would reclassify at least some of these patients as having delirium rather than dementia. After reviewing these 7 studies and adjusting for the presence of delirium as a primary diagnosis instead of dementia, we concluded that fully reversible dementia is no greater than 1.5% of all dementia syndrome cases.

An additional study assessed the prevalence of reversible dementia due solely to vitamin B_{12} deficiency (data not shown in Evidence Table 3).[91] Of 66 memory clinic patients with potentially reversible dementia from this condition, the investigators reported no case of fully reversed dementia syndrome after a mean follow-up period of 7.5 months.

Irreversible Dementia

Our search yielded 205 RCTs and 22 systematic reviews that evaluated treatment for irreversible neurodegenerative and vascular dementia. Among these, 23 RCTs[4,93-114] and 10 systematic reviews[115-125] met our inclusion criteria.

Four systematic reviews[115,119-121] and 9 RCTs[93,95-101,112] evaluated the efficacy of cholinesterase inhibitors in Alzheimer's disease (Evidence Tables 4a and 4b, respectively). One systematic review[118] and 1 RCT[106] evaluated the efficacy of ginkgo biloba in Alzheimer's disease (Evidence Table 5). One systematic review[116] and 1 RCT[103] evaluated the efficacy of selegiline in Alzheimer's disease; the same RCT also evaluated vitamin E and both drugs together (Evidence Table 6). Two RCTs evaluated the effect of estrogen in Alzheimer's disease (Evidence Table 6).[105,114] We identified 1 RCT for prednisone,[108] and diclofenac (Evidence Table 7),[109] and 1 RCT for nimodipine.[104] We also found 1 systematic review for aspirin in vascular dementia (Evidence Table 8).[117] Finally, we found 1 RCT that evaluated the efficacy of rivastigmine in Lewy body dementia.[102] Evidence Table 9a reports on 3 systematic reviews evaluating the efficacy of neuroleptics in healing dementia-related behavioral problems.[122,124,125]

In addition, we identified several RCTs involving pharmacologic interventions for behavioral problems (Evidence Table 9b): 3 concerned neuroleptics;[94,110,113] 1 studied clomepramine;[111] and 1 dealt with sertraline.[4]

The main target of drugs for the treatment of dementia is Alzheimer's disease; the most studied drugs are the cholinesterase inhibitors. In the next subsections, we describe common outcome measures used in the efficacy drug trials for Alzheimer's disease and comment on the natural history of Alzheimer's disease reflected in these outcome measures, including the translation of some of these outcome measures to clinically relevant change. We then present findings for each studied drug on cognition, global change scores, functional ability, behavioral scales, and other outcomes.

Outcome Measures in Dementia

Dementia syndrome in general and Alzheimer's disease in particular are characterized by progressive decline in 3 categories: cognition, functional ability, and behavior. Efficacious therapy might improve, delay, or reverse decline in some or all of these domains. Current standards from the Food and Drug Administration (FDA) for testing drugs in Alzheimer's disease trials require demonstration of "dual efficacy;" that is, trials must show improvement on a performance-based neuropsychologic measure and demonstrate clinically meaningful change. The FDA does not specify the actual tools or outcome measures to be used. Assessments in these studies vary widely, making comparisons across trials very difficult. When evaluating a published clinical trial, reviewers need to consider the selection of appropriate primary and secondary outcome scales, trial design, drug dosage, and inclusion/exclusion criteria.

A systematic review conducted by Demers and colleagues for the Canadian Coordinating Office for Health Technology Assessment assessed the psychometric properties of 50 scales used in 26 RCTs on Alzheimer's disease drug efficacy.[126] They categorized the scales based on the following outcome domains: cognition, global change scores, function/quality of life, and behavior/mood. The review concluded that the function/quality of life and behavior/mood scales have not achieved the same degree of reliability and validity as the cognitive scales.

Cognition

Currently, the cognitive part of the Alzheimer Disease Assessment Scale (ADAS-Cog)[127] is considered the reference standard for evaluating the efficacy of certain medications on the cognitive domain of Alzheimer's disease.[126,128] The ADAS-Cog consists of 11 items designed to assess the extent of impairment of memory, language, orientation, and praxis. Scores range from 0 to 70 according to the number of errors patients make. The higher the score, the more extensive is the impairment. Specific training is required to administer the test, which takes 30 to 45 minutes to complete.

The MMSE requires 5 to 10 minutes to complete.[129] It consists of 5 subtests in the domains of orientation, memory, attention, language, and praxis; the scoring range is 0 to 30, with 30 the optimal score. It tests domains similar to those of the ADAS-Cog and correlates strongly and significantly with ADAS-Cog (r of 0.81 and $P < 0.001$). For each 1 point drop in the MMSE, the ADAS-Cog drops approximately 2.5 points.[130,131]

The scores of outcome measures on previous scales used in dementia drug trials are difficult to interpret unless one can connect the magnitude of changes in the scale scores and clinically relevant outcomes. The best way to understand the clinical relevance of certain scores on cognitive psychometric instruments is to evaluate their correlation with functional

performance. Vitaliano et al. examined the relationship between 5 areas of cognition (memory recall, recognition, orientation, attention, and calculation) derived from subtests of the MMSE and the Dementia Rating Scale (DRS) and 3 functional domains (recreation, communication, and self-care).[132] The investigators found that functional competence could be predicted from scores of memory and attention. Perry and Hodges performed comprehensive cognitive and functional assessments on 24 community-dwelling subjects with Alzheimer's disease and their informal caregivers.[133] Functional assessment correlated well with overall severity as measured by MMSE (r = -0.733) and strongly with the cognitive domain of visuospacial and semantic memory (r = 0.843). The MMSE correlated significantly ($P < 0.001$) with the following everyday functional activities: telling the time correctly (r = -0.714), using a television or radio unassisted (r = –0.704), opening packages without difficulty (r = -0.643), writing with no mistakes (r = -0.624), and making a hot drink competently (r = -0.614). The MMSE did not correlate significantly with the following: taking messages, handling finances, repetitiveness, and maintaining conversational skills.[133]

Global Change

Although either the ADAS-Cog or the MMSE can fulfill the FDA requirement for drug efficacy as a performance-based neuropsychological instrument, one must still demonstrate what constitutes clinically relevant change. Most drug trials use scales that measure the global change in dementia signs and symptoms as observed by health professionals or by family caregivers. The goal of measuring global change is to establish an overall impression of a patient's condition without focusing exclusively on a single function.[134] The International Working Group on Harmonization of Dementia Drug Guidelines states that global scales seek to assess clinically

manifested change, based on comprehensive or multidimensional assessments that include cognitive, behavioral, and daily functional performance.[135]

All global scales consist of a concise patient interview conducted by an experienced clinician; the premise is that the detection of change by an experienced clinician is likely to be clinically meaningful. These scales seek to mimic how physicians assess Alzheimer's disease patients in routine clinical practice.[135] The most common global scale is the Clinician's Interview Based Impression of Change plus caregiver input scale (CIBIC-plus). This scale includes information from both patient and caregiver interviews conducted by an experienced and independent clinician. The CIBIC-plus consists of a semi-structured baseline interview administered to both the patient and the informant caregiver, a follow-up interview with both the patient and the informant, and a clinician's rating of impression of change. The clinician is not informed of the patient's psychometric test score or adverse event reports. The clinician rates the patient on a 7-point scale: 1, very much better; 4, no change; and 7, very much worse. The CIBIC-plus has been shown to be a stable measure of global function and is sensitive to deterioration over time.

Table 9 summarizes the scoring system and interpretation of the 3 most common measurement tools used in the majority of clinical trials: ADAS-Cog, MMSE, and CIBIC-plus. In the discussion of drug trials below, we will state the properties and the interpretation of each functional scale and other outcome measures used. For further details, Appendix C summarizes all the outcome measurement instruments that were used in our systematic evidence review.

Functional Performance

The second way to demonstrate clinically relevant changes in Alzheimer's disease drug trials is to measure functional performance. Investigators do not agree on the best way to evaluate functional changes. Because of this lack of universally accepted measures, investigators use a wide range of functional performance scales. The majority of these scales assess function by examining the patient's ability to perform independently both basic and instrumental activities of daily living (ADLs).[126,129] Basic ADLs include bathing, dressing, grooming, toileting, transferring, ambulation, continence, and feeding;[136] IADLs include the ability to go shopping, manage transportation, climb stairs, manage finances, do housework, use the telephone, do the laundry, manage medications, walk outdoors, drive, hold down a paying job, and prepare meals.[137]

Behavior Related to Dementia

In addition to cognitive decline, patients with dementia suffer from noncognitive problems such as a decline in functional status and disturbed or agitated behaviors. Agitation, disturbed behavior, or behavioral problems related to dementia are different terms that have been used to denote the phenomenon defined as an inappropriate verbal, vocal, or motor activity not explained by needs or confusion.[138] Agitation in dementia is the final step of interplay between cognitive deficit, neurotransmitter deregulation, and environmental factors. It results from underlying distress experienced by the elderly person. This distress can stem from cognitive impairment, psychiatric and medical disorders, or functional impairments.[139] Although there is lack of consensus on the definition of behavioral problems related to dementia,[140] these disturbed

behaviors can be described in four major categories: physical aggression, physical nonaggression, verbal aggression, and verbal nonaggression.[138]

Agitated behaviors are common and are not different within the different types of dementia. Haupt et al. followed 60 patients with mild to severe Alzheimer's disease for a period of 2 years; all experienced agitation at some point.[141] In a prospective study of patients with Alzheimer's disease over a follow-up period of up to 5 years, Devanand et al. reported that agitated behaviors were common and persistent.[142] In a cross-sectional study of 5,092 elderly people in Cache County, Utah, Lyketsos et al. found that 61% of people with dementia had exhibited 1 or more mental or behavioral problems in the past month.[143] Among those behavioral problems, apathy constituted 27%; depression, 24%; and agitation/aggression, 24%. In the United Kingdom, a cross-sectional study estimated the prevalence of individuals with behavioral problems in 178 persons with Alzheimer's disease and reported the following estimates: apathy, 41%; major depression, 24%; agitation/aggression, 20%; wandering, 19%.delusion, 16%; hallucination, 17%; and mania, 3.5%.[123]

Agitated behaviors are associated with earlier nursing home referral, worse prognosis, greater costs, and increased caregiver burden.[144] The behaviors adversely affect the quality of life of patients with dementia syndrome and their caregivers, complicate patient management, and precipitate institutionalization.[138,145] Before the advent of specific pharmacological treatment for Alzheimer's disease (cholinesterase inhibitors), the management of dementia in general and Alzheimer's disease in particular was based on a variety of nonpharmacological interventions that targeted both the cognitive and the noncognitive symptoms of dementia. Pharmacological therapy of severe behavioral problems or disorders related to dementia was based on methods similar to those for treating schizophrenia and bipolar disorder, with no

specific attention to dementia itself as having a different pathophysiology. Over the past decade, however, dementia management has evolved somewhat and specific medications now exist for the treatment of the behavioral disorders. Measuring behaviors in dementia is usually generated by observational methods such as direct observation by the investigators, caregivers rating of the behaviors (staff and family members), or chart reviews. This type of outcome measurement is very subjective and can be biased by the relationship between the caregiver and the care recipient, the caregiver's general stress level, the amount of contact between the caregiver and the patient, and, if covering a long period of assessment such as weeks or months, can induce recall bias. Because of the lack of consensus on both the definition of behavioral problems in dementia and the approach to measure them, numerous instruments have been created that lack complete assessment of their psychometric properties and their responsiveness to clinical changes over time.

Natural History of Alzheimer's Disease

Interpreting the results of clinical trials of potential Alzheimer's disease treatments requires some understanding of the natural history of Alzheimer's disease. As the disease progresses, cognitive, physical and social functioning deteriorate. Patients gradually lose their ability to carry out both ADLs and IADLs (Table 10).

Longitudinal studies have shown that the relationship between baseline disease severity and the rate of cognitive decline is not linear.[88] An expected rate of cognitive decline for untreated patient cohorts can be estimated given their baseline ADAS-Cog or MMSE scores. People with mild dementia (ADAS-Cog score = 15) and people with severe dementia (ADAS-Cog ≥ 55) show an average rate of decline of 5 or fewer ADAS-Cog points per year.

Considering the full range of people with moderate dementia (ADAS-Cog >15 to < 55), longitudinal studies have found a decline in untreated clinic patients of 7 to 11 points annually.[88,146] This rate of decline is equivalent to 2 to 4 points annually on the MMSE.[147,148]

On the ADAS-Cog, an improvement of 3 to 4 points from baseline can mean, for example, that the patient can now remember who came to dinner the previous evening or perform familiar tasks, such as dressing.[149] Given that untreated patients with mild to moderate dementia deteriorate annually by 5 to 11 points on the ADAS-Cog, an improvement of 4 points may be equivalent to a 5- to 10-month delay in the progression of the disease.

Trials of Alzheimer's Disease Drugs

Efficacy of Cholinesterase Inhibitors

The FDA has approved 4 cholinesterase inhibitors: tacrine, donepezil, rivastigmine, and galantamine. We found 4 systematic reviews[115,119-121] that evaluated the efficacy of this class of medication on the cognition, global change and functional status of Alzheimer's disease in patients with mild to moderate stages of the disease (Evidence Table 4a). Our search also yielded 7 RCTs of 6 or less months' duration,[96-101,112] and 2 RCTs of 12 months' duration.[93,95] Two tacrine reviews,[120,121] 1 donepezil RCT,[93] and 1 galantamine RCT[98] also looked at the efficacy of cholinesterase inhibitors on the behavioral symptoms of Alzheimer's disease. One systematic review[119] and 1 RCT[99] evaluated the impact of donepezil on the quality of life of patients with Alzheimer's disease. One RCT conducted an economic evaluation and assessed the efficacy of donepezil on the time that caregivers spent assisting Alzheimer's disease patients with their activities of daily living.[93]

Table 11 summarizes the effect of the 4 different cholinesterase inhibitors on various outcomes in Alzheimer's disease. These are discussed in detail below.

Tacrine. One systematic review evaluated the efficacy of tacrine in patients with mild to moderate Alzheimer's disease examined the data from 12 good quality RCTs with close to 2,000 subjects.[121] This study found that, compared to placebo, patients receiving 3 months of tacrine therapy showed the following: a mean difference of 2.1 points on the 70-point ADAS-Cog scale (see Table 9 for description of scale); an odds ratio (OR) of 1.58 (95% Confidence Interval [CI], 1.18-2.11) showing improvement on the Clinical Global Impression of Change (CGIC, range 1 to 7); no significant change in functional ability; and a mean difference of 0.58 points (P = 0.006) on the 50-point ADAS-noncognitive behavioral scale. A more recent review[120] looked only at 5 RCTs that were included in the previous review. The authors found that the mean difference of 0.14 on the ADAS-Cog and an OR of 1.15 on the CGIC, both in favor of treatment.

Donepezil. Birks et al.[119] summarized the efficacy of donepezil as studied in 4 RCTs with total of 1,100 patients with mild to moderate Alzheimer's disease. The authors found that 6 months of donepezil therapy produced a mean difference of 3 points on the 70-points ADAS-Cog scale and an OR of 2.63 (95% CI, 1.79-3.85) for showing improvement on the CIBIC-plus (range 1 to 7). According to this systematic review, donepezil had no effect on either functional ability or patients' self-rated quality of life.

We found 4 additional RCTs that were not included in the Birks et al. review. These 4 trials also demonstrate that donepezil offers small improvements in cognition and global change scores when compared to placebo. Burns and colleagues assessed the efficacy of 6 months of donepezil therapy in 818 Alzheimer's disease patients.[99] In addition to cognitive and global change, this trial evaluated the effect of donepezil on functional status as measured by the

Interview for Deterioration in Daily living in Dementia (IDDD) scale. The investigators found that, compared to patients receiving placebo, those receiving 10 mg of donepezil for 6 months produced the following: a mean improvement of 2.9 points on the 70-point ADAS-Cog scale; 11% more patients considered improved on the global CIBIC-plus scale; a mean difference of 1 point on the 233-point functional IDDD; and no effect on the patient's quality of life.

Greenberg et al conducted double-blind placebo-controlled crossover study that evaluated the effect of a 3-month 5 mg dose of donepezil therapy in 60 patients.[100] This study found that donepezil produced a mean improvement of 2.1 points on the 70-point ADAS-Cog scale, with no improvement on the global CGIC scale.

In a third study, an RCT conducted in Northern European countries, Winblad and colleagues evaluated the efficacy of 12 months of 10 mg donepezil therapy in 286 patients with mild to moderate dementia.[93] The primary outcome measure in this trial was The Gottfries-Brane-Steen (GBS) scale, a 162-point measure of global change. The secondary outcome measures were the MMSE, a 30-point measure of cognition; the Progressive Deterioration Scale (PDS), a measure of functional status; the NeuroPsychiatry Inventory (NPI), a measure of behavior; caregiver time spent assisting patients in ADLs; and Resource Utilization in Dementia Questionnaire (RUD), a measure of the cost of care.

The investigators found that, compared to patients receiving placebo, 12 months of treatment with donepezil produced statistically significant improvement in global change, cognition and functional status measures.[93] The magnitude of these changes are the following: a mean improvement of 1.9 points on the 30-point MMSE cognitive scale; a mean improvement of 4 points on the 162-point GBS global scale (see Table 9 for description of scale); and a mean improvement of 3.5 points on the 100-point PDS functional performance scale. There was no

significant effect on the behavioral symptoms of Alzheimer's disease. On average, the caregiver in the donepezil group spent 1.1 fewer hours per day giving care than those in the placebo group. This daily difference could not be judged for statistical significance (data were not available). At 12-month follow-up, 6% of the caregivers in the placebo group spent 16 hours or more daily assisting the patient with their functional performance compared to 2% of the caregivers in the donepezil group. This difference was not statistically significant.

Mastey et al. conducted an economic evaluation of donepezil among the patients who enrolled in this study.[150] The authors found that the average annual cost per patient was $1,100 (US dollars) more in the placebo group than in the donepezil group.

The fourth study by Mohs and colleagues was a 1-year, double-blind, placebo-controlled study evaluating the ability of donepezil to preserve or slow the functional decline in 431 community- dwelling patients with mild to moderate Alzheimer's disease who were able to perform 5 out of 6 basic ADLs and 8 out of 10 IADLs.[95] The primary outcome measure was the time to reach a clinically evident decline in functional performance. This decline was defined the patient reaching one of the following criteria: (1) a decline in ability to perform 1 or more basic ADLs; (2) a decline in ability to perform 2 or more IADLs; or (3) an increase in the global Clinical Dementia Rating scale (CDR) of 1 or more points compared to baseline. The authors found that 10 mg donepezil therapy produced a median time to clinically evident decline of 6.9 months for the placebo group versus 11.9 months for the donepezil group, a mean change of 1 point on the 30-point MMSE scale, and mean change of 1.6 points on the 54-point ADFACS functional scale.

Rivastigmine. Birks et al. evaluated the efficacy of rivastigmine by reviewing 7 RCTs with total of 3,370 patients with Alzheimer's disease.[115] The authors found that, compared to

patients receiving placebo, 4 months of 6 mg to 12 mg of rivastigmine therapy produced the following: a mean improvement of 2.4 points on the 70-point ADAS-Cog scale; a mean improvement of 2.4 points on the 100-point Progressive Deterioration Scale (PDS); and no statistically significant effect on the global scale.

An additional RCT assessed the efficacy of 6.5 months of high-dose rivastigmine (6 mg to12 mg daily) in 725 Alzheimer's disease patients.[101] Rivastigmine produced the following: a mean improvement of 2.3 points on the 70-point ADAS-Cog scale; 18% more patients in the treatment group than in the placebo group with an improvement on the global CIBIC-plus scale ($P = 0.001$); and a mean improvement of 3.6 points on the 100-point PDS scale. None of the previous studies evaluated the efficacy of rivastigmine on both the behavioral symptoms of Alzheimer's disease and patients' quality of life.

Rivastigmine was the only drug evaluated in the treatment of Lewy body dementia (LBD) in an RCT of 120 patients.[102] Rivastigmine improved the behavioral symptoms as measured by mean difference of 3.8 points on the 120-point NPI scale (NPI-10) and 2.3 points on the 48-point 4 item-sub-scale (NPI-4) (Appendix C). This effect, although not detected on the global scale, was accompanied by a mean improvement of 1.6 points ($P = 0.072$) on the MMSE.

Galantamine. This new FDA-approved cholinesterase inhibitor was evaluated in 4 RCTs with a total of 2,552 patients with Alzheimer's disease.[96-98,112] Across the 4 trials, compared to patients receiving placebo, patients receiving 24 mg of galantamine daily for 3 to 6 months had a mean difference of 3.3 points on the 70-point ADAS-Cog scale and 14% to 17% more intervention patients than placebo patients stabilized or improved on the 7-point CIBIC-plus global scale. Two trials showed some positive effect on functional performance. One used the Disability Assessment for Dementia scale (DAD: a 100-point scale) and detected a mean

difference of 3.4 points.[96] Another used the Alzheimer's Disease Cooperative Study-Activity of Daily Living (ADCS-ADL: a 78-point scale) and detected a mean difference of 2.3 points.[98] Finally, one trial (978 patients) evaluated the effect of a 24 mg daily dose of galantamine for 5 months on the behavioral symptoms of Alzheimer's disease. This study demonstrated a mean difference of 2 points on the 120-point NeuroPsychiatry Inventory (NPI). Only 1 trial evaluates the impact of this drug on the patient's quality of life; it showed an insignificant effect.[112]

In summary, RCTs of cholinesterase inhibitors for mild to moderate Alzheimer's dementia show modest benefit on measures of cognition and global change scores, but little or no improvements in functional status. Effects on behavior and other outcomes are rarely measured.

Efficacy of Other Medications

Gingko biloba special extract (EGb-761). This alternative medication was studied in 1 systematic review[118] and 1 RCT[106] (see Evidence Table 5) Oken et al. evaluated 5 RCTs with 424 Alzheimer's disease patients; all used a daily dose of 120 mg to 240 mg of gingko biloba for periods of 12 to 26 weeks.[118] They found that gingko biloba produced an improvement of 2.1 points on the 70-points ADAS-Cog scale. Le Bars et al. examined its effect in 309 Alzheimer's disease patients for a period of 13 months.[106] After 6 months, the attrition rate among the placebo and the treatment groups differed significantly, so we report here only the results from the 6-month phase. Gingko biloba had a mean improvement of 2.1 points on the 70-point ADAS-Cog scale. This trial showed no effect on clinical global functioning or on a caregiver rating of cognition, social function and mood.

Anti-oxidants (selegiline, vitamin E). One well-conducted systematic review evaluated 15 RCTs and found that 10 mg of selegiline produced a small improvement on cognitive testing (Evidence Table 6).[116] A statistically significant decrease occurred in

behavioral symptoms as demonstrated by a small improvement of 2.4 points on the 126-point Behavioral Psychiatry Rating Scale (BPRS) and a moderate improvement of 9.6 points on Dementia Mood Assessment Scale (DMAS; range 0 to144 points). A combined global change scale, however, did not reflect this cognitive and behavioral improvement.

Because of the different outcomes measured and the comparison of multiple interventions in addition to selegiline, we also evaluated the Alzheimer's Disease Cooperative Study. In this 2-year RCT, Sano and colleagues tried to determine whether selegiline, vitamin E, or a combination of the 2 pharmacotherapies would slow the functional loss associated with Alzheimer's disease.[103] It enrolled 341 patients residing at home or in skilled-nursing facilities who had moderate Alzheimer's disease, based on a score of 2 on the CDR scale (Evidence Table 6). The primary outcome measured was the time to clinically evident decline in functional status, which was defined as the occurrence of 1 of the following: death, institutionalization, loss of the ability to perform at least 2 basic ADLs, or progression to 3 points (severe impairment). After adjusting for the 2-point difference in the MMSE baseline scores among the groups, the investigators found that the median time to clinically evident decline in functioning was 670 days for the vitamin E group, 655 days for the selegiline group, 585 days for the combined group, and 440 days for the placebo group. These differences were statistically significant. The groups did not differ on either the ADAS-Cog or the MMSE.

Estrogen. One trial evaluated the effect of estrogen (0.625 mg or 1.25 mg daily) in 120 Alzheimer's disease patients (Evidence Table 6).[105] The investigators found no positive effect on cognitive, global, or behavioral domains; they also reported a negative effect of small size on the global function. Another small trial evaluated the effect of Estraderm® (estrogen patch) on specific cognitive domains of 20 women with Alzheimer's disease.[114] The investigators found

that estrogen improved the memory and the attention of the treatment group but that it had no effect on any global cognitive test (MMSE and BMICT) or on functional status.

Anti-inflammatory medication. Two trials evaluated the role of anti-inflammatory medications (Evidence Table 7).[108,109] One studied the effect of 10 mg daily of prednisone for 12 months on 138 Alzheimer's disease patients.[108] The investigators found no effect on cognitive deficits and a negative effect on the behavioral symptoms of Alzheimer's disease. The other trial studied the effect of diclofenac in 41 Alzheimer's disease patients; [109] 50 mg of this nonsteroidal anti-inflammatory drug (NSAID) daily for 6 months had no effect on the cognitive, physical, global, or behavioral outcomes that were measured.

Trials of Drug Therapy for Vascular Dementia

One systematic review evaluated the effect of aspirin on vascular dementia (Evidence Table 8).[117] This review included 70 patients who took 325 mg of aspirin daily for 1 year. These patients demonstrated some improvement in cognitive function, but the change was not statistically significant.

One RCT evaluated the effect of nimodipine in 251 patients with vascular dementia.[104] In this study, 90 mg of nimodipine daily for 6 months produced no effect on measures of global change, cognition, or functional status (Evidence Table 8). The study did not assess the impact of nimodipine on the behavioral symptoms of vascular dementia.

Trials of Drug Therapy for Behavioral Problems Related to Dementia

Efficacy of Neuroleptics

Lanctot et al. systematically reviewed the literature about the role of typical neuroleptics in dementia management (Evidence Table 9a).[122] Their meta-analysis pooled data from 13 RCTs on the proportion of 295 patients who showed clinically significant behavioral improvement. Patients who took any type of neuroleptic had a 26% greater response in their behavioral and psychological symptoms than those taking a placebo.

In 2000, Davidson et al. published a systematic review assessing the role of the atypical neuroleptics (resperidone and olanzepine) in dementia management (Evidence Table 9a).[124] The authors pooled data on the proportion of patients with clinically significant improvement in their behavioral problems from 3 RCTs with 911 subjects. These atypical neuroleptics had modest efficacy compared to placebo (OR, 0.59; 95% CI, 0.44-0.78; NNT, 8; 95% CI, 5-18) in treating behavioral problems related to dementia.

Kirchner et al. studied the efficacy of thioridazine (a typical neuroleptic) in dementia (Evidence Table 9a).[125] The authors found 10 RCTs and were able to perform a meta-analysis on 7 of these (though only 2 compared thioridazine to placebo) involving 670 subjects. Thioridazine treatment for 4 to 8 weeks decreased anxiety symptoms of demented patients (OR, 4.91; 95% CI, 3.21-7.5). However, the authors judged the improvement to be clinically insignificant and concluded that the available data do not support the use of thioridazine in dementia.

Because screening in primary care is likely to identify patients with early dementia, data on treatment of behavioral symptoms in early dementia are most relevant to the USPSTF concerns. In previous RCTs and reviews, patients did not always have mild to moderate

dementia; many were in institutions that usually care for patients in the later stages of disease. In the Davidson et al. review, the mean MMSE was 7.3 of 30 possible points, indicating advanced disease.[124] In the Lanctot et al. review, only 70% of the RCTs included patients with primary dementia.[122] One of the 2 thioridazine RCTs reviewed by Kirchner et al. had 610 subjects living in a nursing home.[125]

Three RCTs of neuroleptic therapy for behavioral problems in dementia met our inclusion criteria and had no fatal methodological flaws (Evidence Table 9b). Teri et al. compared the efficacy between haloperidol, trazodone, behavioral management techniques, and placebo on the behavioral problems related to dementia in 148 individuals who had moderate to severe stage of Alzheimer's disease and suffered from at least two types of disturbed behaviors that occurred once a week prior to the study start.[113] The investigators found no difference among the 4 previous groups. Devanand et al. studied the efficacy of a standard dose (2 mg to 3 mg daily) of haloperidol compared to a low dose (0.5 mg to 0.75 mg daily) or placebo in 66 memory clinic patients with Alzheimer's disease and disruptive behaviors or psychosis at baseline.[94] The standard dose of haloperidol produced a 33% greater improvement in disruptive behavior than those receiving placebo. However, 39% of the subjects had severe dementia. In a pilot study, Auchus et al. found no effect of a 3 mg daily dose of haloperidol compared to fluoxetine or placebo in improving agitation and caregiver stress in 15 community-dwelling patients with mild to moderate Alzheimer's disease with agitation at baseline.[110]

In summary, neuroleptics improve the behavioral problems related to dementia syndrome among patients with moderate to severe stages and who are living in institutional settings.

Efficacy of Antidepressants

In an RCT with a crossover design, Petracca et al. studied the efficacy of 6 weeks of therapy with clomipramine (a tricyclic antidepressant) compared to placebo in 21 patients who had mild to moderate Alzheimer's disease and major depression or dysthymia (Evidence Table 9b).[111] Of patients in the treatment arm, 82% entered remission from depressive symptoms at 6 weeks, compared to 30% of the placebo group ($p = 0.02$; NNT = 2). Clomipramine also decreased the cognition scores of patients but had no effect on functional status. In a more recent study, Lyketsos et al. evaluated the effect of sertraline in 22 individuals with both Alzheimer's disease and major depression (Evidence Table 9b).[4] The investigators found that, after 3 months, 75% of the sertraline group had a partial or full response compared to 20% of the placebo group. The caregivers of individuals who received sertraline reported an 11-point decrease on the Cornell Depression in Dementia Scale compared to only 2 points among those who received placebo.

In summary, 2 RCTs provide evidence that antidepressant medication is effective for mood symptoms in patients with Alzheimer's disease; antidepressants have not been studied for effect on cognition or other outcomes.

Summary of Efficacy Evidence

Review of the evidence for drug treatment of dementia (found in Evidence Tables 4-9) found that full reversal of diseases often grouped as "reversible dementias" occurs in no more than 1.5% of dementia cases. For Alzheimer's disease, multiple RCTs indicate that 6-month and 12-month therapy with cholinesterase inhibitors produces positive effects on cognition and global change scores. The magnitude of the cognitive improvement was 2 to 3 points on the 70-

point ADAS-Cog scale, which is equivalent to a delay of about 4 to 5 months in the natural course of the disease. Based on the results of 1 study, the anti-oxidants vitamin E and selegiline delayed the functional decline of patients with moderate Alzheimer's disease by an average of 7 months. Gingko biloba yielded small improvements in cognitive function. No evidence exists for benefit from anti-inflammatory drugs, estrogen, nimodipine, or aspirin in the treatment of dementia. Both typical and atypical antipsychotic medications have modest benefit in the treatment of agitated behavioral symptoms in patients with dementia. However, most of these medication trials have included patients with mild, moderate, and advanced dementia, limiting their relevance to a screening population of primary care outpatients. One RCT provided evidence that a tricyclic antidepressant reduced symptoms of depression in patients with early dementia and another showed that sertraline improved major depression in patients with mild to moderate Alzheimer's disease.

KEY QUESTION NO. 5: EFFICACY OF NONPHARMACOLOGIC INTERVENTIONS

Our search yielded no study that met our inclusion criteria. Six systematic reviews evaluated a variety of nonpharmacological interventions for patients with dementia syndrome in long-term care settings (Evidence Table 11). These interventions can be categorized into 4 types: sensory, environmental modification, behavioral, and activity-directed interventions.

Forbes did a comprehensive systematic review for any type of interventions.[151] She rated the included articles using a methodology appraisal method that looked at the study design, inclusion criteria, attrition rate, confounders' adjustment, data collection, and statistical analysis.

Applying an appraisal scale to the 45 articles, Forbes included only 1 strong and 6 moderate studies.

When we applied the USPSTF appraisal protocol to these 7 studies, we included only 3 RCTs with 132 subjects (no evidence table). Planned walking with conversation improved the communication functioning of the patient.[152] An attention-focused program improved the activity participation of the patients.[153] Finally, functional skills training increased patients' self-care ability.[154]

Opie et al. looked specifically at behavioral disorders in dementia and evaluated the nonpharmacologic interventions that had been used to manage these disorders or symptoms.[155] The authors searched the literature from 1989 through 1998; of 43 articles that met their inclusion criteria, 5 were RCTs (1 trial was rated poor). One trial found that a combination of an activity program and caregiver education significantly decreased physical aggression among demented patients.[156] Another trial found that a multidisciplinary team approach improved agitation in demented patients; it also met USPSTF quality standards.[157] The other 2 trials in this systematic review showed no efficacy for 2 separate interventions: caregiver education and an activity program treating general agitation.[158,159]

We identified 4 systematic reviews that evaluated specific types of nonpharmacologic interventions. Koger and Brotons found no RCTs in a systematic review of music therapy, but they reviewed 126 articles that supported the use of music therapy in dementia.[160] Neal and Briggs identified 3 RCTs that evaluated the role of validation therapy in dementia, but this evidence was insufficient to support any conclusion about the efficacy of validation therapy.[161] The pooled data showed no effect on either the behavioral or the cognitive symptoms of dementia.

Spector et al. found 2 RCTs that evaluated the efficacy of life reminiscence in dementia.[162] The authors analyzed data on 15 participants with moderate to severe cognitive impairment and found no effect on cognitive or behavioral symptoms of dementia. Spector et al. also performed a meta-analysis of 6 RCTs that looked at the efficacy of reality orientation in dementia.[163] The authors found that no firm conclusions could be drawn about the effectiveness of reality orientation for dementia.

In summary, numerous studies have reported on various nonpharmacologic interventions to treat the behavioral symptoms of dementia. These interventions differ in type and content and may be difficult to replicate. Some evidence supports planned walking, attention-focused programs, functional skills training, activity programs, multidisciplinary team care, reality orientation, and caregiver education to control behavioral symptoms in advanced dementia. No evidence supports reminiscence therapy, music therapy, or validation therapy. These trials have been conducted in institutional settings. We found no trials of nonpharmacologic interventions in early dementia in a community setting.

KEY QUESTION NO. 6: EFFICACY OF CAREGIVER INTERVENTIONS

Rationale for Inclusion in this Review

Among individuals older than 65, 3% to 8% have dementia. Family members, usually elderly spouses, care for 66% to 75% of patients with dementia at home.[27] Caring for patients with dementia can be very challenging and burdensome. Dementia is a progressive syndrome marked by behavioral problems and impaired abilities in self-care. It has negative impacts on the

caregiver and induces a significant level of caregiver burden.[30-32,164] This burden is defined as the financial, physical, and emotional effects of caring for an adult with a disabling condition.[165]

Most studies have found high levels of anxiety and depressive symptoms and increased use of psychotropic medications in caregivers compared to age-matched controls or population means.[28] Reported rates of depression among dementia caregivers vary from 30% in a community sample to 46% of caregivers who sought help.[166,167] In 1 study, 80% of caregivers reported symptoms of chronic fatigue, depression, or anger.[34] Caring for patients with dementia can create a financial burden in addition to the mental and physical ones. Dunkin and Anderson-Hanley estimated that the total cost of caring for very impaired elders in the community, including reimbursable, non-reimbursable, and unpaid labor costs, can be as expensive as nursing home care, or close to $18,256 annually.[27]

Recent data suggest that caregiver burden can be an important determinant of the demented patients' behavioral problems in addition to their need for institutionalization.[27,164] Caregiver burden appears to be mediated by many variables such as social support, financial resources, coping skills, gender, feelings of self efficacy, and ethnicity, as well as the patient's cognitive, functional, and behavioral impairment.[27] Some studies found that behavioral problems appeared to exert greater effects on caregiver burden than did cognitive or functional impairment.[168-171]

Yield of Literature Search

We identified 17 RCTs and 9 systematic reviews that met our screening criteria: patients with mild to moderate dementia syndrome based on DSM or ICD-10 criteria; an MMSE score of 10 or above or a CDR score of 1 or 2; and living at home with their informal caregivers. Of

these, we rated 1 review good (Evidence Table 11a).[172] and 5 RCTs[173-178] fair to good (Evidence Table 11a). We combined 2 RCTs because they used the same participants.[177,178]

The interventions that target caregivers of patients with dementia do not form mutually exclusive categories; they have varied components and target a diverse group of caregivers. Usually they offer 1 or a combination of the following components: support groups, individual or family counseling, skills training, or educational sessions. No study with our inclusion criteria evaluated respite care, although respite care was offered to control groups in some of our included studies. We categorized all study outcomes as either outcomes that target caregivers' stress and coping (depression, sleep problems, and reaction to behavioral problems of the patient) or those that target the patients' functioning (physical, cognitive, or social), behavioral problems, and institutionalization. No study looked at the effect on patients' quality of life, automobile crashes, falls, or other accidents.

Effect on Caregivers' Outcomes

One good quality systematic review by Thompson and Briggs looked at 6 RCTs that met our inclusion criteria (Evidence Table 11a).[172] The authors evaluated the effects of 4 types of caregiver interventions: individualized service assessment and planning, technology-based interventions, caregiver education and training, and a multi-component program versus conventional care or support. They assessed the impact of the interventions on caregivers' burden, mental health, health care utilization, and knowledge of dementia. Thompson and Briggs found no significant differences between any of the intervention and control groups and concluded that little or no evidence exists that interventions to support caregivers of people with Alzheimer's disease yield quantifiable benefit.

In examining articles that had not been included in the Thompson and Briggs systematic review, we found 3 studies evaluating the effect of caregiver intervention on caregiver burden and depressive symptoms (Evidence Table 11b). Of these, 2 (with sample sizes of 36 to 45) found no effect,[175,177,178] and 1 found a positive effort.[174] This trial (42 subjects) found that a 14-session multi-component intervention decreased both the burden and depression among caregivers at 9 and 12 months from entry into the study.[174] The number-needed-to-treat (NNT) to convert a caregiver from being a person with significant psychological morbidity to one without such a level of morbidity was 3 directly at the end of the intervention and 2 at 3 months' follow-up.

To evaluate the effect of caregiver intervention on caregivers' sleep, McCurry et al. studied a multi-component intervention to manage sleep disturbance in 36 caregivers with significant sleep problems (Evidence Table 11b).[175] They were able to improve the quality of sleep among the intervention group and reported that 50% of the caregivers in the treatment arm were considered clinical responders with no more significant sleep problems at the end of the intervention. Two studies examined the effect of intervention on caregiver reaction to behavioral problems among patients with dementia.[175] The authors found no significant effect.[177,178] In the Hebert et al. study, the comprehensive intervention increased the caregivers' knowledge of Alzheimer's disease but did not affect the caregivers' level of stress.[177,178]

In summary, most trials of caregiver interventions showed no benefit to caregivers. One multi-component intervention decreased burden and depression among caregivers. One caregiver intervention that focused on sleep problems showed benefit on this specific outcome.

Effect on Patients' Outcomes

No systematic review evaluated the impact of caregiver interventions on patients' outcomes, but 3 studies examined the effect of caregiver interventions on patients' cognition, function, and behavioral problems. Marriott and colleagues found some effect on behavioral problems and functional status but failed to report whether caregivers perceived these changes as significant.[174] Two other studies (96 and 206 subjects) found that a comprehensive caregiver intervention enabled caregivers to maintain their care recipients at home for a substantially longer period of time (between 11 and 19 months) than those who did not receive the intervention.[173,176]

The Mittelman et al. study looked at the effect of keeping the patient at home on caregiver stress (depression).[173] The authors concluded that depression decreased, but this part of the study was judged to be of poor quality because of a high attrition rate, no reported concealment of the outcome measures, and no intention-to-treat analysis. We found no report of the effect of the caregiver intervention on the caregivers' burden or depression in the Brodaty et al. study.[176] In a third study, Hebert et al. found that multi-component intervention had some effect on nursing home placement.[177,178] The treatment group had a 33% probability of being placed in a nursing home within 2 years compared with 45% probability for the control group, but this effect did not reach statistical significance because of the small sample size (45 subjects).

In summary, 3 studies of caregiver interventions showed a delay in nursing home placement for dementia patients. The procedural details of the interventions varied appreciably among the studies. All these interventions would be difficult to implement in primary care settings, as they require specific expertise and extensive staff training. Most of the outcomes,

except time to nursing home placement, were assessed by small studies and with different measurement tools that lacked clinical and practical implementation.

A very comprehensive multi-component caregiver intervention that includes a support group, skills training, counseling, and education can keep the patient at home for a longer period of time. It may also decrease the burden on caregivers and improve their mood and sleep. Caregiver interventions do not affect patients' function (cognitive, physical, social), behavioral problems, quality of life, or auto crashes, falls or other accidents.

KEY QUESTION NO. 7: ADVERSE EFFECTS OF SCREENING

Our search for articles under the term "Mass Screening" found scant literature on the adverse effects of screening for dementia, particularly in regard to conventional screening techniques. Most articles dealt primarily with the adverse effects of mass screening for genetic markers for an increased likelihood of Alzheimer's disease. The potential negative outcomes for all patients screened dealt primarily with the emotional distress caused by the interview and/or tests.

A 1994 survey by Jorm et al. of patients after they had completed an extensive mental health interview or questionnaire (greater than 110 minutes) found that a large majority reported that the experience had no adverse effect on their emotional state.[179] Less than 5% found the study interview distressing, intrusive, or depressing. The cognitive/dementia portion of the questionnaire administered included 6 of the 25 questions considered distressing. Those who were distressed had more anxiety symptoms and scored more poorly on the reading test administered. The authors concluded that the distress could likely be attributed to subjects

feeling embarrassed when asked to do a particular task that they thought they would execute poorly.

Once screening identifies persons with low cognitive function, clinicians have some concern over the disclosure of information to patients regarding their dementia status. Two case reports of suicide in patients with newly diagnosed Alzheimer's disease by Rohde et al.,[64] in addition to the highly publicized assisted suicide of a 54-year-old patient with possible Alzheimer's disease in 1990,[63] present an infrequent but significant potential adverse event.[63] The risk of such drastic measures may lessen as treatments improve and as clinicians and patients learn about their options.

A theoretical but unproven threat remains to particular patients' autonomy as a result of their being diagnosed with dementia. This danger arises because others may question the individuals' capacity to perform numerous tasks. In fact, questioning patients' capacities may extend to providers. When acting in the role of evaluator for government and other agencies (e.g., driving eligibility), the duty of providers to act on behalf of their patients and the public may come into conflict with their duty to preserve patients' autonomy when addressing issues such as patients' abilities to drive and perform other responsibilities.

All these issues become even more important if a significant number of those falsely identified as having dementia through screening do not have this diagnosis corrected through more comprehensive testing.

KEY QUESTION NO. 8: COSTS OF SCREENING

We found no studies that evaluated the costs of screening for dementia in a primary care setting.

KEY QUESTION NO. 9: ADVERSE EFFECTS OF TREATMENT

We extracted data about dropout rates attributed to adverse effects among demented patients treated with effective pharmacologic interventions in the RCTs and systematic reviews examined for Key Questions 4 and 5 (Evidence Tables 12a – 12d). For cholinesterase inhibitors (Evidence Tables 12a, 12b), these included 9 RCTs[93,95-102] and 4 reviews.[115,119-121] We examined 3 reviews[122,124,125] and 1 RCT[94,122,124] on typical and the atypical neuroleptics (Evidence Table 12c). Finally, we reviewed trials or systematic reviews on several other therapies (Evidence Table 12d): 1 RCT[106] and 1 review[118] on gingko biloba; 2 RCTs[103,116] on selegiline; and 1 trial of the antidepressant clomipramine.[111]

The more common side effects in patients who took any type of cholinesterase inhibitor (Evidence Tables 12a, 12b) were nausea, vomiting, weight loss, and diarrhea. The dropout rate due to adverse events among patients who took 24 mg of galantamine daily ranged from 10% to 23%; the average dropout rate among the placebo groups was 8%. The dropout rate for the effective dose of rivastigmine (6 mg to 12 mg per day) ranged from 12% to 27% compared to a rate of 7% among the placebo groups. Dropout rates did not differ for patients who took 5 mg of donepezil daily and those who took placebo. However, the 10 mg dose of donepezil led to a dropout rate of 18% compared to a rate of 10% for the placebo group. Tacrine has significant gastrointestinal and hepatic side effects. The odds ratio (OR) for dropout due to adverse events among patients who took tacrine compared to those on placebo was 5.7 (95% CI, 4.1-7.9).

Dementia syndrome causes significant behavior disturbances among its victims. The pharmacological treatment of these problems is based on the use of neuroleptics, benzodiazepines, antidepressants, and other agents. In 1 systematic review, Lanctot et al. evaluated patients' tolerance of the typical neuroleptics and found that the dropout rate between

treatment and placebo groups did not differ significantly.[122] However, 51% of patients who took neuroleptics had some adverse effects, as did 25% of the placebo group; the number needed to harm (NNH) was 4 (range 3 to 8).

Davidson et al. assessed the tolerance of the new atypical neuroleptics.[124] The investigators reported an OR for dropout of 1.3 (95% CI, 1-1.7), an OR of 2 for extra-pyramidal side effects (EPS) with an NNH of 13, and an OR of 1.7 for sedation with an NNH of 10. In a trial conducted by Devanand et al. in 1998, 20% of patients who took 2 to 4 mg of haloperidol daily developed moderate to severe EPS compared to 0% among a placebo group.[94]

Tolerance rates did not differ between people who took gingko biloba and those who took placebo. Both groups had a similar dropout rate of 16%. People who took selegiline and those who took placebo both had dropout rates of 20%. In the only antidepressant trial that met our inclusion criteria, Petracca et al. studied the efficacy of clomipramine in the treatment of depression in dementia.[111] All patients who took the drug developed some type of adverse event, but none of these effects led patients to stop the medication.

Chapter 4. Discussion

Major Findings

Our systematic review found no randomized trial that evaluated the overall efficacy of dementia screening in primary care. Therefore, we attempted to evaluate screening by reviewing the literature using a step-wise analytic framework that focused on prevalence of undiagnosed dementia properties of screening tests, studies of treatment options for patients and caregivers, and adverse effects of screening and treatment.

The prevalence of the dementia syndrome increases rapidly in the seventh and eighth decades of life; this ailment affects more than 25% of people who are 85 years of age and older. The burden of this disease also extends to the caregivers. Among all primary care patients over age 65, 1.8% to 12% have undiagnosed dementia, and one-half to two-thirds of all cases of dementia in primary care populations are undiagnosed.

The Mini-Mental State Examination (MMSE) is the best-studied brief screening tool for dementia. A cut-point of 24 to 26 out of 30 points is usually accepted as a positive screen and should lead to diagnostic evaluation with further history, examination, and testing for dementia. Scores must be adjusted for educational attainment. The MMSE can identify cases of dementia with a sensitivity of 71% to 92% and specificity of 56% to 96%.

Dementia is often treatable but rarely curable or reversible. No more than 1.5% of all dementia cases are fully reversible. About 60% of people with dementia syndrome have Alzheimer's disease and 15% have vascular dementia. Nearly all cases of dementia are irreversible, so the clinical benefits of primary care screening will be heavily influenced by the

benefits of early diagnosis and treatment of Alzheimer's disease, vascular dementia, and other irreversible etiologies.

Treatment of Alzheimer's disease with cholinesterase inhibitors for 6 to 12 months results in modest but consistent improvements in cognition and clinician global impression of change scores. Compared with patients receiving no such treatment, patients receiving cholinesterase inhibitors displayed clinically evident positive changes; their decline was delayed and they maintained independence equivalent to 3 to 5 months' delay in the natural history of the disease. One randomized controlled trial (RCT) found that anti-oxidants (selegiline and vitamin E) delayed by 7 months a combined outcome of mortality, nursing home placement, and functional decline in patients with moderate stage Alzheimer's disease. RCTs of nimodipine and aspirin have shown no effect on vascular dementia.

Treatment of behavioral problems and depressive symptoms in early dementia is poorly studied. Two small RCTs demonstrated effective treatment of depression in early dementia. Neuroleptic medications and nonpharmacologic interventions reduce agitated behaviors in later stages of dementia, but these therapies are rarely studied in early dementia or in community or primary care settings. Intensive interventions to support caregivers delayed nursing home placement for Alzheimer's disease patients, but they had little or no demonstrated direct benefits on either patient or caregiver. These interventions are varied and complex; such multi-component interventional programs have not been evaluated in primary care setting and their effectiveness warrants further assessment.

In 2001, the American Academy of Neurology published an evidence-based review of the diagnosis, evaluation, and treatment of dementia.[180] The authors found that, on average, cholinesterase inhibitors produce a small benefit in Alzheimer's disease patients. They

concluded that insufficient data exist to make any recommendations regarding cognitive screening of asymptomatic individuals. The report recommended diagnostic evaluation and monitoring for persons with mild cognitive impairment because of their increased incidence of dementia.[180]

This conclusion is similar to that in the 1996 practice guideline issued by the Agency for Health Care Policy and Research[75] and to the recommendations of the 2001 Canadian Consensus Conference on Dementia[181] in that it recommends a complete evaluation and close follow-up of individuals with memory complaints or functional decline. These reviews did not include 2 recent 12-month RCTs, which showed that the cognitive and clinician global impression of change benefits of cholinesterase inhibitors extended to 1 full year and translated to up to a 5-month delay in clinically evident decline in patients' ability to maintain their independence in instrumental and basic activities of daily living (ADLs).[93,95] Although these trials may provide greater evidence for treatment of diagnosed disease than have been available heretofore, they do not directly address the issue of screening to promote earlier treatment.

The degree to which participants in treatment trials are representative of patients who would be identified by screening is not clear. Nonetheless, the mean MMSE score for individuals in treatment trials was similar to the scores for undiagnosed cases of dementia that were detected by screening.

Limitations of this Literature

Our review has some limitations. First, we limited our review to studies of mild to moderate dementia among community-dwelling patients. These criteria approximated the patient population likely to be identified by primary care screening, but they may exclude

compelling studies of treatment outcomes. Second, we limited our search to English-language articles, and thus we may have excluded studies from similar non-English-speaking populations. We believe that our review successfully captured all studies that met inclusion criteria. A repeat search of 4 data sources – MEDLINE, PsycINFO, EMBASE, and the Cochrane Collaboration library – and extensive peer review of our draft systematic evidence review identified only 1 additional study that met our inclusion criteria.

Benefits and Harms

Data are insufficient to create an outcomes table of screening strategies for dementia. Harms of dementia screening have not been systematically studied. Potential harms include risk of depression and anxiety, the time and cost of screening, and possible labeling effects. Once a diagnosis of dementia is given, patients will be unlikely to qualify for long-term care insurance or acceptance into continuous care retirement communities.

In a survey of elderly and caregivers of Alzheimer's patients, most participants wanted to be told the diagnosis of dementia.[182] In another study, Jha et al. investigated the reaction of elderly patients in outpatient clinics to the disclosure of their diagnosis of dementia compared with depression.[183] The authors found no significant difference between patients with dementia or depression in their wish to know their diagnosis. Patients with dementia, even if they felt upset, preferred to be told their diagnosis.

Benefits of a comprehensive screening strategy have also not been studied directly, but they may be extrapolated from existing studies. Potential benefits would accrue to the 3% to 12% of primary care patients age 65 and older who have undiagnosed dementia. Based on the

strong association between advancing age and the risk of dementia, a proposed screening strategy will have increased yield if it is begun at more advanced ages such as 75 years.

One unstudied potential benefit of dementia screening is the opportunity it affords for advance care planning. Individuals identified with early dementia by screening have the opportunity to discuss the nature of the syndrome, its prognosis, and future planning in regard to health care, safety, and financial planning. They may be able to formulate advance directives, choose a power of attorney for financial and personal care decision making, consent to participate in research, and contemplate issues such as motor vehicle driving, self-neglect, financial victimization, and housing relocation. Some may argue that earlier diagnosis of dementia syndrome, regardless of the cause, allows the patient, family, and physicians to plan more effectively for future events. It may also permit earlier and more effective administration of medication for other coexisting conditions by improving medication adherence and avoiding drug interactions. We found no study that verified or quantified these potential benefits.

Early detection of Alzheimer's disease can offer patients a chance to begin therapy with drugs such as cholinesterase inhibitors, vitamin E, or selegiline. Doing so may delay their functional decline and maintain their independence in performing both basic and instrumental ADLs for approximately 5 to 7 months. It may also lighten the burden on their caregivers and ultimately reduce total health care expenditure by delaying the time to nursing home admission and other costly outcomes.

Treatment of potentially reversible dementia is often proposed as a justification for screening, but we found few of these patients whose dementia was actually reversible with therapy. Thus, screening must benefit the large majority of patients with irreversible causes to demonstrate public health benefit. Patients with Alzheimer's disease account for 60% of cases of

dementia, and both pharmacologic and nonpharmacologic interventions show some clinical benefits in this disease. The efficacy of treatments for other causes of dementia is unproven.

Future Research Needs

Our review highlights important limitations of the current research on screening and treatment of dementia. No study of the overall effectiveness or benefit of screening in primary care has been done. Given the high prevalence of undiagnosed dementia among primary care patients over age 65 and evidence of the efficacy of cholinesterase inhibitor treatment for mild to moderate Alzheimer's disease, a trial of screening would be very helpful. Such a trial should also monitor costs and harms. We are aware of one 4-year RCT at Indiana University that will evaluate the efficacy of an integrated program of screening, diagnosis, and management compared to usual care in a primary care setting (personal communication, Christopher C Callahan, MD; Associate Professor, Indiana University School of Medicine; Director IU Center for Aging, December 19, 2001).

The MMSE is the best studied screening test for dementia, but it has been criticized for limited specificity and the need to adjust scoring based on age and educational attainment. The Clock-Drawing Test is very easy to administer and has good screening test characteristics in enriched referral populations. Future research should examine other promising brief screening tools that may be less education dependent and test their positive and negative predictive value in primary care screening strategies.

Although caregiver burden, health care utilization, and complications in managing comorbid conditions are common in dementia, little work to date has dealt with these important

aspects of the dementia syndrome. Future intervention trials, therefore, should examine outcomes not just for dementia syndrome patients but also for their caregivers.

Future treatment studies should consider expanding the usual outcome measures to include clinically important domains. In addition to standard measures of cognitive function and clinical global impression of change, we recommend inclusion of outcome measures for functional status and behavioral symptoms in all major clinical trials of dementia treatment. In addition, outcomes should be reported in temporal measures such as time to decline or survival analyses, to provide data on stabilization of disease course.

Despite the emergence of cerebrovascular disease as both a direct and an indirect cause for dementia syndrome, the literature offers very limited information about the potential benefit of modifying or treating cerebrovascular disease or atherosclerosis on dementia.[47] One RCT found that therapy (nitrendipine with the possible addition of enalapril, hydrochlorothiazide, or a combination) for isolated systolic hypertension among elderly reduced the incidence of dementia from 7.7 to 3.8 cases per 1,000 person-years.[184] Conversely, another trial did not detect any reduction in dementia incidence with the treatment of hypertension by low-dose diuretic, beta-blocker or both.[185] Another one found no effect of antihypertensive treatment on the cognitive function of older people with isolated systolic hypertension.[186] In addition to the previous primary prevention trials, our systematic review found 1 review that assessed the efficacy of aspirin in vascular dementia.[117] A new RCT of aspirin with and without antihypertensive therapy for early vascular dementia is needed to improve the evidence base for treatment of this common disease.

Much of the current clinical approach to dementia is symptomatic treatment for psychological and behavioral problems related to dementia syndrome, yet study of these

treatments is quite limited. Behavioral problems occur at all stages of dementia and they are the main reason for caregiver stress and institutional placement. Some RCTs have attempted to assess the effect of drug therapy on noncognitive symptoms, but they tended to use instruments that lacked the ability to detect clinically meaningful changes.[140] Future research is needed to fill gaps in the data about the psychometric properties of such instruments, so that they can be applied with greater confidence in trials or effectiveness studies. Future RCTs of interventions to change behavioral symptoms should also include measures of cognition, functional status, and clinical global impression of change, to clarify the mechanism of behavioral change and possible adverse effects.

No RCT has yet evaluated the efficacy of nonpharmacologic interventions on behavioral symptoms in patients with mild to moderate dementia who were living at home. This may be another important direction for research. Depression occurs in about one-third of patients with mild or early dementia, but we found only 2 small RCTs that evaluated the efficacy of antidepressant therapy in this population.[4,111] Future research in dementia therapy should target these symptoms in mild to moderate stages. Such studies should expand outcome measures to include behavioral as well as cognitive and functional measures, and they should incorporate injury prevention, health care utilization, and effect on the clinical management of other comorbid conditions.

Mild cognitive impairment (MCI) has been considered a significant risk factor for the development of Alzheimer's disease because of its high annual conversion rate (close to 16%). Therefore, trials to evaluate the efficacy of the current treatment strategies for Alzheimer's disease, such as cholinesterase inhibitors, gingko biloba, vitamin E, aspirin, and hypertension control, in MCI are warranted.

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APPENDIX A.
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ACKNOWLEDGMENTS

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APPENDIX B
EVIDENCE TABLES

Glossary of Tests and Terms

3MS	Modified Mini-Mental Status Exam
ABID	Antibody Identification
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive
ADAS-Noncog	Alzheimer's Disease Assessment Scale-Noncognitive
ADCS/ADL	Alzheimer's Disease Cooperative Study/Activities of Daily Living
ADFAC	Alzheimer's Disease Functional and Assessment of Change Scale
ADKT	Alzheimer's Disease Knowledge Test
ADL(s)	Activities of Daily Living
AE	Adverse Events
AMT	Abbreviated Mental Test
AR	Attrition Rate
BDI	Beck Depression Inventory
BDRS	Blessed Dementia Rating Scale
BDS	Blessed Dementia Scale
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BFAS	Blessed Functional Activities Scale
BI	Burden Interview
BIMC	Blessed Information Memory Concentration
BMT	Behavior Management Techniques
BOMC	Blessed Orientation Memory Concentration Test
BPRD	Behavioral Problem-Related Dementia

BPRS	Behavioral Psychiatry Rating Scale
BRSD	Behavioral Rating Scale for Dementia
BSI	Brief Symptoms Inventory
BSRS	Behavioral Psychiatry Rating Scale
BSRS-P	Behavioral Psychiatry Rating Scale – Psychosis
BSSD-A	Behavioral Syndromes Scale for Dementia - Agitation
CAMDEX	Cambridge Examination for Mental Disorders of the Elderly
CAPE	Clifton Assessment Procedures for the Elderly
CCAT-SS	Cognitive Concentration Assessment Tool - Speed Second
CCSE	Cognitive Capacity Screening Examination
CDDS	Cornell Depression in Dementia Scale
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CDT	Clock-Drawing Test
CES-D	Center of Epidemiology Studies of Depression
CG	Centigrams
CGE	Clinical Global Evaluation
CGIC	Clinical Global Impression of Change
CI	Confidence Interval
CIBIC-Plus	Clinician's Interview Based Impression of Change Plus Caregiver Input Scale
CIND	Center for Inherited Neurovascular Disease
CMAI	Cohen Mansfield Agitation Inventory

Cog Imp	Cognitive Impairment
CSI	Caregiver Stress Inventory
CSDD	Cornell Scale for Depression in Dementia
d	Day
D+	Diagnosed with Dementia
D-	Not Diagnosed with Dementia
D/O	Drop-out
DAD	Disability Assessment for Dementia
DART	Dutch Version of the National Adult Reading Test
DDD	Daily Dose Dependent
DMAS	Dementia Mood Assessment Scale
DS	Dependency Scale
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-IIIR	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSST	Digit Symbol Substitution Test
DT	Dementia type
EGB	Gingko Biloba Special Extract
EPS	Extrapyramidal Signs
F	Fluoxetine
F/U	Follow-up
FAQ	Functional Activities Questionnaire
FIM	Functional Independence Measure

FIQCODE	Functional Informant Questionnaire on Cognitive Decline in Elderly
FN	False Negative
FP	False Positive
FOM	Fuld-Object Memory
GB	Gingko Biloba
GBS	Gottfries-Brane-Steen Scale
GDS	Global Deterioration Scale
GERRI	Geriatric Evaluation Relative Rating Instrument
GHQ	General Health Questionnaire
GIC	Global Impression of Change
H	Haloperidol
Ham-D	Hamilton Depression
HCUP	Healthcare Cost and Utilization Project
HD	High Dose
HDS	Hierarchical Dementia Scale
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Disease-10th Revision
IDDD	Interview for Deterioration in Daily Living in Dementia
ITT	Intention-to-Treat
LBD	Lewy body dementia
LD	Low Dose
MD	Moderate Dose

mHARS	Modified Hamilton Anxiety Rating Scale
MMSE	Mini-Mental State Examination
MOSES	Multi Observational Scale for Elderly Subjects
MOUSEPAD	Manchester and Oxford Universities Scales for the Psychopathological Assessment of Dementia
MSBS	Minimal Social Behavioral Scale
MSQ	Mental Status Questionnaire
N	Number
NA	Not applicable
NAI	Nuremberg Age Inventory
NNH	Number Needed to Harm
NPI	Neuropsychiatric Inventory
NR	Not Reported
NS	Not Significant
OR	Odds Ratio
P	Probability
PDRS	Progressive Deterioration Rating Scale
PDS	Progressive Deterioration Scale
PGCMS	Philadelphia Geriatric Center Morale Scale
PSMS	Physical Self Maintenance Scale
PSQI	Pittsburg Sleep Quality Index
PT	Physical Therapy
QOL	Quality of Life

RCT	Randomized Controlled Trials
RDS	Rapid Disability Scale
RMBPC	Revised Memory Behavior Problem Checklist
RMBPC(F)	Revised Memory Behavior Problem Checklist - Frequency
ROC	Receiver-Operator Curve
RUD	Resource Utilization in Dementia Questionnaire
SADS	Schedule for Affective Disorders and Schizophrenia
SCB	Screen of Caregiver Burden
SCB-O	Screen of Caregiver Burden – Objective
SCB-S	Screen of Caregiver Burden – Subjective
SD	Standard Dose
SER	Systematic Evidence Review
SKT	Syndrome Kurtz Test
SMAF	Functional Autonomy Measures
SMD	Standard Mean Difference
STMS	Short Test of Mental Status
TRAZ	Trazadone
WF	Word Fluency
WK	Week
WMD	Weight Mean Difference
ZVT-G	Zahlen-Verbindungs-Test-G

Evidence Table 1. Prevalence of Undiagnosed Dementia

Citation	Design	Population	Measures	Results	Quality and Comments
Eefsting et al., 1996[66]	Community survey and general practitioner study of dementia prevalence	Rural area of Holland in 1991, all patients ≥ 65 years of age registered for care with general practitioner. Community survey included all former patients institutionalized. (n = 2,108 for analysis)	Survey screen: Dutch MMSE Clinical evaluation: all MMSE <17; Sample >17 and <27; None >27 Survey and general practitioners: Dementia diagnosed with DSM-IIIR criteria based on CAMDEX, follow-up performed at 1 year to confirm diagnosis	General practitioners: Sensitivity/ Specificity for dementia: 39% (28/71), 99.3% (275/277) General practitioners: Sensitivity/ specificity including Cog Imp as case vs. gold standard dementia: 69% (50/71), 94% (260/277)	Fair Non-US population; did not evaluate for false negatives; also evaluated contact rate effects on sensitivity and specificity
Olafsdottir et al., 2000[12]	Cross-sectional prevalence	Random sample of patients >70 years of age in primary care center from community and institutional care in Sweden 1994-1996 (n=350)	DSM-IIIR criteria by neuropsychiatric evaluation and close informant interview for all Detected cases: cognitive disturbance noted on medical record	Undiagnosed dementia prevalence: 42/350 (12 %) Undiagnosed cases/total cases: 16/21 mild 22/26 moderate 4/10 severe	Good Additional 11 patients with questionable dementia, detection status not noted
Sternberg et al., 2000[13]	Cross-sectional prevalence	Community dwelling patients ≥ 65 years in Canada	Screening: modified MMSE Gold standard: DSM-IIIR Physician recognition: questionnaire for caregiver regarding being seen by a physician or having memory problems	1.8% of patients have undetected dementia (161/9,008 pts)	Fair Undetected cases, not diagnosed based on questionnaire to caregiver

Evidence Table 1. Prevalence of Undiagnosed Dementia (continued)

Citation	Design	Population	Measures	Results	Quality and Comments
Valcour et al., 2000[14]	Cross-sectional prevalence	Patients ≥ 65 years of age in general internal medicine clinic in Asian American community in Honolulu, HI, Aug-Sept 1998 (n=297)	Screening: CASI Reference: Cummings' criteria Physician recognition: questionnaire regarding diagnoses of dementia for each patient seen, chart review	5.7% of patients with undiagnosed dementia (17/297 patients) 66.7% of cases unrecognized at time of visit; 65.4% of cases undocumented	Fair Questionable screening method; reference standard without masking; no evaluation for false negatives; limited further evaluation of dementia (32.6% of patients)

Evidence Table 2a. Effectiveness of Screening Tools: Systematic Review

Reference	Outcome of interest	Search Strategy	Inclusion/Exclusion Criteria	Quality Appraisal	Findings
Costa et al., 1996[75]	Meta-analysis of empirical studies of assessment of mental status instruments for differentiating between persons with and without dementia	No search terms given	Included: Human studies, Adult/elderly subjects, English Assessment of memory complaints, Screening studies, Editorials or commentaries, Meta-analyses Evaluations of instrument effectiveness or discriminability Excluded: Animal studies, children, non-English, etiology or pathology, biological markers, individual case studies, biochemistry, drug models, clinical trials, drug therapy, dexamethasone suppression, toxic encephalopathy, AIDS, syphilis, neurosyphilis, multiple sclerosis, lumbar punctures, cerebrospinal fluid analysis, treatment, management, detection by neuroimaging, pathophysiology, physiological changes, and normal aging changes	Five-phase evaluation scale: I- Narrow spectrum of disease II-Narrow – typical cases vs. healthy controls III-Expanded spectrum of cases vs. healthy controls IV-Inclusion of appropriate comorbidity for cases and controls V-Full spectrum of diseased and non-diseased individuals	Instrument with >1 Phase IV studies-Mean Effect Score (studies evaluated) [z-value compared to MMSE] MMSE-1.78 (12) BIMC-2.49 (2) [z=1.36, NS] BOMC-1.63 (2) [z=0.60, NS] STMS-2.01 (2) [z=0.39, NS] FAQ-2.46 (2) [z=2.81, *P* <0.05] Conclusions/ Recommendations -MMSE, BIMC, BOMC, and STMS largely equivalent -FAQ is particularly useful for initial assessment of functional impairment

Evidence Table 2b. Effectiveness of Screening Tools: Individual Studies

Source	Country	Setting	Study Design	Number of Subjects	Subject Demographics
Braekhus et al., 1995[79]	Norway	Community-based random sample of subjects age 75 and older	3-year and 6-year incidence study of dementia	Initial: n=285 3-year: n=215 6-year: n=129	81% Female Education (years): 0-7: 54% 8+: 46%
Law and Wolfson, 1995[84]	Canada	Community-based from prevalence study	Cross-sectional prevalence	237	64.5% female Mean age (range): 81 (67-97) Informants: 74% female Mean age (range): 57 (27-86) 57.3% children 20.2% spouse 6.3% sibling
Wilder et al., 1995[80]	United States (New York City)	Community-based pilot study for reporting registry	Extended prevalence study	Pilot study: 162	Latino: 45% African-American: 38% Non-Latino white: 17% Age: 65-74: 31% 75-84: 39% 85+: 30% Education (years): <5: 32.6% 5-11: 46.3% 12+: 21.1%

Evidence Table 2b. Effectiveness of Screening Tools: Individual Studies (continued)

Gold Standard	Screening Test(s)	Cutoff Value(s)	TP D+	TN D-	FP	FN	Quality and Comments
DSM-III-R	MMSE	3-year: 30	1	41			Fair
		29	1	54			
		28	3	33			Exclusion of all initial dementia (DSM-III)
		27	3	26			
		26	4	22			
		25	8	11			
		24	3	5			
		6-year: 30	6	27			
		29	10	27			
		28	4	19			
		27	3	15			
		26	2	7			
		25	2	3			
		24	2	2			
DSM-III-R	FIQCODE	3.6	37	180	8	12	Good
	MMSE (French)	23	35	155	33	14	In systematic review by Jorm et al.
DSM-III-R	MMSE	≤24	34	240	10	3	Fair Trained medical student interviewers; diagnosis independent of scores but from initial interview; no discussion of mild dementia or indeterminate results; high dropout rate

*TP D+, true positive, diagnosis of dementia.
† TP D-, true negative, no diagnosis of dementia.

Evidence Table 2b. Effectiveness of Screening Tools: Individual Studies (continued)

Source	Country	Setting	Study Design	Number of Subjects	Subject Demographics
Jitapunkul et al., 1996[78]	Thailand	Survey of "old-person home" for self-caring patients	Cross-sectional prevalence	212	87% female 24% illiterate Resident of home: mean 8.4 years, Standard deviation 6.6
Lindeboom et al., 1996[77]	Holland	Community-based sample; full evaluation for all screening positives and sample of others, confirmed with 1 year follow-up	Cross-sectional prevalence	337	Nondemented: 56% female Education level: < Primary: 58% < Secondary: 40% > University: 1% Mean age: 73.7 Demented: 78% female Education level < Primary: 75% < Secondary: 25% > University:0% Mean age: 79.5
McDowell et al., 1997[76]	Canada (English and French speaking)	Multi-center community based sample	Cross-sectional prevalence	1,600	59% female Mean age (range): 80 (65-99) Mean years of education (range): 8.6 (0-28)

Evidence Table 2b. Effectiveness of Screening Tools: Individual Studies (continued)

Gold Standard	Screening Test(s)	Cutoff Value(s)	TP D+*	TN D-†	FP	FN	Quality and Comments
DSM-III-R	CMT	15	17	176	19	0	Good
	MMSE	16 (18)	13	180	15	4	
	AMT	5 (6) (literate, illiterate)	13	180	15	4	Data difficult to calculate c estimated sensitivity/ specificity rates from references, ROC curve, and prevalence
NINCDS-ADRDA	7 Minute Screen (Temporal Orientation Test, Cued Recall, Clock Drawing Test, and Verbal Fluency Test)	Probability of dementia > 0.7 (based on logistic regression predictive model)	11	124	2	0	Good Actual results: Positive screens: 10 probable Alzheimer's disease Mixed dementia: 1 Refused follow-up: 2 Negative screen: Sample: 25 Normal: 1 (CIND)
DSM-III-R and ICD-10 Revised	MMSE	25/26	316	949	283	52	Good
	3MS	77/78	316	1,072	160	52	Also analyzed multiple cutpoints; some analysis of English vs. French; indeterminate results with CIND

Evidence Table 2b. Effectiveness of Screening Tools: Individual Studies (continued)

Source	Country	Setting	Study Design	Number of Subjects	Subject Demographics
Heun et al., 1998[81]	Germany	Stratified community-based sample including institution-alized Individuals	Cross-sectional prevalence	291	Nondemented: Female: 55% Mean age: 75 Education: 9.6 years Demented: Mean age: 89 92% female Education: 9.0 years
Barberger-Gateau et al., 1999[83]	France	Community survey of 37 parishes	3-year and 5-year incidence study of dementia	Initial: n=2,780 3 year: n=1,582 5 year: n=1,283	Not discussed Dartigues et al.[187] report for same population: 59.8% female Mean age: 74.8 yrs Education: No schooling: 4% Grade school: 61% High School: 29% University: 6%
Solomon et al., 2000[82]	United States	Primary care practice	Cross-sectional prevalence	137	Female: 67% Mean age (range): 77 years (61-88) Education: Mean (range): 11.8 yrs (6-23)

Evidence Table 2b. Effectiveness of Screening Tools: Individual Studies (continued)

Gold Standard	Screening Test(s)	Cutoff Value(s)	TP D+	TN D-	FP	FN	Quality and Comments
DSM-III-R	Dutch	22/23	24	271	30	12	Fair
	MMSE (adjusted for DART and unadjusted)		26	280	21	10	No discussion of reliability; independent evaluation masked
		24/25	30	241	60	6	
			31	244	57	5	
		26/27 (Unadjusted	36	123	178	0	
		Adjusted)	36	147	154	0	
DSM-III by psychologist, confirmed by neurologist	IADL	3 yr: 0	19	1,195			Fair
		1	19	209			
		2	12	72			Exclusion of all prevalent and 1-year incident cases
		3	8	23			
		4	5	20			
		5 yr: 0	17	1,015			
		1	10	155			
		2	4	52			
		3	1	16			
		4	1	12			
DSM-III-R	MMSE	≤24	34	240	10	3	Fair Trained medical student interviewers; diagnosis independent of scores but from initial interview; no discussion of mild dementia or indeterminate results; high dropout rate

*TP D+, true positive, diagnosis of dementia.
† TP D-, true negative, no diagnosis of dementia.

Evidence Table 3. Longitudinal Studies of the Treatment of Potentially Reversible Dementia

Study	N	Follow-up	Settings	Percentage/ Number Potentially Reversible	Percentage/ Number Partially Reversible	Percentage/ Number Fully Reversible	Comment
Larson et al., 1984[92]	100	6 months	Geriatric clinic	15% 15	11% 11	3% 3	Fair Lost to follow-up: 28%
Larson et al., 1985[74]	182	1 year	Geriatric clinic	14.3% 26	11.5% 21	1% 2	Good Lost to follow-up: 0% Living in institutional setting: 7.5%
Cunha et al., 1990[57]	110	2 year	Geriatric clinic	23.6% 26	2.7% 3	1.8% 2	Fair Lost to follow-up: 40% (10/26 with potentially reversible lost to follow-up)
Ames et al., 1992[58]	79	6 months	Geriatric clinic	5.1% 4	0% 0	0% 0	Fair Lost to follow-up: 2%
Massoud et al., 2000[59]	56	N/R	Tertiary care center	12.5% 7	N/R	0% 0	Fair Lost to follow-up: 8.2%
Walstra et al., 1997[60]	170	6 months	Memory clinic	18% 31	0.6% 1	0% 0	Good Lost to follow-up: 6.5%
Freter et al., 1998[61]	196	16 months	Memory clinic	23% 45	2% 4	1.5% 3	Fair Lost to follow-up: 22.5% (4/7 patients with partially or fully reversible dementia had suspected dementia at baseline)

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Evidence Table 4a. Efficacy of Cholinesterase Inhibitors in Treatment of Alzheimer's Disease – Systematic Reviews

Author	N RCT Patients	Intervention			Outcomes
		Drug	Dose	Period (in months)	
Birks et al., 2000[115]	7 RCTs 3,370 pts	Rivastigmine	Low: 1-4 mg/day High: 6-12 mg/day	13-16 weeks	Global (CIBIC-plus, GDS) Cognitive (ADAS-Cog, MMSE) Physical function (PDS)
Birks et al., 2000[119]	4 RCTs 1,102 pts	Donepezil	Low: 5 mg/day High: 10 mg/day	12-24 weeks	Global Cognitive Physical function Quality of life
Qizilbash et al., 1998[121]	12 RCTs 1,984 pts	Tacrine	39-135 mg/day	12 weeks	Global Cognitive Physical function Behavioral
Qizilbash et al., 2000120	5 RCTs 1,434 pts	Tacrine	40-120 mg/day	2-6 weeks 1-30 weeks 1-12 weeks 1-4 weeks	Global Cognitive Behavioral

Evidence Table 4a. Efficacy of Cholinesterase Inhibitors in Treatment of Alzheimer's Disease – Systematic Reviews (continued)

	Result		
Scale	Treatment (Dose)	P value	Quality and comments
CIBIC-plus (OR)	Low: 1.4 High: 1.2	(95% CI, 1.1 to 1.9) NS (95% CI, 0.9 to 1.6) NS	Good
GDS (WMD)	Low: -0.1 High: -0.1	(95% CI, -0.2 to -0.0) (95% CI, -0.2 to -0.1)	Information on 1,403 patients not fully available for meta-analysis; authors conclude that high dose rivastigmine had a modest benefit on cognition & ADLs but not on clinical global impression
ADAS-Co (WMD)	Low: -0.9 High: -2.4	(95% CI, -1.6 to -0.2) NS (95% CI, -3.1 to -1.7)	
MMSE (WMD)	Low: -0.3 High: -0.5	(95% CI, -0.8 to +0.2) NS (95% CI, -1.0 to -0.1)	
PDS (WMD)	Low: +0.4 High: -2.4	(95% CI, -0.9 to +1.8) (95% CI, -3.6 to -1.1)	
CIBIC-plus (OR)	Low: 2.33 High: 2.63	(95% CI, 3.45 to 1.61) (95% CI, 3.85 to 1.79)	Good
ADAS-Cog (WMD)	Low: -2.61 High: -3.01	(95% CI, -3.45 to -1.78) (95% CI, -3.92 to -2.09)	Authors conclude that donepezil produced modest improvements on cognition & clinical global impression with no improve-ment in pt self-rated quality of life
CDR-SB (WMD)	Low: -0.21 High: -0.34	(95% CI, -0.46 to +0.03) NS (95% CI, -0.59 to -0.1)	
QOL (WMD)	Low: 7.1 High: 0.04	(95% CI, -4.5 to +18.7) (95% CI, -17.0 to +17.1)	
CGIC (OR improvement)	1.58	(95% CI, 1.18, 2.11)	Good
ADAS-Cog (Mean Difference)	2.07	(95% CI, 1.36, 2.78)	
MMSE (MD)	0.62	(95% CI, 0.23, 1.00) *P* =.002	
PDS (MD) at 6 wks	0.75	(95% CI, -0.43, +1.93) NS	
ADAS-Noncog (MD)	0.58	(95% CI, 0.17, 1.00) *P* =.006	
CGIC (OR improvement or no change)	1.15 -0.22	(95% CI, 1.64, 0.81) NS (95% CI, -0.32, -0.12)	Good (these 5 trials were included in the previous SER)
ADAS-Cog (Mean Difference)	0.14	(95% CI, -0.02, +0.3) NS	Authors conclude that there is no evidence of clinical effectiveness of tacrine in treating Alzheimer's disease
MMSE (MD)	-0.1	(95% CI, -1.23, +1.024) NS	
ADAS-Noncog (MD)			

Evidence Table 4b. Efficacy of Cholinesterase Inhibitors in Treatment of Alzheimer's Disease -- Studies

Author	N	Intervention			Outcomes
		Drug	Dose	Period (in months)	
Winblad et al., 2001[93]	286	Donepezil	10 mg/day	12	Global Cognitive Physical function Behavior Caregiver time spent assisting patient Health care utilization
Mohs et al., 2001[95]	431	Donepezil	10 mg/day	12	Time to functional decline Cognitive Physical function
Wilkinson and Murray, 2001[112]	285	Galantamine	Low: 18 mg/day Mod: 24 mg/day High: 36 mg/day	3	Cognitive (ADAS-Cog) Global (CGIC) Functional (PDS)
Wilcock et al., 2000[96]	653	Galantamine	Low: 24 mg/day High: 32 mg/day	6	Global Cognitive Physical function
Raskind et al., 2000[97]	636	Galantamine	Low: 24 mg/day High: 32 mg/day	6	Global Cognitive Physical function

Evidence Table 4b. Efficacy of Cholinesterase Inhibitors in Treatment of Alzheimer's Disease -- Studies (continued)

Scale	Result: Treatment	Result: Placebo	Result: P value	Result: NNT	Quality and comments
GBS (mean change)	+8	+12	*P* = 0.054		Good (all outcomes were considered) Dementia type: Alzheimer's disease
MMSE(mean change)	-0.3	-2.2	*P* <0.001		
PDS (mean change)	11.5	15	*P* = 0.011		
NPI (mean change)	-	-	NS		
Percent of caregivers spending ≥ 16hr /day caring for patient					
at 6 months	0%	3%	*P* <0.05		
at 9 months	0%	5%	*P* <0.05		
at 12 months	2%	6%	*P* <0.1		
RUD (mean annual cost per patient in US dollars)	$25,000	$26,100	N/A		
RUD (days spent in hospital)	8	16	N/A		
RUD (caregiver contact with health care professional)	613	811	N/A		
Median time to functional decline (D)	357	208	*P* = 0.0051		Fair (not all outcomes were considered) Dementia type: Alzheimer's disease
MMSE (mean change)	+0.5	-0.5	*P* <0.001		
ADFAC (mean change)	+2.4	+4.0	*P* <0.001		
ADAS-Cog (mean change)	Low: -0.1 Mod: -1.4 High: - 0.7	1.6	NS *P* <0.001 *P* = 0.08		Fair (not all outcomes considered) Attrition rate varies among groups
CGIC (% improved or no change)	Low: 83% Mod: 80% High: 80%	70%	NS NS *P* = <0.05		
PDS (% improved or no change)	Low: 82% Mod: 89% High: 78%	75%	NS NS NS		
CIBIC-plus (percent stable or improve)	Low: 62% High: 66%	50%	*P* <0.05 *P* <0.001	8 6	Fair (not all outcomes were considered) Dementia type: Alzheimer's disease
ADAS-Cog (mean change)	Low: -0.5 High: -0.8	+2.4	*P* <0.001 *P* <0.001		
DAD (difference in mean change treatment vs. placebo)	Low: 2.8 High: 3.4	N/A N/A	NS *P* <0.05		
CIBIC-plus (percent stable or improve)	Low: 70% High: 68%	55%	*P* <0.05 *P* <0.05	7 8	Fair (not all outcomes were considered & some difference in F/U among groups) Dementia type: Alzheimer's disease
ADAS-Cog (mean change)	Low: -2.2 High: -1.4	+2.0	*P* <0.001 *P* <0.001		
DAD (difference in mean change treatment vs. placebo)	N/A	N/A	NS		

Evidence Table 4b. Efficacy of Cholinesterase Inhibitors in Treatment of Alzheimer's Disease -- Studies (continued)

Author	N	Intervention			Outcomes
		Drug	Dose	Period (in months)	
Tariot et al., 2000[98]	4	Galantamine	Low: 8 mg/day Mod: 16 mg/day High: 24 mg/day	5	Global Cognitive Physical function Behavior
Burns et al., 1999[99]	818	Donepezil	Low: 5 mg/day High: 10 mg/day	6	Global Cognitive Physical function (CDR-SB and IDDD) Quality of life
Greenberg et al., 2000[100]	60	Donepezil	5 mg/day	3	Global Cognition
Rosler et al., 1999[101]	725	Rivastigmine	Low: 1-4 mg/day High: 6-12 mg/day	6.5	Global Cognitive Physical function (PDS;GDS)

Evidence Table 4b. Efficacy of Cholinesterase Inhibitors in Treatment of Alzheimer's Disease -- Studies (continued)

Result					
Scale	Treatment	Placebo	P value	NNT	Quality and comments
CIBIC-plus (percent stable or improved)	Low: 53% Mod: 66% High: 64%	49%	NS *P* <0.001 *P* <0.001	6	Fair (not all outcomes were considered) Dementia type: Alzheimer's disease
ADAS-Cog (mean change)	Low: +0.4 Mod: -1.4 High: -1.4	+1.7	NS *P* <0.001 *P* <0.001	7	
ADCS/ADL (mean change)	Low: -3.2 Mod: -0.7 High: -1.5	-3.8	NS *P* <0.001 *P* <0.01		
NPI (mean change)	Low: +2.3 Mod: -0.1 High: 0	+2.0	NS *P* <0.05 *P* <0.05		
CIBIC-plus| (percent improved)	Low: 21% High: 25%	14%	N/A N/A	14	Fair (not all outcomes were considered) Dementia type: Alzheimer's disease
ADAS-Cog (mean change)	Low: +0.1 High: -1.3	+1.6	*P* = 0.002 *P* <0.0001	9	
CDR-SB (difference)	Low: 0.3 High: 0.4		*P* = 0.002 *P* = 0.0387		
IDDD (mean)	Low: 70.5 High: 69.5	71	NS *P* = 0.007		
Caregiver GIC (percent improved) ADAS-Cog (mean change)	24% -1.50	23% +0.62	NS *P* <0.05		Fair: crossover design (analysis done only on the completion of both phases.) Dementia type: Alzheimer's disease
CIBIC-plus (percent improved)	Low: 32% High: 40%	22%	*P* <0.01 *P* <0.001	10	Fair (not all outcomes were considered) Dementia type: Alzheimer's disease
ADAS-Cog (mean change)	Low: -1.24 High: +0.83	-1.45	NS *P* <0.001	6	
PDS (percent of patients with ≥ 10% improvement)	Low: 20% High: 33%	20%	NS *P* <0.01		
GDS (mean change)	Low: -0.2 High: -.03	-0.24	NS *P* <0.05		

Evidence Table 5. Studies of the Efficacy of Gingko Biloba in Treatment of Alzheimer's Disease

Author	N RCTs Patients	Intervention			Outcomes
		Drug	Dose	Period	
Oken et al, 1998[118] (Systematic review)	5 RCTs 424 pts	EGB-761	120-240 mg/day	2-12 weeks 2-24 weeks 1-26 weeks	Cognitive
Le Bars et al., 1997[106]	309 pts	EGB-761	120 mg/day	6.5 months 13 months	Global Cognitive Physical function

Evidence Table 5. Studies of the Efficacy of Gingko Biloba in Treatment of Alzheimer's Disease (continued)

	Result			
Scale	**Trx**	**Placebo**	**P value/ NNT**	**Quality & Comments**
Cognitive function over all effect size	0.413		(95% CI, 0.22, 0.61)	Good
Translate on ADAS-Cog	2.1		(95% CI, 1.12, 3.01)	Authors conclude that there is a small but significant effect of 3-6 months treatment with 120-240 mg of EGB-761 on objective measures of cognitive in Alzheimer's disease
CGIC over all ITT (mean)	4.2	4.2	*P* = 0.77	Fair (not all outcomes were considered)
ADAS-Cog over all ITT (mean change)	+0.1	+1.5	*P* = 0.04	AR at 6.5 months = 25%
ADAS-Cog 6.5 months (mean change)	-0.5	+2.1	*P* = 0.04	AR at 13 months = 58%
ADAS-Cog 13 months (mean change)	-0.3	+1.5	*P* = 0.005	GERRI is not an established instrument.
GERRI over all ITT (mean change)	-0.06	+0.08	*P* = 0.004	Dementia type: Alzheimer's disease
GERRI 6.5 months (mean change)	-0.07	+0.07	*P* = 0.04	
GERRI 13 months (mean change)	-0.09	+0.10	*P* = 0.002	

Evidence Table 6. Efficacy of Anti-Oxidants and Estrogen in Treatment of Alzheimer's Disease

Author	N	Intervention			Outcomes
		Drug	Dose	Period	
Birks and Flicker, 2000[116] (Cochrane review)	15	Selegiline	10 mg/day	10 days to 3 years	Global Cognitive Behavioral
Sano et al., 1997103	341	Selegiline Vitamin E Both drugs	10 mg/day 2000 IU/day Both doses	2 years	Time to functional loss Cognitive (ADAS-Cog, MMSE) Functional (BDS, DS) Behavior (BRSD)

Evidence Table 6. Efficacy of Anti-Oxidants and Estrogen in Treatment of Alzheimer's Disease (continued)

Results				Quality and Comments
Scale	**Treatment**		**P value**	
Combined global tests (SMD)	-0.11 -0.38		(95% CI, -0.49, +0.27) NS (95% CI, -0.60, -0.15)	Good Authors conclude that there is some evidence that selegeline improve the mental function of Alzheimer's disease patients & their behavior and mood, with no effect on clinical global impression
Combined cognitive tests (SMD)	-2.4		(95% CI, -4.11, -0.68)	
BPRS (WMD) 2 RCTs	-9.6		(95% CI, -16.6, -2.6)	
DMAS (WMD)	-0.62		(95% CI, -2.28, +1.04) NS	
Cornell Depression scale (WMD)				
Median time to functional loss (D)	Sel: 655 d Vit. E: 670 d Vit. B: 585 d	440 d 440 d 440 d	*P* = 0.012 *P* = 0.001 *P* = 0.049	Fair (not all outcome were considered and randomization did not work but the analysis was adjusted for covariate)
ADAS-Cog (mean change)	Sel: 8.3 Vit. E: 8.3 Vit. B: 6.5	6.7	NS	
MMSE	----	----	NS	
BDS (mean change)	Sel: 4.2 Vit. E: 4.0 Vit. B: 4.2	5.4	*P* = 0.004	
DS (% pt receiving high score)	Sel: 80% Vit. E: 76% Vit. B: 76%	86% 86% 86%	NS *P* = 0.039 *P* = 0.039	
BRSD (mean change)	Sel: +5.4 Vit. E: +4.4 Vit. B: -1.1	+8.9	*P* = 0.02	

Evidence Table 6. Efficacy of Anti-Oxidants and Estrogen in Treatment of Alzheimer's Disease (continued)

Author	N	Intervention			Outcomes
		Drug	Dose	Period	
Mulnard et al., 2000[105]	120	Estrogen	Low: 0.625 mg/day High: 1.25 mg/day	12 months	Global Cognitive (MMSE, ADAS-Cog) Physical function (CDR, BDRS, DS) Behavior (mood)
Asthana et al., 2001[114]	20	Estrogen patch	0.1 mg/day	8 weeks	Cognitive (global and neuropsychological testing) Functional (IADL, PSMS) Behavioral (BPRS)

Evidence Table 6. Efficacy of Anti-Oxidants and Estrogen in Treatment of Alzheimer's Disease (continued)

Results				Quality and Comments
Scale	**Treatment**	**Placebo**	**P value/ NNT**	
CGIC over all ITT (mean)	4.2	4.2	*P* =0.77	Fair (not all outcomes considered)
ADAS-Cog over all ITT (mean change)	+0.1	+1.5	*P* =0.04	AR at 6.5 months = 25%
ADAS-Cog 6.5 months (mean change)	-0.5	+2.1	*P* =0.04	AR at 13 months = 58%
ADAS-Cog 13 months (mean change)	-0.3	+1.5	*P* =0.005	GERRI is not an established instrument.
GERRI over all ITT (mean change)	-0.06	+0.08	*P* =0.004	Dementia type: Alzheimer's disease
GERRI 6.5 months (mean change)	-0.07	+0.07	*P* =0.04	
GERRI 13 months (mean change)	-0.09	+0.10	*P* =0.002	
Attention domain (seconds)	88	108	*P* = -.02	Fair (not all outcomes considered)
Word recall	8	7	*P* = 0.049	
Immediate recall	25	20	*P* = 0.03	
Paired association test	----	----	*P* = 0.08	
Naming	----	----	*P* = 0.05	
MMSE	----	----	NS	
IADL-PSMS	----	----	NS	

Evidence Table 7. Efficacy of Anti-Inflammatory Medications in Treatment of Alzheimer's Disease

Author	N	Intervention			Outcomes
		Drug	Dose	Period	
Aisen et al., 2000[108]	138	Prednisone	10 mg/day maintenance	12 months	Global (CDR-SB, BDRS) Cognitive Physical function (none) Behavior (Ham-D, BPRS)
Scharf et al., 1999[109]	41	Diclofenac plus Misoprostol	50 mg/day 200 mg/day	6 months	Global (CGIC, caregiver GIC, GDS) Cognitive (ADAS-Co, MMSE) Physical function (IADL, PSMS) Behavior

Evidence Table 7. Efficacy of Anti-Inflammatory Medications in Treatment of Alzheimer's Disease (continued)

Scale	Results			Quality and Comments
	Treatment	Placebo	P value/ NNT	
CDR-SB (mean change)	2.9	2.2	0.07	Fair (not all outcomes were considered)
BDRS (mean change)	1.7	1.7	0.60	
ADAS-Cog (mean change)	8.2	6.3	0.16	
Ham-D (mean change)	1.7	0.7	0.25	
BPRS (mean change)	5.4	2.0	0.003 (placebo favor)	Dementia type: Alzheimer's disease
CGIC (mean change)	4.29	4.57	NS	Fair (not all outcomes were considered)
Caregiver-CGI (mean change)	4.47	4.79	NS	
GDS (mean change)	+0.35	+0.57	NS	
ADAS-Co (mean change)	+0.25	+1.93	NS	
MMSE (mean change)	+0.41	-0.86	NS all $P > 0.125$	Significant difference in AR among groups
IADL (mean change)	0.06	1.86	NS	
PSMS (mean change)	0.53	0.21	NS	
ADAS-Noncog (mean change)	-0.59	+1.36	NS	

Evidence Table 8. Studies of the Treatment of Vascular Dementia

Author	N	Intervention			Outcomes
		Drug	Dose	Period	
Williams et al., 2000[117] (Systematic review)	70	Aspirin	325 mg/day	1 year	Cognitive
Pantoni et al., 2000[104]	251	Nimodipine	90 mg/day	6 months	Global Cognitive (ZVT-G|, FOM, WF, DS, MMSE) Physical function (ADL, IADL, RDS, GBS, CDR)

Evidence Table 8. Studies of the Treatment of Vascular Dementia (continued)

Results				Quality and Comments
Scale	**Treatment**	**Placebo**	**P value/ NNT**	
CCSE (WMD)	-4.1		(95% CI, -9.51 to +1.307)	Good Authors conclude that the evidence to support the use of aspirin in vascular dementia is weak
CGC	----	----	NS	Fair (not all outcomes were considered & unclear outcome measures) Dementia type: Vascular dementia
ZVT-G (time in second)	3.02	13.67	*P* = 0.09	
Multiple cognitive tests	----	----	NS (*P* range .14-.95)	
Multiple physical function tests	----	----	NS (*P* range .14-.95)	

Evidence Table 9a: Efficacy of Pharmacologic Interventions for Behavioral Problems Related to Dementia: Systematic Reviews

Author	RCT/N	Intervention		Period (in weeks)	Outcomes
		Drug	Dose		
Lanctot et al., 1998[122]	13 / 295	Typical neuroleptic	.05-1.2 DDD	At least 4	Behavioral improvement
Davidson et al., 2000[124]	3 / 911	Atypical neuroleptic Respiredone/ olanzepine	--	6 - 12	Behavioral (NPI/BEHAVE-AD)
Kirchner et al., 2000[125]	2 / 670	Thioridazine	--	4, 8, 32	Behavior (modified Hamilton Anxiety Rating Scale (mHARS)) Global (CGE clinical global evaluation impression of change)

Evidence Table 9a: Efficacy of Pharmacologic Interventions for Behavioral Problems Related to Dementia: Systematic Reviews (continued)

Scale	Result Trx	Placebo	P value	NNH	Quality and Comments
Percentage with clinically significant improvement in CGI	61%	38%	*P* = <.0001	4(3, 7)	Good Diagnosis of primary dementia in only 70% of RCTs; all patients had BPRD at baseline; patients not exclusively living at home nor had mild to moderate dementia
Treatment vs. placebo difference	26%				
Efficacy (clinically significant improvement)	OR: 0.59 (95% CI, 044 to 0.78)			8 (5, 18)	Good All patients had BPRD at baseline; mean MMSE <10 (7.3); clinical setting was NHs
mHARS (anxious mood/ tension/fear/insomnia)	OR: 4.9 (95% CI, 3.2 to 7.5)				Good
mHARS (intellect/agitation /depressed mood)	OR: 3.6 (95% CI, 2.4 to 5.5)				One RCT with 610 patients was conducted at NH; dementia severity not specified
CGE	----	----	NS		

Evidence Table 9b: Efficacy of Pharmacologic Intervention for Behavioral Problems Related to Dementia: Randomized Controlled Trials

Author	N	Intervention Drug	Intervention Dose	Period	Outcomes
Teri et al., 2000[113]	148	Haldol	0.5-3 mg/day	16 weeks	Behavioral (BRSD, RMBPC, CMAI, ABID, CGIC) Caregiver burden (SCB) Cognitive (MMSE) Functional (ADL)
		Trazedone	50-300 mg/day		
		BMT	8 weekly + 3 biweekly sessions		
		Placebo			

Evidence Table 9b: Efficacy of Pharmacologic Intervention for Behavioral Problems Related to Dementia: Randomized Controlled Trials (continued)

	Result			
Scale	**Treatment**	**Placebo**	**P value/ NNT**	**Quality and Comments**
CGIC (% improved)	Hal: 32% Traz: 41% BMT: 32%	31%	*P* > 0.5	Fair (not all outcomes considered)
ABID (mean change)	NS for all		NS	Attrition rate 38%
CMAI (mean change)	NS for all		NS	Significant difference between groups at baseline in caregiver gender; analysis adjusted for this
RMBPC (mean change)	NS for all		NS	
BRSD (mean change)	NS for all		NS	
MMSE (mean change)	Hal: -0.6 Traz: -1.97 BMT: -0.05	-0.28	*P* < 0.05	
Basic ADL (mean change)	Hal: 2.5 Traz: 1.6 BMT: -0.3	1.3	*P* <0.05	
Instrumental ADL (mean change)	Hal: 1.8 Traz: 1.8 BMT: 0.2	0.9	*P* < 0.05	
SCB-Subjective (mean change)	Hal: -1.9 Traz: -1.97 BMT: -2.95	-2.6	NS	

Evidence Table 9b: Efficacy of Pharmacologic Intervention for Behavioral Problems Related to Dementia: Randomized Controlled Trials (continued)

Author	N	Intervention Drug	Intervention Dose	Period	Outcomes
Devanand et al., 1998[94]	66	Haldol (standard dose) Haldol (low dose)	2-3 mg/day 0.5-.75 mg/day	6 weeks	Behavioral (BSRS-P, BSSD-A, SADS) Cognitive (MMSE) Functional (BFAS)
Auchus et al., 1997[110]	15	Haldol Fluoxetine	3 mg/day 20 mg/day	6 weeks	Behavior (CMAI, BEHAVE-AD) Caregiver burden (CSI)
Petracca et al., 1996[111]	21	Clomipramine	25-100 mg/day	2-6 weeks crossover design	Depression (Ham-D) Cognitive (MMSE) Functional (FIM)
Lyketsos et al., 2000[4]	22	Sertraline Placebo	25-150 mg/day	13 weeks	Depressive (CDDS, HDS, psychiatrist impression) Functional (ADL, PDRS) Cognitive (MMSE)

Evidence Table 9b: Efficacy of Pharmacologic Intervention for Behavioral Problems Related to Dementia: Randomized Controlled Trials (continued)

Scale	Result Treatment	Placebo	P value	NNT	Quality and Comments
BPRS-Psychosis (% clinically responsive patient)	SD: 60% Low: 30%	30%	*P* < 06	3	Fair (not all outcomes considered)
BSSD-agitation (% clinically responsive patient)	SD: 55% Low: 25%	30%	*P* = .11		
SADS (% clinically responsive patient)	SD: 55% Low: 35%	25%	*P* <.06	3	
MMSE	----	----	NS		
BFAS	----	----	NS		
CMAI mean change	H: -2.4 F: +1.4	-1.4	*P* =.82 NS		Fair (not all outcomes considered)
BEHAVE-AD	H: -2.6 F: +1.8	+1.0	*P* =.35 NS		
CSI	H: +14 F: -16.8	+18.6	*P* =.67 NS		
Ham-D (% pt entered remission at 6 weeks)	82% lower than placebo	30% higher	*P* =.02 *P* <.01 favors placebo NS	2	Possibly poor (questionable use of ITT)
MMSE mean score	--	--			
FIM					
Psychiatrist impression, % full or partial responders	75%	20%	*P* < 0.05		Fair (not all outcomes considered)
CDDS (mean change)	-10.7%	-2.1 %	*P* = 0.03		
HDS (mean change)	- 11.1%	- 3.5%	*P* = 0.2		
MMSE (mean change)	----	----	NS		
ADL /PDRS	----	----	NS		

Evidence Table 10: Efficacy of Nonpharmacologic Intervention for Behavioral Problems Related to Dementia: Systematic Reviews (continued)

Author	N RCT Patients	Intervention	Outcomes
Forbes 1998[151]	1 RCT + 2 randomized trials 132 pts	Music, skills training, visual barriers, exercise, light therapy, pet therapy, sensory integration, reality orientation, hand massage, therapeutic touch, life review, white noise	Social interaction; agitation; wandering; physical aggression; day/night disturbance; self-care; eating problems
Opie et al., 1999[155]	4 RCTs 215 pts	Sensory integration (1 RCT) Activities (1 RCT) Caregiver education (2 RCTs) Multidisciplinary team (1 RCT)	General agitation (4 RCTs) Physical aggression (1 RCT)

Evidence Table 10: Efficacy of Nonpharmacologic Intervention for Behavioral Problems Related to Dementia: Systematic Reviews (continued)

Results			Quality and Comments
None of the included studies met our inclusion criteria.			Good
1 strong trial (planned walking + conversation)	Improved communicative function	*P* = .007	All strong and moderate studies conducted in long term care facilities; we included only trial with moderate or strong validity and random allocation with control group
1 mod trial (attention focused group)	Improve activities participation	*P* <.001	
1 mod trial (functional skills training)	Improved self-care ability	*P* = .04	
Activities program plus caregiver education	Improve physical aggression	*P* = significant	Good
Activities program	No effect on general agitation	*P* = NS	Only 1 RCT used multi-disciplinary team met our inclusion criteria with no fatal methodology flaw
Multidisplinary team	Improved general agitation	*P* = significant	
Caregiver education	No effect on general agitation	*P* = NS	

Evidence Table 10: Efficacy of Nonpharmacologic Intervention for Behavioral Problems Related to Dementia: Systematic Reviews

Author	N RCT Patients	Intervention	Outcomes
Koger and Brotons, 2000[160]	0 RCTs	Music therapy	----
Neal and Briggs, 2000[161]	2 RCTs 102	Validation therapy 2-4 times wk for 36-52 wks	Cognitive (MSQ, PGCMS) Functional: MOSES Behavioral: CMAI, MOSES, MSBS
Spector et al., 2000[162]	2 RCTs 15	Reminiscence therapy 30 min 2-5 times weekly for 4-5 weeks	Cognitive CAPE, MMSE, Behavior CAPE BDI
Spector et al., 2000[163]	6 RCTs 125	Reality orientation 30-60 minutes 2-5 times weekly for 4-21 weeks	Cognitive multiple scales Behavior multiple scales

Evidence Table 10: Efficacy of Nonpharmacologic Intervention for Behavioral Problems Related to Dementia: Systematic Reviews (continued)

	Results		Quality and Comments
No RCT was found			Good
MSQ	WMD:-1.8 (99% CI, -9.7 to +6.1)	NS	Good
PGCMS	WMD: 1.1 (95% CI, -7.5 to +5.3)	NS	Both studies conducted in long term care facility; dementia was moderate to severe in 1 RCT and at least moderate in the second
Self-care MOSES	WMD: -1.1 (99% CI, -4.9 to +2.7)	NS	
Verbal agitation CMAI	WMD: 3.9 (99% CI, -4.1 to +11.9)	NS	
Withdrawal MOSES	WMD: 1.6 (99% CI, -6.0 to +2.8)	NS	
Confusion MOSES	WMD: 3.0 (99% CI, -2.8 to +8.8)	NS	
Social behavior MSBS	WMD: 1.1 (99% CI, -10.3 to +8.1)	NS	
Information/orientation CAPE	WMD: 0.05 (95% CI, -4.37 to +4.77)	NS	Good
Behavioral CAPE	WMD: -3.3 (95% CI, -14.2 to +7.60)	NS	Clinical setting and dementia severity not specified; in 1 RCT, patients had moderate to severe dementia
Cognitive	SMD: -0.59 (95% CI, -0.95 to -0.22)	Significant	Good
Behavior	SMD: -0.64 (95% CI, -1.20 to -0.08)	Significant	Clinical setting and dementia severity not specified; patients in 1 RCT had severe cognitive impairment, other trial had mild dementia. Patients in 1 RCT were institutionalized

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Evidence Table 11a. Efficacy of Caregiver Interventions: Systematic Review

Author	Number of Studies	Interventions	Outcomes	Results	Comments
Thompson and Briggs, 1998 [172]	6 RCTs N (33-102)	(1) Individualized service assessment and planning vs conventional care or support (2) Technology-based interventions vs conventional care or support (3) Career education/ training vs conventional care/support (4) Multi-faceted/ dimensional strategies vs conventional care/support	(1) Caregiver burden, strain, support, quality of life (2) Caregiver mental health: depression, anxiety (3) Service utilization and cost (4) Others: knowledge of Alzheimer's disease, asking for help, decision-making confidence	No significant differences between experimental and control groups for any of these outcomes	Good Limited to 1998 and to caregiver outcomes only

Evidence Table 11b. Efficacy of Caregiver Interventions: Studies

Author	N	Intervention				Outcomes Measured
		Support Group	Skills Training	Counseling	Educational	
Hebert et al., 1994[177] and 1995[178]	45	+	+	+	+	Caregiver: -Burden: BI -Depression: BSI -Reaction to pt's BPRD RMBPC -ADKT -Health care utilization HCUQ Patient: -Nursing home placement -Cognition: 3MS -Functional: SMAF -BPRD: RMBPC (F)
Mittelman et al., 1996[173]	206	+	+	+	+	Patient: Median time to nursing home placement
Brodaty et al., 1997[176]	96	+	+	+	+	Patient: Time to nursing home placement Time to death
McCurry et al., 1998[175]	36	--	+	+	+	Caregiver: -Burden: SCB -Depression: CES-D -Sleep problems: PSQI -Reaction to patients' BPRD: RMBPC
Marriott et al., 2000[174]	42	--	+	+	+	Caregiver: -Burden: GHQ -Depression: BDI Patient: -Cognition: MMSE -Depression: CSDD -BPRD: MOUSEPAD -Functional status: CDR

Evidence Table 11b.Efficacy of Caregiver Interventions: Studies (continued)

Results				
Scale	Treatment Arm	Control Arm	P Value	Quality and Comments
BI	34.90	36.06	NS	Good
BSI	33.57	30.20	NS	
RMBPC(R)	1.39	1.73	NS	Difficult to implement
ADKT	9.52	6.53	*P* = 0.004	
HCUQ	----	----	NS	
P (nursing home placement)	0.33	0.45	*P* = 0.31	
3MS	40.63	36.53	NS	
SMAF	35.67	36.73	NS	
RMBPC (F)	1.58	1.63	NS	
Days to nursing home placement	1,03	874	*P* = 0.02	Fair (not all outcomes considered) Difficult to implement
Time to nursing home placement (in months)	47.5	27.6	*P* < 0.05	Fair Difficult to implement in-patient setting
Time to death (in months)	65	53	*P* = 0.08	
SCB	----	----	NS	Fair
CES-D	----	----	NS	
PSQI	7.8	10.6	*P* < 0.05	Difficult to implement; attrition rate varied between the 2 groups at follow-up, but not at immediate post treatment; (included only the results of post treatment); caregivers had sleep problems before entry
RMBPC	----	----	NS	
GHQ @ 9 ms	6.0	12.7	*P* = 0.001	Good
GHQ @ 12 ms	3.9	10.8	*P* = 0.001	
BDI @ 9 ms	6.9	11.8	*P* < 0.01	Difficult to implement; caregiver had significant psychological morbidity at entry to the trial.
BDI @12ms	6.1	11.8	*P* = 0.001	
MMSE	----	----	NS	
CSDD	----	----	NS	
MOUSEPAD @ 9 ms	4.9	5.6	*P* = 0.01	
MOUSEPAD @12ms	5.3	5.2	NS	
CDR(ADL) @9ms	5.4	5.1	NS	
CDR(ADL) @ 12ms	5.5	6.4	*P* = 0.043	

Evidence Table 12a. Adverse Effects of Dementia Therapy: Cholinesterase Inhibitors – Systematic Reviews

Author	Intervention	Result					Comments
		Effect	Treatment	Placebo	P	NNH	
Birks et al., 2000[115]	Rivastigmine 6-12 mg/day	D/O to AE	OR: 2.6 (95%CI, 2.0 to 3.2)			5	Good
Birks et al., 2000[119]	Donepezil Low dose: 5 mg/day	D/O to AE	Low: OR: 0.8 (95%CI, 0.5 to 1.2)		NS	---	Good
	High dose: 10 mg/day		High: OR: 1.8 (95%CI, 1.2 to 2.7)		Sig-nifi-cant	---	
Qizilbash et al., 1998[121]	Tacrine	D/O	OR: 3.6 (95%CI, 2.8 to 4.7)			4	Good
Qizilbash et al., 2000[120]	Tacrine	D/O to AE	OR: 5.7 (95%CI, 4.1 to 7.9)		NR	---	Good

Evidence Table 12b. Adverse Effects of Dementia Therapy: Cholinesterase Inhibitors -- Studies

		Result					
Author	**Intervention**	**Effect**	**Treatment**	**Placebo**	**P**	**NNH**	**Comments**
Burns et al.,1999[99]	Donepezil Low dose: 5 mg/day High dose: 10 mg/day	D/O to AE	Low: 9% High: 18%	10%	NR	---	Fair
Greenberg et al., 2000[100]	Donepezil 5 mg/day	D/O to AE # pt	3 patients	1 pt		---	Fair
Mohs et al., 2001[95]	Donepezil 10 mg/day	D/O AE %	11%	7%	NR	---	Fair
Winblad et al, 2001[93]	Donepezil 10 mg/day	D/O to AE %	7%	6.3%	NR	---	Good
Raskind et al., 2000[97]	Galantamine Low dose: 24 mg/day High dose: 32 mg/day	D/O to AE%	Low: 23% High: 32%	8%	NR	---	Fair
Tariot et al., 2000[98]	Galantamine Low dose: 16 mg/day High dose: 24 mg/day	D/O to AE %	Low: 7% High: 10%	7%	NR	---	Fair
Wilcock et al., 2000[96]	Galantamine Low dose: 24 mg/day High dose: 32 mg/day	D/O to AE%	Low: 14% High: 22%	9%	NR	---	Fair
Rosler et al., 1999[101]	Rivastigmine 6 – 12 mg/day	D/O 2 AE %	27%	7%	NR	---	Fair
McKeith et al., 2000[102]	Rivastigmine 6 – 12 mg/day	D/O 2 AE %	12%	11%	NR	---	Fair

Evidence Table 12c. Adverse Effects of Dementia Therapy: Typical and Atypical Neuroleptics

Author	Intervention	Result					Comments
		Effect	Treatment	Placebo	*P*	NNH	
Lanctot et al., 1998[122]	Neuroleptic	D/O % Any AE%	20% 51%	16% 25%	*P* = .5 NS *P* <.001	-- 4 (3, 8)	Good
Davidson et al., 2000[124]	Atypical neuroleptic	D/O	OR: 1.31 (95% CI, 1 to 1.7)				Good
		EPS	OR: 2.04 (95%CI, 1.24 to 3.33)		---	13 (8, 40)	
		Sedation	OR: 1.74 (95%CI, 1.18 to 2.57)		---	10 (7, 22)	
Kirchner et al., 2000[125]	Thioridazine	AE	OR: .41 (95%CI, .09 to 1.86) NS		---		Good
Devanand et al., 1998[94]	Haloperidole (2 - 3mg/day)	D/O % EPS % (mod-severe)	5% 20%	17% 0%	NR *P* =.08	---	Fair
		Any AE%	100%	70%	NR		

Evidence Table 12d. Adverse Effects of Dementia Therapy: Other

Author	Intervention	Result					Comments
		Effect	Treatment	Placebo	*P*	NNH	
Petracca et al., 1996[111]	Clomipramine	D/O %	9%	20%	NR	---	Fair (not clear if intention-to-treat analysis)
LeBars et al., 1997[106]	Gingko biloba 120 mg/day	D/O to AE	6%	3%	NR	---	Fair
		D/O to CG request	15%	18%	NR	---	
		Any AE	30%	31%	NR	---	
Oken et al., 1998[118]	Gingko biloba 120-240 mg/day	No difference between groups; average D/O 16%					Good
Sano et al, 1997[103]	Selegiline 10 mg/day Vit E 2000 IU daily Both	Drop-off to AE O% in all groups except Lost to F/U %	Sel: 5% Vit E: 9% Both: 6%	placebo: 7%			Fair
Birks and Flicker, 2000[116]	Selegiline 10 mg/day	No difference between groups; average D/O 20%					Good

APPENDIX C.
DETAILED DESCRIPTION OF STANDARD SCALES USED

DETAILED DESCRIPTION OF STANDARD SCALES USED

Alzheimer's Disease Functional Assessment of Change Scale (ADFACS)

The ADFACS is a 16-item functional assessment instrument based on both basic ADLs and IADLs. A trained clinician or research assistant obtains information directly from both the patient and the caregiver. Each of the basic ADL items is scored on a scale of 0 (no impairment) to 4 (severe impairment) and each IADL item is scored on a scale ranging from 0 (no impairment) to 3 (severe impairment). The total score for the 16-item scale ranges from 0 to 54. Table 11 shows the specific items that are included in this scale.

Clinical Dementia Rating Scale (CDR)

The CDR a global measure of 6 domains, including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Its total score ranges from 0 (no impairment) to 3 (severe impairment).[188]

Gottfries-Brane-Steen Scale (GBS)

The Gottfries-Brane-Steen (GBS) scale is a 27-item global scale for rating dementia symptoms based on a semi-structured interview by the clinician, with both the patient and the caregiver.[189 190] The GBS assesses 4 domains: intellectual impairment (orientation, memory,

concentration [12 items]), self-care motor function (6 items), emotional reaction (3 items), and behavioral symptoms (6 items). A 7-point scoring system from 0 to 6 is used for each of the 27 items of this scale, giving a total score range of 0 to 162 points, with an increase in score representing clinical deterioration.

Interview for Deterioration in Daily living in Dementia Scale (IDDD)

This scale assesses functional disability in basic ADLs (16 items) and IADLs (17 items) of patients living in the community. The caregiver assesses patients' severity of impairment in each item on a 7-point scale, where 1 to 2 points denotes no or slight impairment, 3 to 4 points denotes mild impairment, 5 to 6 points denotes moderate impairment, and 7 points denotes severe impairment. The total score range is 33 to 231 points.

Neuropsychiatry Inventory Scale (NPI)

The NPI evaluates the frequency and severity of 10 neuropsychiatric disturbances that occur frequently in dementia: agitation, irritability, anxiety, dysphoria, hallucinations, delusions, apathy, euphoria, disinhibition, and aberrant motor behavior. Each item on the NPI is scored on a 1- to 4-point frequency scale and a 1- to 3-point severity scale. The severity score is then multiplied by the frequency score, resulting in a total score ranging from 10 to 120 points.[191]

Progressive Deterioration Scale (PDS)

The PDS is a self-administered scale for caregivers that examines the ability of patients to accomplish basic ADLs and IADLs in 11 areas.[192] Each item is scored using a 100 mm bipolar

visual analogue scale, then a total score range from 0 to100 is derived from the average across the items.[126]

Resource Utilization in Dementia Questionnaire Scale (RUD)

The RUD scale is completed by caregivers and compiles data on the use of social services, frequency and duration of hospitalizations, unscheduled contacts with health care professionals, use of concomitant medications by both the caregiver and the patient, amount of time the caregiver spends caring for the patient and missing work, and patients' use of study medication.[123]

Table 1. Inclusion Criteria, Search Strategy, and Results of Searches

Key Question/Issue	Inclusion Criteria*	Number of Systematic Reviews Found	Number of Full Articles Reviewed	Number of Systematic Reviews and Articles that Met Criteria
1 Direct Effect of Screening on Outcome	• Study designs: RCTs • Participants: Age 60 or older • Dementia diagnosed by DSM or ICD • Any of 6 outcomes from the analytic framework	0	0	0
2 Prevalence of Undiagnosed Dementia	• Study designs: Systematic reviews Cross-sectional prevalence • Participants: Age 60 or older in community or primary care setting • Reference standard for all subjects • Blinded, independent evaluation for dementia diagnosed by DSM or ICD • Exclusion of patients with prior diagnosis of dementia • Data provided for true positives	0	MEDLINE - 6 PsycINFO - 1 Total: - 7	Studies - 4
3 Effectiveness of Screening Tools	• Study designs: Systematic reviews RCTs Prospective cohort Cross-sectional prevalence • Participants: Age 60 or older in community or primary care setting • Reference standard for all subjects • Blinded, independent evaluation for dementia diagnosed by DSM or ICD • Data provided for true positives/negatives and false positives/negatives	Cochrane - 1 PsycINFO - 1 Additional search - 1 Total - 3	MEDLINE - 44 PsycINFO - 21 Additional search - 10 Total - 75	Reviews - 1 Studies - 9 Total - 10

* RCTs, randomized controlled trials; DSM, Diagnostic and Statistical Manual; ICD, International Classification of Diseases

Table 1. Inclusion Criteria, Search Strategy, and Results of Searches (continued)

Key Question/Issue	Inclusion Criteria	Number of Systematic Reviews Found	Number of Full Articles Reviewed	Number of Systematic Reviews and Articles that Met Criteria
4 Primary Treatment of Potentially Reversible Dementia	• Study designs: Systematic reviews Longitudinal studies RCTs • Study participants: Age 60 or older in community or outpatient clinics • Mild to moderate dementia diagnosed by DSM or ICD • Intervention: Treatment of potentially reversible conditions • Outcomes: Any of the 6 outcomes from the analytic framework	Cochrane - 0 MEDLINE - 2 Total - 2	Cochrane - 0 MEDLINE - 19 Total - 19	Systematic reviews - 0 RCT studies - 0 Longitudinal studies - 7 Total - 7
Primary Treatment of Irreversible Dementia	• Study design: Systematic reviews RCTs • Participants: Age 60 or older. Dementia diagnosed by DSM or ICD • Intervention: Pharmacologic treatment targeting the primary pathophysiology of the disease • Outcomes: Any of the 6 outcomes from the analytic framework	Cochrane - 12 MEDLINE - 5 EMBASE - 2 Total - 19	MEDLINE - 147 PsycINFO - 5 EMBASE - 14 Other - 4 Total - 170	Systematic reviews - 7 RCT studies - 16 Total - 23

Table 1. Inclusion Criteria, Search Strategy, and Results of Searches (continued)

Key Question/Issue	Inclusion Criteria	Number of Systematic Reviews Found	Number of Full Articles Reviewed	Number of Systematic Reviews and Articles that Met Criteria
5 Secondary Treatment for Dementia (pharmacologic interventions)	• Study design: Systematic reviews RCTs • Participants: Age 60 or older Dementia diagnosed by DSM or ICD Patients with overt behavioral problems • Intervention: Pharmacologic treatment targeting behavioral problems related to dementia • Outcomes: Any of 6 outcomes from the analytic framework	MEDLINE - 2	MEDLINE - 21 PsycINFO - 2 EMBASE - 6 Total - 29	Systematic reviews - 3 Studies - 3 Total - 6
Secondary Treatment for Dementia (non-pharmacologic interventions)	• Study design: RCTs Systematic reviews • Participants: Age 60 and older Dementia diagnosed by DSM or ICD • Intervention: Nonpharmacologic, targeting and symptomology • Outcomes: Any of the 6 outcomes from the analytic framework	Cochrane: 3 MEDLINE: 4 EMBASE: 1 Total: 8	MEDLINE: 45 PsycINFO: 0 EMBASE: 7 Total: 52	Systematic reviews - 6 RCTs - 0 Total: 6

Table 1. Inclusion Criteria, Search Strategy, and Results of Searches (continued)

Key Question/Issue	Inclusion Criteria	Number of Systematic Reviews Found	Number of Full Articles Reviewed	Number of Systematic Reviews and Articles that Met Criteria
6 Interventions for Caregivers of Patients with Dementia	• Study design: RCTs Systematic reviews • Participants: Caregivers of patients with dementia Dementia diagnosed by DSM or ICD • Intervention: Nonpharmacologic interventions targeting the caregivers of patients with dementia • Outcomes: Any of 6 outcomes from the analytic framework	Cochrane - 1 MEDLINE - 8 Total - 9	29	Systematic review - 1 Studies - 5 Total - 6
7 Adverse Effects of Dementia Screening	• Study design: Systematic reviews Prospective cohort Cross-sectional prevalence • Participants: Age 60 or older Reference standard for all subjects • Intervention: Any treatment method • Outcomes: Any possible adverse effects of screening	0	0	0

Table 1. Inclusion Criteria, Search Strategy, and Results of Searches (continued)

Key Question/Issue	Inclusion Criteria	Number of Systematic Reviews Found	Number of Full Articles Reviewed	Number of Systematic Reviews and Articles that Met Criteria
8 Cost of Dementia Screening	• Study design: Systematic reviews Prospective cohort RCTs • Participants: Age 60 or older Dementia diagnosed by DSM or ICD Community-dwelling • Intervention: Any treatment method • Outcomes: Any possible adverse effects of screening	0	MEDLINE - 41	MEDLINE - 0
9 Adverse Effects of Dementia Treatment	• Study design: Systematic reviews RCTs • Participants: Age 60 or older Dementia diagnosed by DSM or ICD • Intervention: Any effective treatment method • Outcomes: Any possible side effects that affect mortality or morbidity of the patient or caregiver	Cochrane - 12 MEDLINE - 9 EMBASE - 2 Total - 23	Cochrane - 0 MEDLINE - 187 PsycINFO – 7 EMBASE - 20 Other - 2 Total - 216	Systematic reviews - 9 Studies - 10 Total - 19

Table 2. Estimates of Undiagnosed Dementia in Primary Care Practices

Study	Quality Rating	Setting	Age of Patient Population	Reference Standard*	Prevalence of Missed Dementia in All Patients
Eefsting et al. 1996[66]	Fair	Community and general practices, Netherlands	≥ 65 years	DSM-IIIR	3.2%
Olafsdottir et al. 2000[12]	Good	Primary health center, Sweden	> 70 years	DSM-IIIR	12.0%
Sternberg et al. 2000[13]	Fair	Community Canada	≥ 65 years	DSM-IIIR	1.8%
Valcour, et al. 2000[14]	Fair	General internal medicine clinic, Hawaii, U.S. (Asian-Americans)	≥ 65 years	DSM-IIIR	5.7%

*DSM-III-R, Diagnostic and Statistical Manual III, Revised.

Table 3. Estimates of the Prevalence of Dementia (%)

Study and Population	Age Groups						
	65-69	70-74	75-79	80-84	85-89	90-94	95+
Hendrie et al., 1995[67] African-Americans in Indianopolis, Indiana (n = 2,212)		1.83*		6.73†		17.07‡	
White et al., 1996[68] Asian-American men in Honolulu, Hawaii (n = 3,734)	NR	2.1	6.2	12.9	33.4	NR	NR
Graves et al., 1996[69] Japanese-Americans in King County (Seattle), Washington (n = 1,985)	0.76	1.35	6.26	12.67	29.69	50.20	74.28

NR, not reported.
* Ages 65-74 years
† Ages 75-84 years
‡ Ages 85+ years

Table 4. Diagnostic Categories for Subtypes of Dementia

Study	Diagnostic Category for Subtypes of Dementia (% of cases)			
	Alzheimer's Disease	Vascular Dementia	Mixed Alzheimer's Disease/Vascular Dementia	Other
Hendrie et al., 1995[67]	75.4	15.4	NA	16.9
Graves et al., 1996[69]	57.3	23.5	NA	NA
Breitner et al., 1999[72]	60.0	16.4	6.9	16.7
Gurland et al., 1999[73]	74.1	4.8	15.6	5.4

NA, not available.

Table 5. Characteristics and Results of Six Studies Evaluating Properties of the Mini-Mental State Examination (MMSE)

Study	Number of Subjects	Cut-off Value* (Rationale)	Percentage with Dementia	Sensitivity	Specificity	False Positives (% of all subjects)	False Negatives (% of all subjects)	Notes
Law and Wolfson, 1995[84]	237	23 ("Conventional")	20.7	71	82	13.9	5.9	French version
Wilder et al., 1995[80]	162	23/24 (90% sensitivity)	24.0	90	56	33.3	2.5	Firm 90% sensitivity
Jitapunkul et al., 1996[78]	212	16/18 (illiterate/literate) (ROC)	8.0	76	92	7.1	1.9	Thai version
McDowell et al., 1997[76]	1,600	25/26 (ROC)	23.0	86	77	17.7	3.3	English and French versions
Heun et al., 1998[81]	291	24/25 (ROC)	12.7	92	96	3.4	1.0	German version

* ROC, receiver-operator curve.

Table 6. Likelihood Ratios (LR) for Prediction of Dementia Using the Mini-Mental State Examination (MMSE)

MMSE score	3-Year Incidence of Dementia	LR for 3-Year Incidence Dementia (n = 215)	3- to 6-Year Incidence of Dementia	LR for 3- to 6-Year Incidence of Dementia (n = 129)
30	0.024	0.20	0.182	0.77
29	0.018	0.15	0.270	1.28
28	0.083	0.76	0.174	0.73
27	0.103	0.96	0.167	0.69
26	0.154	1.51	0.222	0.99
25	0.421	6.07	0.4	2.30
24	0.375	5.01	0.5	3.45

Source: Braekus et al., 1996[79]

Table 7. Reliability Data for Mini-Mental Status Examination

MMSE Adminstration Language	Reliability Measure	Value
French	Alpha internal consistency	0.78
	Split-half reliability	0.76
English	Alpha internal consistency	0.79
	Split-half reliability	0.73

Source: McDowell et al., 1997[76]

Table 8. Likelihood Ratios (LR) for Prediction of Dementia with Instrumental Activities of Daily Living (IADL)

IADL Score	3-year Incidence of Dementia	LR for 3-Year Incidence of Dementia (n = 1,574)	5-Year Incidence of Dementia	LR for 5-Year Incidence of Dementia (n = 1,283)
0	0.016	0.38	0.016	0.63
1	0.083	2.19	0.061	2.44
2	0.143	4.01	0.071	2.91
3	0.258	8.38	0.059	2.36
4	0.200	6.02	0.077	3.16

Source: Barberger-Gateau et al., 1999.[83]

Table 9. Summary Description of Three Common Scales Used in Alzheimer's Disease Drug Trials

Scale	Assessment Domain	Range and Interpretation
Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog)	Cognition	0 to 70 • 70 = severe impairment • Untreated patients decline annually by 7 to 11 points • For example, 3 to 4 points improvement from baseline can mean patients remember who came to dinner last evening
Mini-Mental Status Examination (MMSE)	Cognition	0 to 30 • 30 = no impairment • Untreated patients decline annually by 2 to 4 points • For example, improvement of 2 points from baseline can mean patients are able to name common objects • 1.6 points on MMSE = 4 points on ADAS-Cog
Clinician Interview Based Impression of Change plus caregiver input (CIBIC-Plus)	Global measure of behavior, cognition, activities of daily living	1 to 7 • 1 = very much improvement • 4 = no change • 7 = very much deterioration

Table 10. Specific Domains of Basic and Instrumental Activities of Daily Living

Basic Activities of Daily Living	Instrumental Activities of Daily Living
Toileting	Use of telephone
Feeding	Household tasks
Dressing	Using household appliances
Personal hygiene and grooming	Managing money
Bathing	Shopping
Walking	Food preparation
	Ability to get around inside and outside home
	Hobbies and leisure activities
	Handling personal mail
	Grasp of situation or explanations

Source: McDowell and Newell, 1996[129]

Table 11. Efficacy of Cholinesterase Inhibitors in Alzheimer's Disease

Drug	Cognitive Function	Clinician-assessed Global Function	Physical Function: Activities of Daily Living (ADLs)	Behavioral Symptoms	Quality of Life	Caregiver Burden
Tacrine	+	+	NS	NS	NT	NT
Donepezil	+	+	+	NS	NS	+
Rivastigmine	+	+	+	NS	NT	NT
Galantamine	+	+	+	NS	NT	NT

Key:
+ Statistically significant effect
NS No significant effect
NT Not tested