Dementia – Diagnostic and Therapeutic Interventions

A Systematic Review

Volume 2

June 2008

The Swedish Council on Technology Assessment in Health Care
SBU • Statens beredning för medicinsk utvärdering

SBU Evaluates Healthcare Technology

SBU (the Swedish Council on Technology Assessment in Health Care) is a government agency that assesses the methods employed by medical professionals and institutions. In addition to analyzing the costs and benefits of various health care measures, the agency weighs Swedish clinical practice against the findings of medical research. The objective of SBU's activities is to provide everyone who is involved in decisions about the conduct of health care with more complete and accurate information. We welcome you to visit our homepage on the Internet at www.sbu.se.

SBU issues three series of reports. The first series, which appears in a yellow binding, presents assessments that have been carried out by the agency's project groups. A lengthy summary, as well as a synopsis of measures proposed by the SBU Board of Directors and Scientific Advisory Committee, accompanies every assessment. Each report in the second, white-cover series focuses on current research in a particular healthcare area for which assessments may be needed. The Alert Reports, the third series, focus on initial assessments of new healthcare measures.

To order this report (No 172E/2) please contact:

SBU
Mailing Address: Box 5650, SE-114 86 Stockholm, Sweden
Street Address: Tyrgatan 7
Tel: +46 8 412 32 00 Fax: +46 8 411 32 60
Internet: www.sbu.se E-mail: info@sbu.se

Graphic Design: pmochco, www.pm.se
Printing: Elanders Infologistics Väst AB, Mölnlycke 2008
ISBN 978-91-85413-24-9 • ISSN 1400-1403

Dementia – Diagnostic and Therapeutic Interventions

A Systematic Review

Project Group

Olof Edhag (Chair)
Hedda Aguero-Eklund
Ove Almkvist
Kenneth Asplund
Kaj Blennow
Sirkka-Liisa Ekman
Knut Engedal
Elisabet Englund
Sture Eriksson
Johan Fastbom
Laura Fratiglioni
Lars Gustafson
Ingrid Håkanson (Project Assistant)
Aki Johanson
Ingvar Karlsson
Mona Kihlgren
Lena Kilander
Elisabet Londos
Jan Marcusson
Astrid Norberg
Anders Norlund (Project Director)
Liisa Palo-Bengtsson
Magnus Sjögren
Eva von Strauss
Lars-Olof Wahlund
Gunhild Waldemar
Anders Wallin
Anders Wimo
Dag Årsland

Scientific Reviewers

Per Edebalk
Serge Gauthier
Lars Lannfelt
Kim Lützén
Rurik Löfmark
Hans Melander
Ingalill Rahm Hallberg
Anneli Sarvimäki
Hilkka Soininen
Matti Viitanen

Reference Group

Ann Hedberg Balkå (Swedish Association of Local Authorities and Regions)
P-O Sandman (Umeå University)
Bengt Winblad (Karolinska Institute)
Members from the Alzheimer Association of Sweden and from the Dementia Association

The Swedish Council on Technology Assessment in Health Care

SBU • Statens beredning för medicinsk utvärdering

Content

Checklists regarding assessment of study quality for different chapters of this report are included in the electronic version of the SBU report on Dementia diseases at www.sbu.se

9. Diagnosing Dementia Disorders

Background

Diagnostic evaluation of dementia

Cognitive complaints and symptoms may result from normal aging or from a wide range of neurological, psychiatric or internal medical conditions. The diagnostic workup and management of a patient with cognitive complaints and symptoms is a multidisciplinary task, involving physicians from several medical specialties, as well as psychologists, occupational therapists, other health professions and other social care providers. A diagnostic evaluation should be initiated in all patients with subjective cognitive complaints and symptoms that seem to either persist or worsen, as well as in patients for whom the complaints are associated with other cognitive or behavioral changes or with impaired activities of daily living. Some patients with dementia have reduced insight into their own problems. If family members often report of memory loss or cognitive impairment in such patients, diagnostic evaluation should also be carried out. Diagnostic evaluation should be considered even when symptoms are not sufficiently severe to meet international criteria for dementia, given that patients with mild symptoms may have potentially reversible conditions and need appropriate management.

The dementia syndrome is diagnosed using specific criteria such as ICD-10 [1] or DSM-IV [2] criteria. There are no specific diagnostic markers for the most common dementia disorders. Therefore, the specific underlying disorder causing cognitive impairment and dementia is diagnosed using operational diagnostic criteria.

The concept of mild cognitive impairment (MCI)

One issue with the abovementioned criteria is that the degree of cognitive decline must be below a certain level. That leads to problems when cognitive impairment is present but not severe enough to meet

the criteria for dementia. The term MCI was one operational way to describe such patients. The vague terminology implies that MCI has a heterogeneous origin. A majority of MCI patients, though far from all, have very early Alzheimer's disease (AD), given that the conversion from MCI to AD is around 15% per year.

In current diagnostic workups, different sources of information are used, the patient's medical history being the most important. The history obtained from the patient should be complemented by information from relatives or other informants. A skilled, experienced specialist at a memory clinic has a high probability of correctly diagnosing the specific dementia disorder based on diagnostic criteria. A number of investigations are usually recommended as part of the diagnostic workup in general practice and at memory clinics.

- Physical, including neurological, examination
- Neuropsychological assessment
- Psychiatric/behavioral assessment
- Evaluation of activities of daily living
- Laboratory screening (blood) tests and ECG
- Cranial CT (or MRI)

In experienced hands, these basic examinations help the clinician identify the most common causes of cognitive impairment and dementia. However, up to 20% of all patients with dementia may have rarer conditions, the diagnosis of which may require a more extensive workup.

The prevalence of dementia in patients referred to memory clinics is often quite high, ranging from 50 to 100%. Prevalence is much lower in general practice, approaching that of the general population. However, many elderly people, including patients in general practice, have subjective memory complaints. The most important role of the general practitioner is to identify patients who may have a dementia disorder and to initiate diagnostic evaluation, screening for potentially reversible causes. The role of the general practitioner in completing a diagnostic evaluation may vary according to local healthcare organization, as well as individual knowledge, skills and experience.

Guidelines for the diagnostic evaluation of dementia

Guidelines for the diagnostic evaluation of dementia have been developed on a regional or national level in many countries. However, there are only a few published guidelines in international journals. Only one guideline was developed by an international group [3]. The published guidelines represent a mixture of expert consensus and evidence-based recommendations. Most guidelines were developed for either general practitioners or a particular group of specialists. Only rarely were guidelines based on evidence found in the literature, such as the guidelines recently published by the American Academy of Neurology [4,5].

"Evidence-based Dementia Practice", published in 2002, Chui points out the lack of systematic analyses of diagnostic methods (likelihood ratios, predictive values sensitivity and specificity) for use in dementia workups [6].

European federation of neurological societies (EFNS) guidelines [3]

- Cognitive assessment is central to the diagnosis and management of dementia disorders.
- Assessment of behavioral disorders is essential for the diagnosis and management of dementia. Assessment of activities of daily living should be included in the diagnostic evaluation and management of dementia.
- Neuroimaging should be performed once in all cases of dementia. Non-contrast CT will suffice, but MRI is preferable if available and may be used to show specific abnormalities.
- Functional imaging should not be used routinely, but may be helpful when there is clinical suspicion of degenerative disorders and structural imaging is normal.
- Laboratory screening should be included in the general screening of a patient who presents with cognitive disturbances. The following blood tests are generally proposed for all patients: blood sedimentation rate, complete blood cell count, electrolytes, glucose, renal and

liver function tests, and thyroid-stimulating hormone. Serological tests for the detection of borrelia, syphilis and HIV, serum lipids, and vitamin B_{12} are optional. More extensive tests are often required in individual cases.

- Electrocardiography (ECG) is recommended in all patients aged 50 and above for screening purposes, in patients with cardiac symptoms or cerebrovascular lesions, and for monitoring possible side-effects in patients receiving drug therapy (such as acetylcholine-esterase-inhibitors). Chest X-ray is indicated if relevant to the symptoms.
- CSF analysis (with routine cell count, protein, glucose and protein electrophoresis) is optional and recommended in patients with clinical suspicion of certain diseases, as well as in those with atypical clinical presentations.
- Electrophysiological examination is not recommended on a routine basis.
- Brain biopsy is recommended in carefully selected cases only.

American Academy of Neurology guidelines [5]

- The clinical criteria for dementia (DSM-II-R) [7], AD (DSM-III-R and NINCDS-ADRDA [8]) and Creutzfeldt-Jakob disease have sufficient reliability and validity. They should be used, whereas the criteria for vascular dementia (VaD), dementia with Lewy bodies and frontotemporal dementia may be used but have imperfect reliability and validity.
- Structural neuroimaging should be performed as part of the initial evaluation of patients with dementia.
- Screening for depression, vitamin B_{12} deficiency and hypothyroidism should be performed.
- Other neuroimaging methods, genetic markers, CSF markers (except 14-3-3 protein for Creutzfeldt-Jakob disease) and screening for neurosyphilis are not recommended on a routine basis.

Aims

This evidence-based review has focused on the most commonly used methods in the diagnostic evaluation of patients who present with cognitive complaints and symptoms. The aims have been to assess the role and validity of the methods in:

- Identifying secondary and reversible causes of cognitive impairment
- Confirming the presence of dementia
- Identifying specific dementia disorders.

Methods

Selection of papers

Diagnostic tests

We have selected the most commonly used diagnostic tests that can identify the most prevalent causes of dementia and conditions or reversible cognitive impairment. However, we have not searched for evidence that depression and drugs with anticholinergic effect can cause reversible cognitive impairment, given that there is general consensus among researchers and clinicians supporting this view [5]. Nor have we sought evidence for which diagnostic tests could be useful to identify rare metabolic and neurological causes of dementia (for instance, parathyroid disease, Wilson's disease). The following diagnostic tests have been evaluated:

- Caregiver information rating scales
- Short cognitive mental tests
- Neuropsychological tests
- Selected laboratory screening tests
- Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain
- Single photon emission tomography (SPECT)
- Electroenchephalography (EEG)
- Apoliprotein genotyping
- Examination of amyloid-beta and tau-protein in cerebrospinal fluid.

The selected laboratory screening tests were vitamin B_{12}, folate, homocysteine, thyroid stimulating hormone (TSH) and tests for syphilis, given that vitamin B_{12} and folate deficiency, thyroid disease, and neurosyphilis are commonly referred to as potentially reversible causes of cognitive deficits [3,5].

Inclusion criteria for papers to be reviewed

- The papers included in this study were to describe at least 20 cases and 20 controls or at least 30 cases (in studies for which controls were not appropriate).
- The patients must have been properly examined for dementia, including physical and psychiatric examinations, cognitive tests, blood tests and imaging of the brain.
- The patients must have been diagnosed according to well-known and standardized clinical or neuropathological criteria.
- Appropriate statistical methods must have been used. Except for tests that could detect reversible conditions causing cognitive impairment, information should be available to calculate the test's sensitivity, specificity and likelihood ratio.
- Only papers written in English published before July 2004 have been included.

Exclusion criteria

Due to differences in criteria regarding the selection of studies, meta-analysis papers have been excluded.

Quality assessment of papers

The papers have been classified according to the design of the study, the selection of patients, control and contrast groups and the setting – such as university hospitals, memory clinics or outpatient clinics – in which they have been carried out. The papers representing the highest class of study quality are defined as Ia papers, which describe prospective studies on a broad spectrum of patients and controls (population based studies and consecutive series of a broad spectrum of patients) who have been followed up with clinical diagnostic assessments over time and examined

post-mortem. The lowest classs of study quality represents 2b papers from cross-sectional studies of highly selected patients and controls. The tables present the papers in hierarchical order according to how the patients were recruited and the gold standard of the dementia diagnosis.

Ia = Population based or consecutive-series prospective studies, diagnosis verified neuropathologically
Ib = Selected patients and controls, prospective studies, diagnosis verified neuropathologically
IIa = Population based or consecutive-series retrospective studies, diagnosis verified neuropathologically
IIb = Selected patients in retrospective studies, diagnosis verified neuropathologically
1a = Population based or consecutive-series prospective studies, clinical diagnosis
1b = Selected patients and controls, prospective studies, clinical diagnosis
2a = Population based or consecutive-series retrospective studies, clinical diagnosis
2b = Selected patients in retrospective studies, clinical diagnosis.

Presentation of the results

Except for the laboratory screening tests, the results are presented as the diagnostic test's sensitivity, specificity and likelihood ratio (LR) for a positive test (LR+) or a negative test (LR–). The reason that results are presented with LRs and not negative and positive predictive values is that the LR is a robust measure independent of prevalence rates in the tested populations.

Sensitivity and specificity

Sensitivity is defined as a test's probability of finding a target disease. According to Table 9.1, it can be expressed as "true test positive" or a/a + c. Specificity is defined as a test's probability of finding a normal person without the target disease. According to Table 9.1, it can be expressed as "true test negative" or d/b + d. The same table indicates that the false positive rate is b/b + d and the false negative rate is c/a + c.

Table 9.1 *Validation of a diagnostic test against a target disease or gold standard of a target disease.*

	Target disease	
	+	–
Test positive	a (true positive)	b (false positive)
Test negative	c (false negative)	d (true negative)

Pre-test probability

The clinician's impression of a patient is important for the pre-test probability of a disease such as dementia. Through an interview with the patient and a caregiver, an experienced clinician will have information that makes the pre-test probability of dementia very high. Because a less experienced clinician cannot take equal advantage of information from such an interview, the pre-test probability will be lower. If there is no information about the symptoms of a disease, the pre-test probability will be equal to the prevalence of the disease in the age-cohort of the person. For instance, the pre-test probability of dementia in an unexamined and unselected population of a cohort of people aged 50 will be very low (less than 1%), whereas the pre-test probability among people aged 80 and above who have been admitted to a memory clinic because of memory complaints will be very high (above 50%). In the first case, powerful tests are necessary to detect dementia, whereas less powerful tests may be beneficial among people in their 80s with memory complaints.

Likelihood ratio and post-test probability

The likelihood ratio for a positive test result (LR+) is defined as:
The probability of a positive result in a person with the target disease/ probability of a positive result in a person without the target disease.

This is equivalent to the ratio of true test positive to false test positive = sensitivity/(100% – specificity).

The likelihood of a negative test result (LR–) is defined as:
The probability of a negative result in a person with the target disease/ probability of a negative result in a person without the target disease.

This is equivalent to the ratio of false negative to true negative = (100%– sensitivity)/specificity.

In other words, LR is a test's discriminatory power and indicates the degree to which the pre-test probability will increase or decrease. There are practical guidelines for evaluating the power of LR+ and LR–.

LR = 1	The post-test probability will be equal to the pre-test probability – thus, the test is of no value.
LR+ = 1–2	(or LR– = 0.5–1.0) Alter pre-test probabilities to a small (and rarely important) degree.
LR+ = 2–5	(or LR– = 0.5–0.2) Have a small (but sometimes important) impact on the pre-test probability.
LR+ = 5–10	(or LR– = 0.1–0.2) Produce moderate shifts in the pre-test probability.
LR+ = >10	(or LR– = <0.1) Will often conclusively change the pre-test probability.

To calculate how much the pre-test probability will increase after introducing a test (post-test probability), a calculation can be performed by means of the test's LR+. The post-test probability of a positive result = post-test odds/post-test odds + 1. Fagan has developed a simple nomogram for this purpose, making it possible to quickly and easily calculate the post-test probability (Figure 9.1 [9]).

A good diagnostic test must have a high LR+ and low LR–, but the test's quality cannot be judge on the basis of those variables only. If the result of a test is specified in terms of a scale, the cut-off score can be manipulated so that the specificity is very high, etc. That could improve the LR+ but make the test less useful due to lower sensitivity. For instance, using MMSE as a diagnostic marker of dementia might entail a cut-off

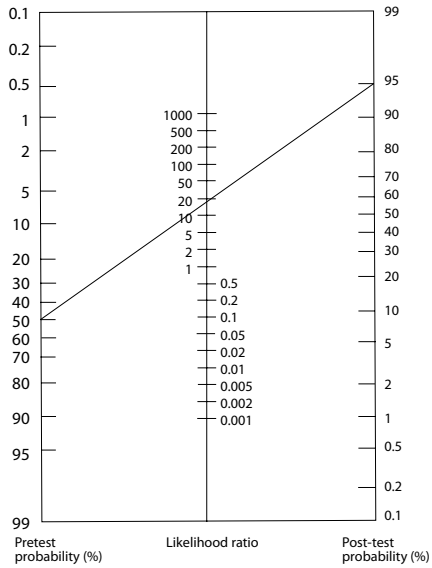

Figure 9.1 *Fagan's nomogram shows the post-test probability of a disease (95%) applying a test with LR+ of about 20 in a person with a pre-test probability of a disease of 50% [9]. (Copyright with permission from the American Medical Association.)*

value of 20. That would guarantee very high specificity, perhaps 98%, but low sensitivity, perhaps 50%. LR+ would be high at 50/100–98 = 25, but only half of the people with dementia would be detected. On the other hand, if the MMSE cut-off were 28, high sensitivity (maybe 90%) would be guaranteed but specificity could drop to 50%. In this case, LR– would be 0.1 (100–95/50). Thus, half of the patients without dementia would be defined as cognitively impaired.

Most studies have been performed in well-characterized groups of patients, defined by clinical criteria. Even with very high sensitivity, specificity and likelihood ratios, the added clinical value (above a strict clinical evaluation) in the routine clinical setting may not be known. In general, there is a lack of studies designed to address this issue.

Classification of evidence

Table 9.2 *For each diagnostic test, the evidence was classified according to the table below.*

Classification of evidence	Criteria
General criteria for all classes of evidence*	Sensitivity >80%, specificity >80%, LR+ ≥5
Evidence Grade 1 (strong evidence)	2 type 1a or Ia studies. All should meet the general criteria
Evidence Grade 2 (moderately strong evidence)	≥2 type 1a, Ia, 2a, or IIa OR ≥4 type 1b, Ib, 2b, or IIb studies. The majority of studies should meet the general criteria
Evidence Grade 3 (limited evidence)	1 type 1a or Ia study OR ≥2 type 2a or IIa studies OR ≥3 type 1b, Ib, 2b, IIb studies. The majority of studies should meet the general criteria
No evidence	No type 1a or Ia study OR only 1, type 2a or IIa study OR <3 type 1b, Ib, 2b, or IIb studies. The majority of studies should meet the general criteria OR non, or only the minority, of the available studies meet the general criteria

* For laboratory screening tests the concepts of sensitivity and specificity and LR were not relevant, because the tests were done to exclude other conditions and not in order to diagnose dementia. Therefore the general criteria were not applied for these tests.

Summary of evidence

Laboratory screening tests that might detect reversible cognitive impairment

There is no evidence of a relationship between marginally low vitamin B_{12} values in the blood and cognitive impairment and AD.

There is moderately strong evidence of an association between low levels of folic acid and cognitive impairment and limited evidence of an association between low levels of folate and AD.

There is strong evidence of an association between raised homocysteine levels in the blood and poor cognitive function and moderately strong evidence of an association between raised homocysteine levels and AD.

Tests that can be used to detect a dementia disorder

There is strong evidence that neuropsychological tests contribute substantially to the diagnosis of dementia and AD. There are few accepted studies on the diagnostic entity of MCI compared to dementia or AD and in relation to healthy people, so no conclusions can be drawn concerning this issue.

Single cognitive tests

There is moderately strong evidence that the single cognitive test CAMCOG contributes substantially to the diagnosis of dementia (LR+ 9.8, LR– 0.13). There is also strong evidence that Clock tests contribute significantly to the diagnosis of AD. There are no accepted studies on the diagnostic entity of MCI compared to dementia or AD and in relation to healthy people, so no conclusions can be drawn concerning this issue. There are no accepted studies or evidence concerning other single cognitive tests (although many are in use) for diagnosing dementia, AD or MCI.

Tests that identify specific dementia disorders

ApoE

ApoE genotyping does not contribute significantly to the diagnosis of AD. Nor does the method differentiate AD from other dementia disorders. No study in this review had a sensitivity of 80% or above and a LR+ of 5 or above. Thus, there is no evidence for the use of ApoE genotyping in the diagnostic and differential diagnosis of AD.

Methods of diagnosing dementia disorders

Structural imaging (MRI/CT)

There is strong evidence (Evidence Grade 1) that medial temporal lobe atrophy assessed with structural imaging (MRI and CT) contributes to the diagnostic workup in differentiating AD from controls and other dementia disorders.

Functional imaging (PET, SPECT)

There is moderately strong evidence (Evidence Grade 2) that reduction in regional cerebral blood flow or glucose metabolism contributes to the diagnostic workup in differentiating AD from controls and other dementia disorders.

Neurophysiological methods (EEG, EEG)

There is limited evidence (Evidence Grade 3) that visually rated EEG or quantitative EEG contribute to the diagnostic workup in differentiating AD from controls and other dementia disorders.

CSF analyses

There is strong evidence (Evidence Grade 1) that CSF T-tau (Total tau), CSF Aß42 and the combination of CSF T-tau and Aß42, and moderately strong evidence (Evidence Grade 2) that CSF P-tau (Phosphorylated tau), contribute to the diagnostic workup in differentiating AD patients from controls and other dementia disorders.

Table 9.3 *Alzheimer's disease vs Healthy control.*

	LR+ (median)		
	<5	**5–10**	**>10**
Informant interview		5.0	
NP test			14
Single tests			
MMSE (only one study is included)			
Clocktest			14.8
ApoE genotype	2.0		
MRI/CT		9.0	
Spect/PET	4.2		
EEG	3.9		
CFS Aß		6.2	
T-tau			
P-tau		9.6	11.8
	LR– (median)		
	<0.1	**0.1–0.2**	**>0.2**
Informant interview		0.20	
NP test		0.18	
Single tests			
MMSE (only one study is included)			
Clocktest		0.12	
ApoE genotype			0.64
MRI/CT		0.21	
Spect/PET		0.18	
EEG			0.25
CFS Aß		0.18	
T-tau		0.10	
P-tau		0.12	

The distribution of likelihood ratios from the different methods evaluated. High LR+ and low LR– indicate high diagnostic ability of the method (test). The LR values represent median values based on studies having variations of constructions of tests (for details, see the method section of each test).

Methodological considerations

One criterion for inclusion was the quality of the methods used in the various studies (design, selection of patients, comprehensiveness of clinical investigation, diagnostic procedure, statistical analysis, representati-

veness and predictor variable). The classification of studies based on the methods used needs comment.

Lack of gold standard

The diagnoses of the different dementia disorders are based on clinical criteria. Definite diagnoses are possible only at histopathology, which should serve as a gold standard. Since histopathology was rarely available in the majority of studies, clinical diagnosis in accordance with specific criteria was used as a surrogate gold standard.

Selection bias

Studies based on homogeneous sampling demonstrated higher LR+ values than studies based on heterogeneous sampling. Given that homogeneous samples are characterized by a smaller standard deviation of the predictor variable than heterogeneous samples, differentiation of patient and control groups is more easily detected. That suggests higher sensitivity and specificity and thereby higher LR+ values. In order to ensure a homogeneous group, the selection procedure has to be more demanding and the clinical investigation more advanced.

Setting

One consequence of the above is the importance of a setting in which the patient is examined and diagnosed: primary care or a highly specialized unit at a university hospital. In primary care, patients are more similar to the general population in terms of background characteristics, whereas a patient at a university hospital is usually highly selected by means of the referral procedure. This difference places varying demands on the diagnostic instruments. In general, there is a lack of studies on health care organization in terms of diagnostic evaluation in dementia, and many of the more advanced methods have not been evaluated in primary care. On the other hand, some of these methods (such as MRI and CSF studies) may not be relevant for introduction on a routine basis in primary care.

Circularity bias

Moreover, many of the studies do not tell us whether the predictor (test) was judged independently of the outcome (workup bias). That could represent a significant problem when evaluating the studies included in the present review. Thus, the results of those studies should be interpreted with caution. Knowledge about predictor results may have influenced the diagnosis and confounded the estimate of sensitivity, specificity and likelihood ratio.

Most studies have been performed in well-characterized groups of patients, defined by clinical criteria. Even with very high sensitivity, specificity, and likelihood ratios, the added clinical value (above a strict clinical evaluation) in the routine clinical setting may not be known. In general, there is a lack of studies designed to address this issue.

Recommendations for future research

In terms of arriving at a conclusive diagnosis in cases of suspected dementia (early diagnosis), we have found evidence for inclusion of a variety of single predictive tests. However, we have little evidence for implementation of a certain combination of tests that might be recommended for the diagnostic workup. Thus, until such evidence has been established, we will have to rely on a number of tests and the diagnostic procedure will continue to be both costly and time-consuming.

Dementia symptoms defined in accordance with the clinical criteria of DSM-IV and ICD-10 provide a synthetic means of understanding dementia diseases. These criteria heavily influence the stage at which dementia diseases can be diagnosed and what diagnostic instruments may be useful, given that the requirement for making a dementia diagnosis is that the syndrome is present. The other problem that needs to be addressed involves the concepts of cognitive impairment and mild cognitive impairment (MCI). There are a variety of definitions of this syndrome, none of which is clear enough to be operational. Impaired memory is not necessarily part of the initial presentation of a dementia

disorder, and MCI is not necessarily a preclinical stage of a dementia disorder. We have to get over this way of thinking and search for biological diagnostic tests that can detect a specific dementia disorder in a very early phase, as well as distinguish dementia from non-progressive condition that cause cognitive impairment. If we cannot do so, we must study cognition in large groups of adults and the elderly in prospective population based studies to devise new definitions of cognitive impairment, MCI and dementia among people of various social classes, as well as cultural and ethnic backgrounds. The same holds true for the clinical criteria of the various dementia diseases, which are not defined well enough by DSM-IV, ICD-10, the American Academy of Neurology or others.

A minority of younger patients with a dementia disorder suffer from a single disease that causes the observed symptoms. For example, post-mortem studies of very old people, for whom the prevalence of dementia is high, have shown cerebrovascular pathology in a majority of those with AD. Thus, the observed symptoms in these patients could be a consequence of AD as well as structural changes due to a cerebrovascular disease. It would appear that existing neuropathological criteria for the various dementia diseases are not gold standards and that they must be improved.

If the goal is to diagnose a dementia disorder in asymptomatic individuals for the purpose of intervening early, biomarkers for AD and other brain diseases that cause dementia are critically needed. Such tests must be validated, and a definite dementia diagnosis requires histopathological verification. Speculating about which diagnostic test(s) will be available in the future is beyond the scope of the present review. We recommend that various lines of development be followed in order to develop tests with better sensitivity and specificity than those currently in use. Thus, new biomarkers at the molecular level should be developed, explored and studied, along with imaging techniques for detection of brain pathology, specific cognitive features and behavioral abnormality, as well as discerning reports by close informants.

References

1. American Psychiatric Association. DSM-IV, Diagnostic and Statistical Manual of Mental Disorders. Washington DC: APA; 1994.

2. World Health Organization. ICD-10, World Health Organization Tenth Revision of the International Classification of Diseases. Geneva: WHO; 1992.

3. Waldemar G, Dubois B, Emre M, Scheltens P, Tariska P, Rossor M. Diagnosis and management of Alzheimer's disease and other disorders associated with dementia. The role of neurologists in Europe. European Federation of Neurological Societies. Eur J Neurol 2000;7:133-44.

4. Practice parameter for diagnosis and evaluation of dementia. (summary statement) Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1994;44:2203-6.

5. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1143-53.

6. Chui H, Zhang Q. Evaluation of dementia: a systematic study of the usefulness of the American Academy of Neurology's practice parameters. Neurology 1997;49:925-35.

7. American Psychiatric Association. DSM-III-R, Diagnostic and statistical manual of mental disorders. Washington DC: APA; 1987.

8. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939-44.

9. Fagan TJ. Letter: Nomogram for Bayes theorem. N Engl J Med 1975; 293:257.

10. **Identifying Secondary Dementia or Potential Reversible Cognitive Impairment**

Thyroid disease and dementia

Background

Hypothyroidism may be associated with the slowing of mental functions, dementia-like symptoms and depression. Hyperthyroidism is associated with anxiety, restlessness and subjective cognitive symptoms, as well as depression and psychosis on occasion. The potential relationship between thyroid disease and dementia is also described in Section III.7.5, "Evidence-based Dementia Practice".

Because hyperthyroidism and hypothyroidism, which are treatable disorders, may be associated with cognitive symptoms and a dementia-like syndrome, laboratory screening with TSH (thyroid stimulating hormone) is generally recommended in guidelines for the diagnostic evaluation of dementia.

Literature search for evidence

In searching the literature, the following three types of evidence for a potential relationship between thyroid disease and dementia were identified as relevant.

- Evidence that clinical or subclinical thyroid disease may be associated with cognitive symptoms, memory loss or dementia.

- Evidence that TSH screening in specific patient groups (the elderly, people with cognitive symptoms or dementia) helps to identify patients with abnormal TSH and/or clinically significant thyroid disease.
- Evidence that the treatment of thyroid disease improves cognitive functions.

Search strategy

"Cognition" [MeSH] OR
"Delirium, Dementia, Amnestic, Cognitive Disorders" [MeSH] OR
"Memory Disorders" [MeSH] OR
"Memory" [MeSH] OR
"Behavioral symptoms" [MeSH]
AND
"thyrotropin/blood" OR [MeSH Terms]
"thyrotropin/analysis" OR [MeSH Terms]
"thyrotropin/deficiency" OR [MeSH Terms]
"thyrotropin/diagnostic use" OR [MeSH Terms]
"thyroid diseases"
Limits: Only papers with abstracts, English language, human.

Results

A total of 172 papers were found. Based on a review of titles and abstracts, 132 papers were excluded, due mainly to irrelevance to the topic or the absence of original research. The remaining 40 papers of potential relevance were reviewed in greater detail. Seventeen were reports of 1 to 7 cases and 6 were reviews. The evidence in the remaining 17 original papers was reviewed and classified together with 1 other report identified from references in the papers (Table 10.1).

Comments

Generally speaking, there is little evidence that hypothyroidism or hyperthyroidism causes dementia, and (for ethical reasons) no placebo-controlled treatment studies have investigated whether treatment can reverse cognitive symptoms. However, both hypothyroidism and hyperthyroidism can cause cognitive and psychiatric symptoms and may thereby mimic a dementia disorder with insidious onset. Untreated thyroid disease leads to other symptoms and risks. Despite the lack of data on dementia, detection of hypothyroidism remains important in patients with dementia in view of its high prevalence in the elderly and its association with depression and psychotic symptoms. Thyroid replacement improves physical symptoms and general well-being. Treatment of co-existing medical problems in patients with dementia may improve both cognition and quality of life. Uncontrolled follow-up studies have shown that, while treatment of the thyroid disease may improve or reverse many symptoms, some patients continue to experience disabling cognitive and psychiatric symptoms. Although detection and management of thyroid failure should be a component of the general medical assessment of any elderly person, the available data indicate that the finding of hypothyroidism in a patient with dementia should not lead to a confident prognosis of improved cognitive function. The same considerations apply to hyperthyroidism.

Thus, even if treatment does not reverse cognitive symptoms, thyroid disorders should be identified and treated.

Table 10.1 *Thyroid disease and dementia.*

Author Year Reference Country	Topic	Hypo- or hyper-thyroidism	Sample (N)	Age mean (years)
Fäldt et al 1996 [1] Sweden	1	Both	$N_P = 173$ $N_c = 0$	79
Wahlin et al 1998 [2] Sweden	1	Both	N = 200	83.9
Bommer et al 1990 [3] Germany	1	Hypothyroidism	$N_p = 45$ $N_c = 51$	45
Kalmijn et al 2000 [4] The Netherlands	1	Both	N = 1 843	68.8
Baldini et al 1997 [5] USA	1+3	Hypothyroidism	$N_{hypo} = 19$ $N_{euthyroid} = 17$	52.9
Osterweil et al 1992 [6] USA	1+3	Hypothyroidism	$N_{hypo} = 54$ $N_{euthyroid} = 30$	68.6 63.7

Population/selection	Setting	Authors' conclusion	Reviewers' comments
Consecutively referred for possible organic brain disease	Psychogeriatric department	High prevalence (25%) of abnormal TSH and/or free thyroid hormones. No significant difference between demented and non-demented	Objective of the study not clear
Selected non-demented individuals from population >75 years	Population based study	In healthy volunteers there is a significant correlation between TSH and episodic memory	Patients with thyroid related disease were excluded
Formerly hyperthyroid patients examined when euthyroid	Hospital based	Remitted hyperthyroidism was associated with cognitive and psychiatric symptoms and with impaired neuropsychological function in 43%	Long-term follow-up needed
Epidemiological population based prospective study	Population based study in Rotterdam	Subclinical hyperthyroidism was associated with an increased risk of dementia and Alzheimer's disease	RR 3.5 for reduced TSH. RR 23.7 for reduced TSH with positive TPO-Abs
Goiter patients with either subclinical hypothyroidism or normal thyroid function	Out-patient endocrinological clinic	Patients with subclinical hypothyroidism had memory deficits which improved on treatment	Only 3 months follow-up. No psychiatric symptoms
Referred patients without dementia, selected controls	Endocrine and geriatric services	Hypothyroidism is associated with impaired learning, word fluency, visual-spatial abilities etc and lower MMSE. Treatment was associated with improvements in the cognitive tests	Treatment study uncontrolled for ethical reasons

The table continues on the next page

***Table 10.1** continued*

Author Year Reference Country	Topic	Hypo- or hyper-thyroidism	Sample (N)	Age mean (years)
Yoshimasu et al 1991 [7] Study A USA	1	Hashimoto's thyroiditis	N = 198	NA
Yoshimasu et al 1991 [8] Study B USA	2	Both	N_{AD} = 646 N_c = 646	NA
Bahemuka et al 1975 [9] United Kingdom	2	Hypothyroidism	N = 2 000	80
Luboshitzky et al 1996 [10] Israel	2	Hypothyroidism	N_p = 751	76.4
Schlote et al 1992 [11] Germany	2	Hyperthyroidism	$N_{subclinical}$ = 35 $N_{manifest}$ = 60 $N_{euthyroid}$ = 60	NA
Ganguli et al 1996 [12] USA	2	Hypothyroidism	N_{TOTAL} = 194 N_{CDR0} = 122 $N_{CDR0.5}$ = 29 $N_{CDR>1}$ = 43	78.6

Population/selection	Setting	Authors' conclusion	Reviewers' comments
All patients with tissue proven HT who had follow-up – retrospective review of medical records	Hospital based	Patients with thyroid disease did not have an significantly increased risk for developing AD (8 vs 5.3 expected)	Prospective study with systematic description of mental functions and dementia would be needed
Retrospective case-control comparison	Hospital based	OR 0.45 for Grave's disease – protective association? No significant relation with other disorders	Problem with underreporting of previous diseases in AD patients not accounted for
Consecutive referrals, all patients >60	Geriatric department	46 cases (2.3%) had hypothyroidism, 13 with classical symptoms and 23 with unspecific or psychiatric symptoms	Large sample. Symptoms described from medical records only
All patients above 65 years in 9 kibbutzim. Review of medical files	Population based study – primary health care	Elevated TSH in 14% of the elderly. Mild untreated hypothyroidism was not associated with cognitive deficits	Cognitive function measured with MMSE only. Patients not stratified for occurrence of dementia
Inpatients or outpatients referred during a certain time period	Hospital	Subclinical thyroid disease was associated with psychiatric symptoms but not cognitive deficits	Selection of euthyroid controls not well described, consecutive referrals? Age not reported
First 194 patients evaluated for possible dementia a large population	Community-based population study >65 years	Elevated TSH was significantly associated with dementia. Elevated/low TSH was found in 14.4%/ 5.2% of all patients	Low TSH was not associated with dementia

The table continues on the next page

Table 10.1 *continued*

Author Year Reference Country	Topic	Hypo- or hyper-thyroidism	Sample (N)	Age mean (years)
Heyman et al 1984 [13] USA	2	Both	N_{AD} = 40 N_C = 80	NA
Lopez et al 1989 [14] USA	2	Both	N_{AD} = 31 N_C = 31	72.3 72.7
Tappy et al 1987 [15] Switzerland	2	Both	$N_{psychog}$ = 157 $N_{csurgical}$ = 194	80.1 80.9
Small et al 1985 [16] USA	2	Both	N_{AD} = 61 N_C = 38	71.7 73.6
Fox et al 1975 [17] USA	2	Both	N = 40	75

Population/selection	Setting	Authors' conclusion	Reviewers' comments
Case-control study in patients with Alzheimer's disease and in community controls	University hospital	Higher frequency of prior thyroid disease in women patients (25%) than in controls	Age not reported. Selection of controls not well described. Type of thyroid disorder not well described
Retrospective record review of patients with neuropathological diagnosis of AD and non-demented controls	University hospital longitudinal study on dementia	No relation between AD and thyroid disease	High frequency of thyroid disease. Retrospective study. Uncertain selection of controls
Consecutive referrals (controls were non-consecutive)	Psychogeriatric department (vs surgical dept)	6 hypothyroid patients in psychogeriatric group (all had dementia or neurotic depression) and 2 in surgical group. 1 patient had hyperthyroidism	
Recruited from project	University hospital	No significant difference between patients and controls for prior thyroid disease (13%), history of thyroid medication (16%) or abnormal T4 (13%)	Small sample
Consecutive referrals where a diagnosis of senile dementia was made – with the aim to study reversible dementia	Neurological dept, university hospital	2 patients with hypo-thyroidism were identi-fied, both improved	Senile dementia syndrome not clearly defined

The table continues on the next page

Table 10.1 *continued*

Author Year Reference Country	Topic	Hypo- or hyper-thyroidism	Sample (N)	Age mean (years)
Genovesi et al 1996 [18] Italy	2	Antithyroid antibodies	N_{AD} = 34 N_c = 30	65.2
Clarfield 1988 [19] Canada	2+3	Hypothyroidism	2 781	NA

Topic 1: Evidence that clinical or subclinical thyroid disease may be associated with cognitive symptoms, memory loss, or dementia.
Topic 2: Evidence that TSH screening in patient groups (elderly patients, patients with cognitive symptoms or dementia) leads to identification of patients with abnormal TSH and/or clinical significant thyroid disease.
Topic 3: Evidence that treatment of thyroid disease improves cognitive functions.

AD = Alzheimer's disease; MCSAb = Antimicrosomial autoantibodies; MMSE = Mini-mental state examination; NA = Not applicable; Nc = Number of controls; Np = Number of psychogeriatric patients; OR = Odds ratio; RR = Relative risk; T4 = Thyroxine; TgAb = Thyroidea globulin antibodies (Antithyreoglobulin); Tpo-Abs = Antibodies to thyroid peroxidase; TSH = Thyroid stimulating hormone

Population/selection	Setting	Authors' conclusion	Reviewers' comments
Selection of patients and controls not reported	Hospital	Significant increase in TgAb and MCSAb	Presence of clinical thyroid disease in the two groups not described
Meta-analysis of cases from studies of etiology in dementia	Hospital settings	18 cases reported as dementia due to hypothyroidism (1 was reversible)	Different criteria for dementia and for reversibility in the various studies

References

1. Faldt R, Passant U, Nilsson K, Wattmo C, Gustafson L. Prevalence of thyroid hormone abnormalities in elderly patients with symptoms of organic brain disease. Aging (Milano) 1996;8:347-53.

2. Wahlin A, Wahlin TB, Small BJ, Backman L. Influences of thyroid stimulating hormone on cognitive functioning in very old age. J Gerontol B Psychol Sci Soc Sci 1998;53:P234-9.

3. Bommer M, Eversmann T, Pickardt R, Leonhardt A, Naber D. Psychopathological and neuropsychological symptoms in patients with subclinical and remitted hyperthyroidism. Klin Wochenschr 1990;68:552-8.

4. Kalmijn S, Mehta KM, Pols HA, Hofman A, Drexhage HA, Breteler MM. Subclinical hyperthyroidism and the risk of dementia. The Rotterdam study. Clin Endocrinol (Oxf) 2000;53:733-7.

5. Baldini IM, Vita A, Mauri MC, Amodei V, Carrisi M, Bravin S, et al. Psychopathological and cognitive features in subclinical hypothyroidism. Prog Neuropsychopharmacol Biol Psychiatry 1997;21:925-35.

6. Osterweil D, Syndulko K, Cohen SN, Pettler-Jennings PD, Hershman JM, Cummings JL, et al. Cognitive function in non-demented older adults with hypothyroidism. J Am Geriatr Soc 1992; 40:325-35.

7. Yoshimasu F, Kokmen E, Hay ID, Beard CM, Offord KP, Kurland LT. Study A: The association between Alzheimer's disease and thyroid disease in Rochester, Minnesota. Neurology 1991;41:1745-7.

8. Yoshimasu. Study B. 1991 (see [7]).

9. Bahemuka M, Hodkinson HM. Screening for hypothyroidism in elderly inpatients. BMJ 1975;2:601-3.

10. Luboshitzky R, Oberman AS, Kaufman N, Reichman N, Flatau E. Prevalence of cognitive dysfunction and hypothyroidism in an elderly community population. Isr J Med Sci 1996;32:60-5.

11. Schlote B, Nowotny B, Schaaf L, Kleinbohl D, Schmidt R, Teuber J, et al. Subclinical hyperthyroidism: physical and mental state of patients. Eur Arch Psychiatry Clin Neurosci 1992;241: 357-64.

12. Ganguli M, Burmeister LA, Seaberg EC, Belle S, DeKosky ST. Association between dementia and elevated TSH: a community-based study. Biol Psychiatry 1996;40:714-25.

13. Heyman A, Wilkinson WE, Stafford JA, Helms MJ, Sigmon AH, Weinberg T. Alzheimer's disease: a study of epidemiological aspects. Ann Neurol 1984; 15:335-41.

14. Lopez O, Huff FJ, Martinez AJ, Bedetti CD. Prevalence of thyroid abnormalities is not increased in Alzheimer's disease. Neurobiol Aging 1989;10:247-51.

15. Tappy L, Randin JP, Schwed P, Wertheimer J, Lemarchand-Beraud T. Prevalence of thyroid disorders in psycho-

geriatric inpatients. A possible relationship of hypothyroidism with neurotic depression but not with dementia. J Am Geriatr Soc 1987;35:526-31.

16. Small GW, Matsuyama SS, Komanduri R, Kumar V, Jarvik LF. Thyroid disease in patients with dementia of the Alzheimer type. J Am Geriatr Soc 1985;33:538-9.

17. Fox JH, Topel JL, Huckman MS. Dementia in the elderly – a search for treatable illnesses. J Gerontol 1975;30: 557-64.

18. Genovesi G, Paolini P, Marcellini L, Vernillo E, Salvati G, Polidori G, et al. Relationship between autoimmune thyroid disease Rand Alzheimer's disease. Panminerva Med 1996;38:61-3.

19. Clarfield AM. The reversible dementias: do they reverse? Ann Intern Med 1988;109:476-86.

11. **Neurosyphilis and Dementia**

Background

The introduction of antibiotics led not only to appropriate treatment of patients with primary syphilis, but to the incidental treatment of unidentified syphilis in patients treated for other infections. The incidence of neurosyphilis has fallen dramatically since then. Clinicians have become unfamiliar with the diversity of presentations, and neurosyphilis continues to appear in various guises at many different hospital departments. In patients with untreated asymptomatic neurosyphilis, the overall cumulative probability of progression to clinical neurosyphilis is about 20% in the first 10 years but increases with time.

Although mixed features are common, the major clinical categories of symptomatic neurosyphilis are meningeal, meningovascular, and parenchymatous syphilis. The last category includes general paresis and tabes dorsalis. However, symptomatic neurosyphilis often presents not according to a classic concept, but as mixed and subtle or incomplete syndromes.

Patients with meningeal syphilis may present with headache, nausea, vomiting, neck stiffness, cranial nerve palsies, seizures and changes in mental status. Patients with meningovascular syphilis may present with a stroke syndrome. However, unlike the usual thrombotic or embolic stroke syndrome of sudden onset, meningovascular syphilis often manifests after a subacute encephalitic prodrome, followed by a progressive vascular syndrome. The manifestations of general paresis include abnormalities corresponding to the mnemonic paresis: **p**ersonality, **a**ffect, **r**eflexes (hyperactive), **e**ye (such as Argyll Robertson pupils), **s**ensorium (illusions, delusions, hallucinations), **i**ntellect (deterioration of short-term memory and the capacity for orientation, calculations, judgment and

insight) and **s**peech. Tabes dorsalis presents as ataxic wide-based gait and foot slap, paresthesia, bladder disturbances, impotence and areflexia, as well as loss of position, deep pain and temperature sensations.

Literature search for evidence

In searching the literature, the following three types of evidence for the potential relationship between thyroid disease and dementia were identified as relevant

- Evidence that neurosyphilis may be associated with cognitive symptoms, memory loss, behavioral symptoms or dementia.
- Evidence that laboratory screening in specific groups (elderly patients, patients with cognitive symptoms or patients with dementia) helps identify people with neurosyphilis.
- Evidence that the treatment of neurosyphilis improves cognitive functions.

Search strategy

"Cognition" [MeSH] OR
"Delirium, Dementia, Amnestic, Cognitive Disorders" [MESH] OR
"Memory Disorders" [MeSH] OR
"Memory" [MeSH] OR
"Behavioral symptoms" [MeSH] OR
"Dementia" [MeSH Terms]
AND
"Syphilis" [MeSH] OR
"Syphilis Serodiagnosis" [MeSH]
Limits: Only papers with abstracts, English language, human.

Result

Fiftytwo papers were found. Based on a review of titles and abstract, 27 papers were excluded, mainly due to irrelevance to the topic. The remaining 25 papers of potential relevance were reviewed in more detail. Twelve were reports of 1 to 10 cases and 3 were reviews or letters of correspondence. The evidence in the remaining 10 original papers was reviewed and categorized (Table 11.1).

Comments

Many case reports and reports on cohorts of patients with neurosyphilis confirm an association of neurosyphilis with cognitive and psychiatric symptoms, including a wide variety of presentations from one case to the other. There are no population based studies – and only a few hospital-based studies in patients referred for cognitive symptoms, neurological patients or psychiatric patients – from which the outcome of screening can be determined in terms of identifying neurosyphilis. In those studies, 3–11% of elderly patients, as well as patients referred for evaluation of possible dementia, have positive serology. However, neurosyphilis was identified in less than 1% of patients referred for possible dementia. In the largest study, which included 672 referred patients – of whom 402 had lumbar puncture – 3% had positive serology, but only 1 patient (0.15%) was identified with neurosyphilis. However, none of them were systematic prospective studies. For ethical reasons, no randomized controlled trials have been conducted to confirm the effectiveness of treatment for cognitive symptoms. In case reports and two uncontrolled follow-up studies, treatment was followed by improvements in mental and psychiatric symptoms, although the condition may not have been reversed entirely.

In conclusion, neurosyphilis should be identified and treated, and awareness of the many different and subtle presentations is important. Because of the lack of sufficiently high quality studies, it is not possible to draw any firm conclusions as to the outcome of screening for neurosyphilis in populations with cognitive symptoms.

Table 11.1 *Neurosyhpilis and dementia.*

Author Year Reference Country	Topic	Sample (N)	Age mean (years)	Population/selection
Nordenbo et al 1981 [1] Denmark	1	N = 23	48.8	Hospital records
Russouw et al 1997 [2] South Africa	1	N_{NS} = 20 N_C = 20	36.9	Consecutive referrals with psychiatric symptoms
Roberts et al 1995 [3] South Africa	1+3	N = 19	38	Consecutive referrals. Prospective, longitudinal 12 months follow-up
Rodgers et al 1997 [4] United Kingdom	1	N = 172	50	Retrospective case note review of patients with positive serology
Rao 1954 [5] India	1+3	N = 34	NA	First admissions with general paresis
Boodhoo 1989 [6] United Kingdom	2	N = 800	NA	Patients >65, medical records
Powell et al 1993 [7] USA	2	N = 376	74	Retrospective study in patients with dementia
Freemon 1976 [8] USA	2+3	N = 60	66.2	Consecutive referrals for intellectual deterioration – searching for reversible causes

Setting	Authors' conclusion	Reviewers' comments
Hospital departments (neurology, dermatovenereology, neurosurgery)	Incidence was 0.3 per 100 000 per year. General paresis and meningovascular syphilis most common forms	History of venereal infection in only 50%
General hospital	Patients had dementia, delirium major depression, hallucinations, mania or schizophrenic symptoms	Main aim of the study was MRI findings in neurosyphilis
Psychiatric inpatients	Median change in MMSE was +4 and in BPRS –8 at 12 months (not significant)	Small sample size and poor follow-up rate
Hospital based. Dept of Genioto-urinary Medicine	10 patients diagnosed with neurosyphilis	
Hospital setting	Many had mental/ psychiatric symptoms. Improvement after treatment	Insufficient follow-up. Uncontrolled treatment study
Psychiatric and medical hospital patients	21 (2.6%) had positive serology	
Neurological patients	Positive serology in 37 (10.9%), unlikely that syphilis caused dementia	
Hospital setting	1 patient had neurosyphilis	No change in cerebral function after treatment

The table continues on the next page

***Table 11.1** continued*

Author Year Reference Country	Topic	Sample (N)	Age mean (years)	Population/selection
Hammerstrom et al 1985 [9] USA	2	N = 80	NA	All patients >55 years with presumed dementia. Retrospective review of medical records
Becker et al 1985 [10] USA	2	N = 672 N_{CSF} = 402	66	Retrospective chart review of all patients referred for evaluation of dementia

Topic 1: Evidence that neurosyphilis may be associated with cognitive symptoms, memory loss, behavioral symptoms or dementia.
Topic 2: Evidence that laboratory screening in patient groups (elderly patients, patients with cognitive symptoms or dementia) leads to identification of patients with neurosyphilis.
Topic 3: Evidence that treatment of neurosyphilis improves cognitive functions.

BPRS = Brief psychiatric rating scale; C = Control; CSF = Cerebrospinal fluid; MMSE = Mini-mental state examination; MRI = Magnetic resonance imaging; NC = Normal controls

	Setting	Authors' conclusion	Reviewers' comments
	Psychiatric department	42% had lumbar puncture – no cases of neurosyphilis were detected	Small sample size
	University hospital. Neurology, general medicine and psychiatry	21 patients with abnormal serology, including 1 with neurosyphilis (an already known diagnosis)	

References

1. Nordenbo AM, Sorensen PS. The incidence and clinical presentation of neurosyphilis in Greater Copenhagen 1974 through 1978. Acta Neurol Scand 1981;63:237-46.

2. Russouw HG, Roberts MC, Emsley RA, Truter R. Psychiatric manifestations and magnetic resonance imaging in HIV-negative neurosyphilis. Biol Psychiatry 1997;41:467-73.

3. Roberts MC, Emsley RA. Cognitive change after treatment for neurosyphilis. Correlation with CSF laboratory measures. Gen Hosp Psychiatry 1995;17:305-9.

4. Rodgers CA, Murphy S. Diagnosis of neurosyphilis: appraisal of clinical caseload. Genitourin Med 1997;73: 528-32.

5. Rao S. Neurosyphilis; the common types in Hyderabad. J Indian med Assoc 1954;24:48-51.

6. Boodhoo JA. Syphilis serology screening in a psychogeriatric population. Is the effort worthwhile? Br J Psychiatry 1989;155:259-62.

7. Powell AL, Coyne AC, Jen L. A retrospective study of syphilis seropositivity in a cohort of demented patients. Alzheimer Dis Assoc Disord 1993;7:33-8.

8. Freemon FR. Evaluation of patients with progressive intellectual deterioration. Arch Neurol 1976;33:658-9.

9. Hammerstrom DC, Zimmer B. The role of lumbar puncture in the evaluation of dementia: the University of Pittsburgh Study. J Am Geriatr Soc 1985;33:397-400.

10. Becker PM, Feussner JR, Mulrow CD, Williams BC, Vokaty KA. The role of lumbar puncture in the evaluation of dementia: the Durham Veterans Administration/ Duke University Study. J Am Geriatr Soc 1985;33:392-6.

12. **Vitamin B_{12}, Folic Acid and Homocysteine, Cognitive Impairment and Alzheimer's Disease**

Conclusions

There is no evidence of a relationship between marginally low vitamin B_{12} concentrations in the blood and cognitive impairment or AD (Alzheimer's disease).

There is moderately strong evidence of an association between low levels of folic acid and cognitive impairment, and limited evidence of an association between low levels of folate and AD.

There is strong evidence of an association between elevated homocysteine levels in the blood and poor cognitive function, and moderately strong evidence for an association between elevated homocysteine levels and AD.

No evidence exists that treatment with vitamin B_{12} or folate improves cognitive function in patients with cognitive impairment or dementia who have either low concentrations of vitamin B_{12} or folic acid or high levels of homocysteine.

Background

Vitamin B_{12} deficiency has been considered for decades to cause cognitive impairment or potential reversible dementia due to demyelination processes in the brain. An association has also been found between folate deficiency and cognitive impairment, but the extent to which it is cause

or effect is not yet clear. Low intake of folate could be a consequence of mental dysfunction. Two evidenced-based reports have found that the relationship between vitamin B_{12} and folic acid deficiencies and dementia is inconclusive [1,2].

Several studies in the last ten years have reported high levels of homocysteine in the blood of people with cognitive impairment and dementia. It has been suggested that homocysteine can be neurotoxic, but the possible mechanism involved is far from being established.

Literature search strategy

In searching for evidence of an association between cognitive impairment or dementia and vitamin B_{12} or folic acid deficiencies, or high levels of homocysteine in the blood, papers were searched for that could answer the following three questions:

1. What is the evidence of an association between low concentrations of vitamin B_{12} or folic acid, or high levels of homocysteine, in the blood and cognitive impairment in the elderly?

2. What is the evidence of an association between low concentrations of vitamin B_{12} or folic acid, or high levels of homocysteine, in the blood and AD?

3. What is the evidence that treatment with vitamin B_{12} or folate can improve cognitive impairment or reverse dementia?

Searches were conducted in Medline among papers published up until June 1, 2004. The keywords were "dementia or cognitive impairment or cognition" and "cobalamin or vitamin B_{12}, or vitamin B_{12} deficiency or folic acid or folic acid deficiency or homocysteine or elevated homocysteine". Only papers written in English were requested. Additionally, a thorough review of Chapters III.7.6 and III.7.7 in "Evidence-based Dementia Practice" [2], and report results from the Cochrane Library was undertaken. Only original papers were included, neither those reporting meta-analysis or review articles nor case reports.

Threehundredthirty titles were found, while a review of the abstracts indicated that 91 were relevant to answering the three questions. For various reasons 44 were excluded, such as insufficient description of clinical assessment, inadequate use of standardized diagnosis, reporting less than 20 + 20 subjects, lack of relevance to the three questions or the fact that they were case reports or review papers.

Many of the studies reported levels of vitamin B_{12}, folate, and homocysteine in the blood of the same people. Thus, information for two or all three markers can be found in the same paper. Table 12.1 shows the main findings from 16 population based studies of the elderly that analyzed the association between vitamin B_{12} or folic acid concentrations, or homocysteine levels, in the blood and cognitive function. Ten studies reported on cross-sectional data, whereas six contained data from longitudinal studies. Nine studies reported results on Vitamin B_{12}, 10 on folate and 13 on homocysteine levels.

Table 12.2 shows the results from 25 studies that reported on the association between vitamin B_{12}, folic acid or homocysteine levels in the blood and AD. Four were population based and 21 were patient-based. Eighteen examined the relationship between vitamin B_{12} and AD, 5 examined folate and AD, and 16 provided information about homocysteine levels in the blood of AD patients as compared to controls.

The search for drugs trials revealed one unblinded placebo-controlled study by Kwok et al that included 50 patients [3]. Two double-blind placebo controlled studies were included, one by Fioravanti et al [4] with 30 patients (exception from the rule of only reviewing papers with at least 40 patients) and the VITAL study [5], which included 147 patients (Table 12.3). The studies by Sommer et al and van Asselt et al included fewer than 20 patients and were thereby excluded from this review [6,7]. The study by Seal et al [8] and Bryan et al [9] were not included due to lack of information about either dementia diagnosis or mild cognitive impairment.

Comments

Vitamin B_{12}

Three of the nine studies on vitamin B_{12} reported an association between marginally low levels of vitamin B_{12} and poor cognitive function. None of the three that correlated positively were of type 1a or 2a study quality. Eight of 18 studies reported an association between low levels of vitamin B_{12} and AD. One of the eight was a type 1a/2a study.

Folic acid

Six of 10 studies reported an association between low levels of folate and poor cognitive function, and four of the six positive studies were either type 1a or 2a. In three of five studies, low levels of folate in the blood was associated with AD, but only one of the three was a type 1a/2a study.

Homocysteine

Eleven of 13 studies reported an association between high levels of homocystein in the blood and cognitive impairment, while 7 of the 11 were type 1a or 2a studies. Fifteen out of 16 studies showed an association between high levels of homocysteine and AD, but only 1 of the 15 was a type 1a/2a study.

Treatment with vitamin B_{12} or folate

None of the three treatment studies demonstrated that treatment with vitamin B_{12} or folate improved cognition in people with cognitive impairment or dementia. Only one of the double-blind random controlled trials included more than 20 + 20 patients.

Table 12.1 *Studies of the relationships between low level of vitamin B_{12}, folate acid or raised level of homocysteine and cognitive impairment.*

Author Year Reference Country	Sample	Age (years)	Blood measure
Goodwin et al 1983 [10] USA	260	60+	Vitamin B_{12} Folate
Riggs et al 1996 [11] USA	70	54–81	Vitamin B_{12} Folate Hct
Kalmijn et al 1999 [12] The Netherlands	702	55+	Hct
Lindeman et al 2000 [13] USA	199	60+	Vitamin B_{12} Folate
Budge et al 2000 [14] United Kingdom	156	60–91	Hct
Robins Wahlin et al 2001 [15] Sweden	230	75–96	Vitamin B_{12} Folate
McCaddon et al 2001 [16] United Kingdom	32	65+	Vitamin B_{12} Folate Hct
Morris et al 2001 [17] USA	1 227	60+	Vitamin B_{12} Folate Hct

Main results	Quality of study
Low levels of folate in blood was significantly associated with poorer cognitive performance, also after controlling for age, gender, education and level of income	1b
Lower concentration of B_{12}, folate, and higher concentration of Hct were associated with poorer spatial copying skills	2b
No association was found between high levels of Hct and cognitive impairment after 2.7 years	1a
Low level of folate was significantly associated with various meausures of poor cognitive performance, even after adjustment for presence of depression	1a
CAMCOG scores after 3 years follow-up were related to Hct independently of age, gender, mood and IQ	1b
Low levels of folate and B_{12} were significantly associated with poorer results measuring fast and accurate novel information	2a
Hct predicted development of cognitive decline at 5 years follow-up, measured by MMSE word recall, orientation and spatial copying skills	1b
Raised Hct and lowered folate was significantly associated with poor recall, and the association between hyperhomocysteinemi and poor recall was partly idenpendently offolate status	1a

The table continues on the next page

***Table 12.1** continued*

Author Year Reference Country	Sample	Age (years)	Blood measure
Stewart et al 2002 [18] United Kingdom	248	55–75	Folate Hct
Prins et al 2002 [19] The Netherlands	1 077	55+	Hct
Duthie et al 2002 [20] Scotland	183 148	75+ 60+	Vitamin B_{12} Folate Hct
Dufouil et al 2003 [21] France	1 241	61–73	Hct
Ravaglia et al 2003 [22] Italy	650	65+	Vitamin B_{12} Folate Hct
Miller et al 2003 [23] USA	1 789	60+	Hct
Sachdev et al 2004 [24] Australia	385	60–64	Hct
Teunissen et al 2003 [25] The Netherlands	144	30+	Vitamin B_{12} Folate Hct

CAMCOG = Cambridge cognitive examination; Hct = Homocysteine;
MMSE = Mini-mental state examination

Main results	Quality of study
Raised Hct was associated with cognitive impairment, but modified by educational level, not by vascular factors	2a
Elevated Hct was associated with cognitive impairment, most markedly for motor speed	2a
Elevated Hct and low B_{12} was associated with development of cognitive decline	1b
Elevated Hct was associated with cognitive impairment as measured by a variety of cognitive tests. The odds for developing cognitive decline after 4 years was 2.8 for the people with the highest level of homocysteine	1a
Elevated Hct was associated with cognitive impairment as measured with MMSE. The association was graded and independently of age, medical condition and lifestyle factors	2a
A modest inverse association between Hct and a variety of cognitive tests, including MMSE was found ($p<0.05$)	1a
Hct level in blood was significantly associated to verbal memory and motor speed. After correction for levels of folate, vitamin B_{12}, creatinine and life-stile factors the association disappeared	1a
Hct level in blood was significantly associated with cognitive impairment at baseline, and during 6 years follow-up. Folate was significantly associated with delay recall test, whereas vitamin B_{12} levels in blood was not associated with cognitive impairment	1a

Table 12.2 *Studies of the relationship between low levels of vitamin B_{12} or folate, or raised homocysteine in blood and Alzheimer's disease (AD).*

Author Year Reference Country	**Sample**	**Age (years)**	**Blood measure**
Cole et al 1984 [26] Canada	AD = 20 OD = 20 Co = 20	65+	B_{12} <150
Levitt et al 1992 [27] Canada	AD = 40 CIND = 26 OD = 31	68 72 71	B_{12} ≤140
Regland et al 1992 [28] Sweden	De = 102 Co = 32	66	B_{12}, no cutpoint
Kristensen et al 1993 [29] Denmark	AD = 26 OD = 24 Co = 20	73 59 73	B_{12} <135 MMA >0.9
Basun et al 1994 [30] Sweden	De = 153 AD = 93 Co = 392	75+	B_{12} <150
Crystal et al 1994 [31] USA	De = 61 Co = 349	75–85	B_{12} <150
Nilsson et al 1996 [32] Sweden	De = 295 Co = 215	77 76	B_{12} <110 Hct >15

Clinical criteria	Main results	Quality of study
Roth/Hanchinski	6 of 20 AD patients had low level of B_{12} values compared to one of 40 without AD	2b
DSM-III-R NINCDS-ADRDA	B_{12} was significantly associated to MMSE score in AD patients, but not in the other groups	2b
DSM-III-R	B_{12} differed significantly across groups (AD, VaD, OD, controls)	2b
DSM-III NINCDS-ADRDA	7 of 26 AD patients had elevated MMA or low level of B_{12}, compared to 4 of 69 without AD	2b
DSM-III-R	No differences were found between patients with AD, demented and controls regarding B_{12}. Those living at home had significantly lower level of B_{12} compared to the patients in nursing homes	1a
DSM-III-R NINCDS-ADRDA	During 5 years follow-up the incidence of AD in patients with low levels of B_{12} was 4.5%, compared to 7.5% in patients with high level of B_{12}	1b
DSM-III-R	Hct was significantly associated with all forms of dementia. Patients with VaD or dementia with CVD had the highest levels, and the control subjects the lowest	2b

The table continues on the next page

***Table 12.2** continued*

Author Year Reference Country	Sample	Age (years)	Blood measure
Joosten et al 1997 [33] Belgium	AD = 52 Co = 50 Co = 80	83 81 80	B_{12} <139 Hct >13.9 MMA >247
Nagga et al 1998 [34] Sweden	AD = 44 VaD = 78 OD = 28 Co = 42	78 80 79 79	B_{12} <135
Clarke et al 1998 [35] United Kingdom	AD = 164 Co = 108	73	B_{12}, Hct, folate, no cutpoint
McCaddon et al 1998 [36] United Kingdom	AD = 30 Co = 30	79	Hct, no cutpoint
Lehmann et al 1999 [37] Sweden	AD = 64 VaD = 66 CIND = 108 Co = 69	64–76 77 72	B_{12} <150 Hct >15
Wang et al 2001 [38] Sweden	AD = 60 Co = 310	75+	B_{12} <150 Folate ≤10
Tripathi et al 2001 [39] Italy	AD = 38 VaD = 36 OD = 26	62 60 58	B_{12} <157
Postiglione et al 2001 [40] Italy	AD = 74 Co = 74	69	B_{12}, Hct, no cutpoint defined

Clinical criteria	Main results	Quality of study
DSM-III-R NINCDS-ADRDA	Hct was significantly higher in AD patients compared to non-demented elderly. MMA was higher in AD patients compared to in institutions	2b
DSM-IV	No differences were found between AD, VaD and OD patients and elderly no-demented regarding B_{12} level in blood	2b
NINCDS-ADRDA CERAD (path) in 76	AD patients with a clinical or pathological diagnosis had significantly lower levels of B_{12} and folate and higher levels of Hct than the controls	IIb 2b
DSM-III-R	Hct was significantly higher in AD patients compared to controls, independently of nutritional status	2b
NINCDS-ADRDA NINDS-AIREN	Hct was elevated in patients with AD and CIND, and correlated inversely with cognitive performance	2b
DSM-IV	Low level of B_{12} and folate was significantly associated with development of AD after 3 years	1a
DSM-IV NINCDS-ADRDA	The prevalence of low level of B_{12} was significantly higher in AD patients (39.5%), compared with VaD (13.9%), and OD (11.5%)	2b
NINCDS-ADRDA	Hct was significantly higher and B_{12} and folate lower in AD patients compared to controls. The differences disappeared when controlling for age, creatinine and duration of dementia	2b

The table continues on the next page

***Table 12.2** continued*

Author Year Reference Country	Sample	Age (years)	Blood measure
Seshadri et al 2002 [41] USA	De = 111 AD = 83 Co = 981	76	Hct >14
McIlroy et al 2002 [42] United Kingdom	AD = 83 VaD = 78 Co = 71 Stroke = 64	77	Hct, no cutpoint defined
Miller et al 2002 [43] USA	AD = 43 Co = 37	78	Hct >12 PLP <25
Nilsson et al 2002 [44] Sweden	De = 203 Co = 62	77 72	B_{12} <150 Hct >19.9
Selley 2003 [45] Australia	AD = 25 Co = 25	76 75	Hct, no cutpoint defined
Religa et al 2003 [46] Poland	AD = 99 MCI = 98 Co = 100	74 71 71	B_{12}, Hct, folate, no cutpoint defined
Nagga et al 2003 [47] Sweden	AD = 47 VaD = 59 Co = 101	75 78 69	B_{12} <200, folate <75 Hct >18, MMA >0.37
Mizrahi et al 2003 [48] USA	AD = 64 Co = 64	74	Hct, no cutpoint defined

Clinical criteria	Main results	Quality of study
DSM-IV NINCDS-ADRDA	Hct >14 nearly doubled the risk for developing AD during follow-up of 8 years (OR 1.8)	1a
NINCDS-ADRDA NINDS-AIREN	Hct was elevated significantly in AD, VaD and stroke patients compared to normal controls, also after adjusting for vascular factors, nutrition and creatinine	2b
NINCDS-ADRDA	High levels of Hct and low levels of PLP (indicator of vitamin B_6 deficiency) was significantly associated with AD	2b
DSM-III-R	Hct was significantly higher in patients with VaD and mixed AD/VaD compared to controls	2b
NINCDS-ADRDA DSM-IV	Hct was elevated significantly in AD patients compared to control people	2b
NINCDS-ADRDA DSM-IV	Hct was elevated significantly in AD patients compared to MCI patients and normal controls, and depended on the MTHFR T/T genotype in the presence of low folate levels	2b
ICD-10	Hct was significantly higher in the AD and VaD group compared to the controls. MMA was significantly higher in VaD patients compared to controls	2b
NINCDS-ADRDA	Hct did not differ significantly between AD patients and controls	2b

The table continues on the next page

***Table 12.2** continued*

Author Year Reference Country	Sample	Age (years)	Blood measure
Quadri et al 2004 [49] Switzerland	AD = 74 MCI = 81 Co = 55	79 76 76	B_{12}, folate, Hct, Hct >14.6
Nilsson et al 2004 [50] Sweden	AD = 159 Co = 59	76 75	Hct, no cutpoint defined

AD = Alzheimer's disease; B_{12} = Vitamin B_{12}; CDR = Clinical dementia rating scale; CIND = Cognitive impairment, no dementia; Co = Non-demented controls; CVD = Cerebrovascular disease; De = Dementia; Hct = Homocysteine; MCI = Mild cognitive impairment; MMA = Methtyl malonic acid; MMSE = Mini-mental state examination; OD = Other dementias; PLP = Indicator of vitamin B_6 deficiency; VaD = Vascular dementia

Clinical criteria	Main results	Quality of study
NINCDS-ADRDA	Hct was significantly higher in AD patients compared to controls, whereas folate was significantly lower in AD and MCI (CDR 0.5) patients	2b
NINCDS-ADRDA	Hct was significantly higher in AD patients with and without cardiovascular disease compared to controls, after adjustment for creatinine levels	2b

Table 12.3 *Treatment with vitamin B_{12} or folate in patients with cognitive impairment or dementia.*

Author Year Reference Country	**Design**	**Sample**	**Clinical criteria**
Fioravanti et al 1997 [4] Italy	DB-RCT	N = 30	MMSE <20 ads staging
Kwok et al 1998 [3] Hong Kong	NB-RCT	N = 50	MMSE <20
Clarke et al 2003 [5] United Kingdom	DB-RCT 2x2x2 factorial design	N = 147 AD = 84 OD = 12 MCI = 51	DSM-IV

AD = Alzheimer's disease; DB = Double blind; MCI = Mild cognitive impairment; MMSE = Mini-mental state examination; NB = Not blinded; OD = Other dementias; RCT = Randomized controlled trial

Treatment	Main results
Folate for 2 months	No effects as measured by a variety of cognitive tests
B_{12} for 6 months	No effects as measured by MMSE and a variety of cognitive tests
B_{12} and folate for 12 weeks	No effects as measured by MMSE and other tests

References

1. Knopman DS, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1143-53.

2. Wahlund LO, Basun H, Waldemar G. Reversible or arrestable dementias, in Evidence-based dementia practice. Editors. 2002, Blackwell Science: Oxford. p 330-40.

3. Kwok T, et al. Randomized trial of the effect of supplementation on the cognitive function of older people with subnormal cobalamin levels. Int J Geriatr Psychiatry 1998;13:611-6.

4. Fioravanti M, et al. Low folate levels in the cognitive decline of elderly patients and efficacy of folate as a treatment for improving memory deficits. Arch Gerontol Geriatr 1997;26:1-13.

5. Clarke R, Harrison G, Richards S. Effect of vitamins and aspirin on markers of platelet activation, oxidative stress and homocysteine in people at high risk of dementia. J Intern Med 2003;254:67-75.

6. Sommer BR, Hoff AL, Costa M. Folic acid supplementation in dementia a preliminary report. J Geriatrc Psychiatry Neurol 2003;16:156-9.

7. van Asselt DZ, et al. Cobalamin supplementation improves cognitive and cerebral function in older, cobalamin-deficient people. J Gerontol A Biol Sci Med Sci 2001;56:M775-9.

8. Seal EC, et al. A randomized, double-blind, placebo-controlled study of oral vitamin B12 supplementation in older pateints with subnormal or borderline vitamin B12 concentrations. J Am Geriatr Soc 2002;50:146-51.

9. Bryan J, Calvaresi E, Hughes D. Short-term folate, vitamin B-12 or vitamin B-6 supplementation slightly affects memory performance but not mood in women of various ages. J Nutr 2002;132:1345-56.

10. Goodwin JS, Goodwin JM, Garry PJ. Association between nutritional status and cognitive functioning in a healthy elderly population. JAMA 1983;249:2917-21.

11. Riggs KM, et al. Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the Normative Aging Study. Am J Clin Nutr 1996;63:306-14.

12. Kalmijn S, et al. Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam Study. Am J Epidemiol 1999;150:283-9.

13. Lindeman RD, et al. Serum vitamin B12, C and folate concentrations in the New Mexico elder health survey: correlations with cognitive and affective functions. J Am Coll Nutr 2000;19:68-76.

14. Budge M, et al. Plasma total homocysteine and cognitive performance in volunteer elderly population. Anns N Y Acad Sci 2000;903:407-10.

15. Robins Wahlin TB, et al. The influence of serum vitamin B12 and folate status on cognitive functioning in very old age. Biol Psychol 2001;56:247-65.

16. McCaddon A, et al. Homocysteine and cognitive decline in healthy elderly. Dement Geriatr Cogn Disord 2001; 12:309-13.

17. Morris MS, et al. Hyperhomocysteinemia associated with poor recall in the third National Health and Nutrition Examination Survey. Am J Clin Nutr 2001;73:927-33.

18. Stewart R, Asonganyi B, Sherwood R. Plasma homocysteine and cognitive impairment in an older British African-Caribean population. J Am Geriatr Soc 2002;50: 1227-32.

19. Prins ND, et al. Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study. Neurology 2002; 59:1375-80.

20. Duthie SJ, et al. Homocysteine, B vitamin status, and cognitive function in the elderly. Am J Clin Nutr 2002;75:908-13.

21. Dufouil C. et al. Homocysteine, white matter hyperintensities, and cognition in healthy elderly people. Ann Neurol 2003;53:214-21.

22. Ravaglia G, et al. Homocysteine and cognitive function in healthy elderly community dwellers in Italy. Am J Clin Nutr 2003;77:668-73.

23. Miller JW, et al. Homocysteine and cognitive function in the Sacramento Area Latino Study on Aging. Am J Clin Nutr 2003;78:441-7.

24. Sachdev P, et al. Homocysteine and the brain in midadult life: evidence for an increased risk of leukoaraiosis in men. Arch Neurol 2004;61:1369-76.

25. Teunissen CE, et al. Homocysteine: a marker for cognitive performance? A longitudinal follow-up study. J Nutr Health Aging 2003;7:153-9.

26. Cole MG, Prchal JF. Low serum vitamin B12 in Alzheimer-type dementia. Age Ageing 1984;13:101-5.

27. Levitt AJ, Karlinsky H. Folate, vitamin B12 and cognitive impairment in patients with Alzheimer's disease. Acta Psychiatr Scand 1992;86:301-5.

28. Regland B, et al. Vitamin B12 in CSF: reduced CSF/serum B12 ratio in demented men. Acta Neurol Scand 1992;85:276-81.

29. Kristensen MO, et al. Serum cobalamin and methylmalonic acid in Alzheimer dementia. Acta Neurol Scand 1993;87: 475-81.

30. Basun H, Fratiglioni L, Winblad B. Cobalamin levels are not reduced in Alzheimer's disease: results from a Population based study. J Am Geriatr Soc 1994;42:132-6.

31. Crystal HA, et al. Serum vitamin B12 levels and incidence of dementia in a healthy elderly population: a report from the Bronx longitudinal aging study. J Am Geriatr Soc 1994;42:933-6.

32. Nilsson K, et al. Hyperhomocysteinaemia – a common finding in a psychogeriatric population. Eur J Clin Invest 1996;26:853-9.

33. Joosten E, et al. Is metabolic evidence for vitamin B-12 and folate deficiency more frequent in elderly patients with Alzheimer's disease? J Gerontol A Biol Sci Med Sci 1997;52:M76-9.

34. Nagga AK, Marcusson J. Associated physical disease in a demented population. Aging (Milano) 1998;10:440-4.

35. Clarke R, et al. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol 1998;55:1449-55.

36. McCaddon A, et al. Total serum homocysteine in senile dementia of Alzheimer type. Int J Geriatr Psychiatry 1998;13: 235-9.

37. Lehmann M, Gottfries CG, Regland B. Identification of cognitive impairment in the elderly: homocysteine is an early marker. Dement Geriatr Cogn Disord 1999;10:12-20.

38. Wang HX et al. Vitamin B(12) and folate in relation to the development of Alzheimer's disease. Neurology 2001;56:1188-94.

39. Tripathi M et al. Serum cobalamin levels in dementias. Neurol India 2001; 49:284-6.

40. Postiglione A et al. Plasma folate, vitamin B(12), and total homocysteine and homozygosity for the C677T mutation of the 5,10-methylene tetrahydrofolate reductase gene in patients with Alzheimer's dementia. A case-control study. Gerontology 2001;47:324-9.

41. Seshadri S et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346: 476-83.

42. McIlroy SP et al. Moderately elevated plasma homocysteine, methylenetetrahydrofolate reductase genotype, and risk for stroke, vascular dementia, and Alzheimer disease in Northern Ireland. Stroke 2002;33:2351-6.

43. Miller JW et al. Homocysteine, vitamin B6, and vascular disease in AD patients. Neurology 2002;58:1471-5.

44. Nilsson K, Gustafson L, Hultberg B. Relation between plasma homocysteine and Alzheimer's disease. Dement Geriatr Cogn Disord 2002;14:7-12.

45. Selley ML. Increased concentrations of homocysteine and asymmetric dimethylarginine and decreased concentrations of nitric oxide in the plasma of patients with Alzheimer's disease. Neurobiol Aging 2003;24:903-7.

46. Religa D, et al. Homocysteine, apolipoproteine E and methylenetetrahydrofolate reductase in Alzheimer's disease and mild cognitive impairment. Dement Geriatr Cogn Disord 2003;16:64-70.

47. Nagga K, et al. Cobalamin, folate, methylmalonic acid, homocysteine, and gastritis markers in dementia. Dement Geriatr Cogn Disord 2003;16:269-75.

48. Mizrahi EH, et al. Plasma total homocysteine levels, dietary vitamin B6 and folate intake in AD and healthy aging. J Nutr Health Aging 2003;7:160-5.

49. Quadri P, et al. Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. Am J Clin Nutr 2004;80: 114-22.

50. Nilsson K, Gustafson L, Hultberg B. Plasma homocysteine concentration relates to the severity but not to the duration of Alzheimer's disease. Int J Geriatr Psychiatry 2004;19:666-72.

13. **Evidence for Tests that can be used to Diagnose Dementia**

Informant interview in the diagnostic evaluation of patients with dementia

Background

The inclusion of caregivers in the management of patients with dementia has obvious advantages. As for the diagnostic process, the initial interview of a patient with possible dementia will often include an interview with a caregiver. During the interview, important information about prior disease, medication, etc, can be checked and supplemented. Furthermore, the caregiver can often contribute important information about current condition and symptoms and has often noticed changes in the patient for a very long time. Brief cognitive tests, such as the MMSE, are used widely in screening for dementia. Informant reports on cognitive function and its impact on everyday life may provide relevant supplementary data for the detection of dementia. The advantages of including a caregiver/informant interview are many:

- The patient may have reduced awareness of symptoms
- Relevance to everyday life
- Greater international cross-cultural and cross-educational applicability
- Direct assessment of changes from earlier stages in life
- Possibility of assessment by mail or phone.

However, there are also disadvantages associated with the use of caregiver interviews: the results depend on the extent and quality of the relationship between the patient and the caregiver, as well as the emotional state of the caregiver. Finally, a significant number of patients do not have a reliable caregiver. A series of questionnaires have been developed to quantify caregiver data. The aim of this review was to identify evid-

ence for the use of structured informant interviews as a diagnostic aid in patients with possible dementia. "Evidence-based Dementia Practice" did not review the evidence for the use of caregiver interviews [1].

Literature search

A search was planned for papers that describe the use of structured informant interviews in the diagnosis of dementia.

Search strategy

"Informant" [Title] AND "dementia" [Title]
OR
"Dementia" [MeSH Terms] AND "Caregivers" [MeSH Terms]
AND
"Interview" OR "Interviews" OR "Interviewing" [Text Words]
AND
"Diagnosis" [MeSH Subheading] OR "Screening" [Text Word]
Limits: English language.

Results

Fiftyfive papers were found. Based on a review of titles and abstracts, 37 papers were excluded, mainly due to lack of relevance to the topic or the fact that it was not an original research paper. The remaining 18 potentially relevant papers were reviewed in more detail. One was a meta-analysis of previous studies, and 5 were not relevant or did not contain sufficient data. The evidence in the remaining 12 original papers, all of which presented data from which the sensitivity, specificity, and likelihood ratio could be derived, were reviewed and categorized along with other reports identified from citations in the papers (see Table 13.1).

Comments

The likelihood ratio in the studies with the highest quality ranged from 2 to 8, indicating a moderate impact on the diagnosis to separate AD patients from controls. Due to a lack of studies, there is little evidence for the predictive value of informant interviews in patients with MCI.

The brief structured caregiver interviews deserve to be used more frequently and may serve as a supplement to brief cognitive tests in primary health care.

Table 13.1 *Studies on the diagnostic value of a structured informant interview in dementia. All studies with presentation of data, which enabled the calculation of sensitivity (SS), specificity (SP), and a positive likelihood ratio (LR+).*

Author Year Reference Country	**Name of interview/ scale (number of items)**	**Sample (N)**	**Age mean (year)***	**Population/ selection**	**Setting**
Krishnan et al 2001 [2] USA	BCS (18)	N_{DEM} = 66 N_{MCI} = 28 N_{CON} = 26	73.2 74.1 72.8	Other study populations Selection?	University hospital
Jorm et al 1989 [3] Australia	IQCODE (26)	N_{AD} = 362 N_{CON} = 613	NA	Volunteer sample from general population and informants to AD patients from Alzheimer Association	Population study
Morales et al 1995 [4] Spain	S-IQCODE (26)	N_{DEM} = 7 N_{CON} = 61	74.8 72.9	Population based study	Population
Del-Ser et al 1997 [5] Spain	S-IQCODE (26)	N_{DEM} = 38 (AD:24) N_{NOTDEM} = 15	69.1	Consecutive Referrals for possible dementia	Clinical setting outpatients
Koss et al 1993 [6] USA	MSRQ (32)	N_{AD} = 83 N_{CON} = 39	72.4 70.1	All patients and healthy controls in an AD research center registry	Clinical setting

Diagnostic criteria	Condition	SS %	SP %	LR+	LR–	Quality of study	Reviewers' comments
AD: NINCDS-ADRDA VaD: ? MCI: ?	Dementia vs control MCI vs control	80 80	90 80	8.0 4.0	0.22 0.22	2b	Small samples, no follow-up in MCI, criteria and selection not well described. Independent rater? Diagnostic classification not performed as a part of the study
NA	Dementia vs general population	92.7	88.1	7.8	0.03	2a	Cut-off score 4. 5.7% in the control sample said they were reporting on a person with dementia. Diagnostic classification was not performed
DSM-III-R	Mild dementia vs controls	86	92	10.8	0.15	1b	Independent rater. Small sample
DSM-III-R	Dementia vs not demented patients S-IQCODE MMSE and S-IQCODE	 84 84	 73 93	 3.1 12.0	 0.22	1b	Independent rater. Cut-off score 94. Small sample
NINCDS-ADRDA	AD vs control	94	100	NA	0.06	2b	Control subjects completed the questionnaire on their own. Controls were also caregivers to patients. Cut-off score 40. Diagnostic classification was not part of the study

The table continues on the next page

Table 13.1 *continued*

Author Year Country Reference	Name of interview/ scale (number of items)	Sample (N)	Age mean (year)*	Population/ selection	Setting
Mulligan et al 1996 [7] Switzerland	IQCODE (26)	N_{DEM} = 33 N_{DEPR} = 11 $N_{DEPR+DEM}$ = 2 N_{OTHER} = 30	 81.8	Referred patients	Geriatric hospital
Morales et al 1997 [8] Spain	S-IQCODE (26)	Urban: 97 (N_{DEM} = 11) Rural: 160 (N_{DEM} = 23)	75.2 73.5	Population based study	Population study
Ritchie et al 1992 [9] France	DECO (19)	N_{DEM} = 155 N_{CON} = 120	146>80	Recruited from different sources	
Fuh et al 1995 [10] China	IQCODE (26)	N_{DEM} = 61 N_{CON} = 399	73.3 68.1	Population based study. Illiterate subjects	From community sources and memory clinic
Mackinnon et al 1998 [11] Switzerland	IQCODE (16)	N_{DEM} = 58 N_{DEPR} = 9 $N_{DEPR+DEM}$ = 2 N_{OTHER} = 28	 80.3	Hospital patients (selection?)	Geriatric hospital
Carr et al 2000 [12] USA	One simple question	N_{CDR0} = 158 $N_{CDR0.5}$ = 165 $N_{CDR0.5}$ = 159	77.0 74.4 73.2	Prospective with 2–5 years follow-up	University AD research center
Jorm et al 1991 [13] Australia	IQCODE	N = 29 N_{CON} = 40	80.0		Hospital and clinic

Diagnostic criteria	Condition	SS %	SP %	LR+	LR–	Quality of study	Reviewers' comments
DSM-III-R	Dementia vs not dementia	76	70	2.5	0.34	1a	Cut off 3.6. Independent observer?
DSM-III-R	Dementia vs not dementia	82 83	90 83	8.2 4.9	0.2 0.23	1a	Cut-off 85/86
DSM-III	Dementia vs not dementia	90	80	4.5	0.13	1a	Cut-off 31/32
DSM-III-R	Dementia vs not dementia	89	88	7.4		1a	Cut-off 3.4. Cases and controls were from two different populations
DSM-IV	Dementia vs not dementia IQCODE MMSE and IQCODE	 90 86	 65 85	 2.6 5.7	 0.15 0.16	1a	IQCODE cut-off score 3.6. MMSE cut-off 25. Independent observer. Cross sectional study. No information about informants
Clinician evaluation	Dementia vs not dementia	92	86	6.6	0.09	1a	Informant reported memory loss also predicted future diagnosis of AD
DSM-III-R	Dementia vs not dementia	69	80	3.5	0.38		

The table continues on the next page

Table 13.1 *continued*

Author Year Country Reference	Name of interview/ scale (number of items)	Sample (N)	Age mean (year)*	Population/ selection	Setting
Jorm 1994 [14] Australia	IQCODE	N = 52 N_{CON} = 632	77.0		Community
Law et al 1995 [15] Canada	IQCODE	N = 49 N_{CON} = 114	81.0		Community
Jorm et al 1996 [16] Australia	IQCODE	N = 24 N_{CON} = 120	73.0		Community
Harwood et al 1997 [17] United Kingdom	IQCODE	N = 21 N_{CON} = 180	76.0		Hospital

None of the studies had neuropathological confirmation of diagnosis.
* Age for index cases/controls/patients.

AD = Alzheimer's disease; BCS = Behavioral cognitive scale; CDR = Clinical dementia rating scale; CON = Controls; DECO = Détérioration cognitive observée [9]; DEM = Dementia; DEPR = Depression; IQCODE = Informant questionnaire on cognitive decline in the elderly [3]; MCI = Mild cognitive impairment; MMSE = Mini-mental state examination; MSRQ = Memory self report questionnaire [18]; NA = Not applicable; S-IQCODE = Spanish version of the IQCODE; VaD = Vascular dementia

Diagnostic criteria	Condition	SS %	SP %	LR+	LR–	Quality of study	Reviewers' comments
DSM-III-R	Dementia vs not dementia	79	83	4.6	0.25		
NINCDS + ICD-10	Dementia vs not dementia	76	96	19	0.25		
ICD-9	Dementia vs not dementia	79	65	2.3	0.32		
DSM-III-R	Dementia vs not dementia	100	86	7.1	0		

References

1. Qizilbash N, Schneider L, Chui H, Tariot P, Brodaty H, Kaye J, et al. Evidence-based Dementia Practice. Blackwell Publishing Company, UK; 2002.

2. Krishnan KR, Levy RM, Wagner HR, Chen G, Gersing K, Doraiswamy PM. Informant-rated cognitive symptoms in normal aging, mild cognitive impairment, and dementia. Initial development of an informant-rated screen (Brief Cognitive Scale) for mild cognitive impairment and dementia. Psychopharmacol Bull 2001;35: 79-88.

3. Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med 1989;19: 1015-22.

4. Morales JM, Gonzalez-Montalvo JI, Bermejo F, Del-Ser T. The screening of mild dementia with a shortened Spanish version of the "Informant Questionnaire on Cognitive Decline in the Elderly". Alzheimer Dis Assoc Disord 1995;9:105-11.

5. Del-Ser T, Morales JM, Barquero MS, Canton R, Bermejo F. Application of a Spanish version of the "Informant Questionnaire on Cognitive Decline in the Elderly" in the clinical assessment of dementia. Alzheimer Dis Assoc Disord 1997;11:3-8.

6. Koss E, Patterson MB, Ownby R, Stuckey JC, Whitehouse PJ. Memory evaluation in Alzheimer's disease. Caregivers' appraisals and objective testing. Arch Neurol 1993;50:92-7.

7. Mulligan R, Mackinnon A, Jorm AF, Giannakopoulos P, Michel JP. A comparison of alternative methods of screening for dementia in clinical settings. Arch Neurol 1996;53:532-6.

8. Morales JM, Bermejo F, Romero M, Del-Ser T. Screening of dementia in community-dwelling elderly through informant report. Int J Geriatr Psychiatry 1997;12:808-16.

9. Ritchie K, Fuhrer R. A comparative study of the performance of screening tests for senile dementia using receiver operating characteristics analysis. J Clin Epidemiol 1992;45:627-37.

10. Fuh JL, Teng EL, Lin KN, Larson EB, Wang SJ, Liu CY, et al. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening tool for dementia for a predominantly illiterate Chinese population. Neurology 1995;45: 92-6.

11. Mackinnon A, Mulligan R. Combining cognitive testing and informant report to increase accuracy in screening for dementia. Am J Psychiatry 1998;155:1529-35.

12. Carr D, Gray S, Baty J, Morris JC. The value of informant versus individual's complaints of memory impairment in early dementia. Neurology 2000;55:1724-6.

13. Jorm AF, Scott R, Cullen JS, MacKinnon AJ. Performance of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening test for dementia. Psychol Med 1991;21:785-90.

14. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. Psychol Med 1994; 24:145-53.

15. Law S, Wolfson C. Validation of a French version of an informant-based questionnaire as a screening test for Alzheimer's disease. Br J Psychiatry 1995;167:541-4.

16. Jorm AF, Christensen H, Henderson AS, Jacomb PA, Korten AE, Mackinnon A. Informant ratings of cognitive decline of elderly people: relationship to longitudinal change on cognitive tests. Age Ageing 1996;25:126-9.

17. Harwood D, Hope T, Jacoby R. Cognitive impairment in medical inpatients I: Screening for dementia – is history better than mental state? Age Ageing 1997;26: 31-5.

18. Riege W, Kelly, K, Klane, L. T. Age and error differences on Memory-for-Designs. Percept Mot Skills 1981;52:507-13.

14. Neuropsychological Tests as a Diagnostic Marker of Dementia

Conclusion

There is strong evidence that neuropsychological tests contribute substantially to the diagnosis of dementia and AD (Alzheimer's disease). Because few accepted studies compare the diagnostic entity of MCI with dementia or AD, or relate it to healthy individuals, no conclusions can be stated on this issue.

Introduction

Chapter II.3.1 and II.4.4 of "Evidence-based Dementia Practice" describe state-of-the-art research regarding evidence-based evaluation of neuropsychological tests as a means for predicting dementia [1]. In addition, there are a number of review articles on this issue [2,3]. These studies typically make use of various methods for evaluation. Many review studies refer to the likelihood ratio (LR). However, methods other than LR are frequently utilized as well. In these studies, regression analysis or predictive value or validity may be used as the operational means of evaluation [4].

Aim

The aim was to perform a systematic review of (sets of or single) neuropsychological tests in order to predict dementia or allow a differential diagnosis of dementia.

Search strategy

A prerequisite for the present study is the definition of a neuropsychological test. It is defined as a task-based assessment of cognitive function, including documented scaling properties and norms that refer to a normal population. The search was performed on neuropsychological tests in the Medline database using a search profile (description) to cover research from 1966 through July 2004.

Dementia
AND
Neuropsychological Tests
Wechsler Scales
Psychiatric Status Rating Scales
MMSE [Text Word]
AND
Sensitivity and Specificity
Sensitivity [Text Word]
Specificity [Text Word]
Accuracy [Text Word]
NOT
Letter [Publication Type]
Editorial [Publication Type]
Review [Publication Type]
Case Report

Description of studies included and excluded

There were 399 articles found subjected to a selection procedure. First, all studies lacking information on sensitivity and specificity were excluded. The remaining studies were evaluated with regard to methodological quality as described in Methods. Studies were excluded due primarily to a lack of comprehensiveness (at least 4 out of 6 domains: general, verbal, spatial, executive, attention and memory) of cognitive domains assessed (n = 27), as well as the absence of brain imaging (n = 15) and

insufficiently comprehensive clinical investigation (n = 11). Nine studies were ultimately included. Worth noting is that the selection procedure excluded studies, such as MMSE, and DRS, that use screening tests to assess cognitive function. A separate section entitled "Single tests as a diagnostic marker of dementia" deals with this topic.

The majority of accepted studies compared two or more levels of cognitive deterioration, starting with 1) unimpaired cognitive function and followed by 2) very mild and mild cognitive impairment and 3) pronounced cognitive deficits in moderate and severe dementia. Groups of patients with unspecified dementia were compared with controls (n = 3). Alternatively, patients with specified dementia (AD) were compared with controls (n = 5). Another group of studies investigated stages in the course of the disease. For instance, the focus might be on the transition from unimpaired to impaired cognitive function (n = 1), most often referred to as MCI. Worth noting is that the certainty of unimpaired cognitive function varies a good deal. Some studies include rigorous health screening, whereas others use a screening procedure or no evaluation of health status, although stating that the participants have normal cognitive function.

A minority of accepted studies concerned two or more diseases, such as a comparison of AD and VaD or AD and FTD.

Results

The mean and confidence interval of LR+ and LR– for various contrasts appear in Table 14.1.

The results (Table 14.1) indicate that strict methodological requirements left very few studies for our evidence-based assessment. In particular, few studies using neuropsychological methods are based on a definite neuropathological diagnosis. Furthermore, no studies were found that met the methodological requirements for specific dementia diseases other than AD. These findings may serve as a reminder for researchers to consider

the design of future studies in order to ensure valuable and reliable information on diagnosis that uses neuropsychological methods. However, we should point out that many excluded studies contain valuable information that largely agree with the conclusion presented in this review.

Discussion

A number of concerns will be discussed briefly: the contrast between groups that were compared, the arbitrariness of cut-off in the predictor variable, and group-based vs individual-based prediction of impairment.

A major problem concerns the degree of deterioration in clinical groups and the possible enrichment of the control group with regard to health status. The contrast between the studied clinic group and the control group may be enhanced by selecting a more advanced disease group. Similarly, the selection of a healthy control group may further increase the contrast. Choosing groups that differ markedly in terms of cognitive function may make the resulting likelihood ratio very large, while the diagnostic value may be relatively low. On the other hand, when the contrast between groups in terms of cognitive function is relatively modest, the value of a diagnostic method may be high even when the likelihood ratio indicates a low level of diagnostic power.

In the neuropsychological assessment of individuals, there is no consensus regarding the cut-off level for abnormal test results. In relation to the normal distribution of performance for control subjects, should the cut-off be –2 standard deviations or something else, perhaps the 5th percentile? This choice will have a large impact on the specificity value and consequently on the value of LR+. Giving priority to a high specificity value may make the LR+ extremely large. So the dilemma is to have some standard for the cut-off in cognitive function. The solution to the dilemma might be the "area under the curve" analysis (AUC).

In the research reviewed, all comparison is directed towards mean values of a group in focus in relation to a control group, ie, an *inter*-individual comparison based on population data of normal performance. However, the true comparison should be the premorbid value, in relation to the morbid value, of the same individual, ie, an *intra*-individual comparison. The dilemma is that there is seldom any reliable knowledge about true premorbid functioning. This difference between optimal and feasible comparison will introduce an error in the prediction that is beyond the reach of present routines for assessing cognitive function.

Table 14.1 *Summary of accepted studies on neuropsychological tests that fulfilled criteria of inclusion showing median SS and SP as well as mean LR+ and LR– and grade of evidence in comparison of groups varying in degree of cognitive dysfunction and diagnosis (D, AD, MCI, and C).*

Comparison group	No of studies	No of probands (1 vs 2)	SS median	SP median
D-C	3	184/167	0.82	0.95
AD-C	5	342/400	0.86	0.94
D-MCI	1	16/104	0.83	0.85

AD-MCI 0 (no study out of 3 accepted fulfilled the combined 3 criteria: SS >0,8 and SP >0,8 and LR+ >5).
MCI-C 0 (no study out of 3 accepted fulfilled the combined 3 criteria: SS >0,8 and SP >0,8 and LR+ >5).

AD = Alzheimer's disease; LR = Likelihood ratio; MCI = Mild cognitive impairment; SP = Specificity; SS = Sensitivity

LR+ median	LR– median	Grade of evidence
16.4	0.19	Strong
14.3	0.12	Strong
5.7	0.2	No evidence, one study only

Table 14.2 *Neuropsychological test(s) as markers of type and degree of dementia based on studies with clinical (Arabic digit) and/or neuropathological verification (Roman digit) of diagnosis.*

Author Year Reference Country	Sample (n) Follow-up (y)	Age (years)	Stage CDR/ MMSE/ GDS	Diagnostic criteria Clin/ neuropath	Inde-pendence
D–C n = 3					
Derrer et al 2001 [5] USA	D, n = 37 C, n = 37	74 74	CDR: I CDR: 0	NINCDS/no	
Storandt et al 1989 [6] USA	mD, n = 66 VmD, n = 41 C, n = 83	72±5 74±5 72±5	CDR: I CDR: 0.5 CDR: 0	DSM-III/no	Yes
Swearer et al 1998 [7] USA	D, n = 40 NoD, n = 47 C, n = 53	73 64 70	Mi-mod	DSM-IV/no NINCDS	
AD-C n = 6					
Albert et al 2001 [8] USA	qD, n = 123 C, n = 42 Follow-up: 3	72.2 71.4	CDR: 0.5 CDR: 0	NINCDS/no CDR: ISP	
Kluger et al 1999 [9] USA	Decl, n = 74 NoDec, n = 139 AD, n = 56 NoDec, n = 123	72.7±8.6 69.7±8.2	GDS: >3 GDS: 1–3	Follow-up: 3.6 years/no	Yes
La Rue 1989 [10] USA	AD, n = 19 DNUD, n = 20 Depr, n = 41	60–90 60–90 60–90	17.2±5.6 19.8±4.7 23.9±4.0	DSM-III/no	Yes

Contrast	Test(s)	SS	SP	LR+/–	Quality of study	Reviewers' comments
D C	WlistA LM VR	1	0.95	20/0.00	1a	
mD-C	LM+ BN+ DiSy	0.82	0.95	16.4/0.19	1a	
VmD-C		0.65	0.95	13		
D NoD	Orient LM: Im+De	0.81	0.98	40.5/0.19	1a	
C-AD	CVLT, VR, TMTB	0.83	0.94	13.8/0.18	1a	Plus: cog Communitybased volunteer, selected samples
C-qD	CVLT, SOT	0.71	0.81	3.7		Covariance analysis: ApoE ns
qD-AD	CVLT, VR, TMTB	0.74	0.83	4.4		
Dec	DePR NoDecl DiSy	0.73 AL	0.91	8.1	1a	Plus: demo incl
NoDec	DSf	0.89	0.97	27.9/0.12		
AD vs depr	Fuld: Learn + del MMSE	0.9 0.67	0.83 0.76	5.2/0.12 2.7		Cross-sect Lim: mod cog dysf

The table continues on the next page

Table 14.2 *continued*

Author Year Reference Country	**Sample (n) Follow-up (y)**	**Age (years)**	**Stage CDR/ MMSE/ GDS**	**Diagnostic criteria Clin/ neuropath**	**Inde-pendence**
Locascio et al 1995 [11] USA	NC, n = 60 AD, n = 123 Follow-up: 5.5	68.9±11.2 70.7±8.5 Mi Mod Sev	IMC: 0.9 IMC: 11.6 IMC: 7.1 IMC: 13.4 IMC: 21.6	NINCDS/few	
Masur et al 1989 [12] USA	NE, n = 134 AD, n = 21 AD	79.5±3.0 68.3±11.2		NINCDS/no	
D-MCI n = 1					
Hänninen et al 1995 [13] Finland	AAMI, n = 104 D, n = 16 MCI, n = 13 SubjM, n = 17 OthDis, n = 15 No, n = 9 Follow-up: 3.6	71.7±5.0		AAMI/no DSM-III-R	No
AD-MCI n = 0					
MCI-C n = 0					

AD = Alzheimer's disease; BN = Boston Naming test; C = Control; CDR = Clinical dementia rating scale; D = Dementia; Dec = Deceased; Decl = Declaration; DiSy = Diagnostic system; DNUD = Dementia no ultimate definition; GDS = Geriatric depression scale; HD = Huntington's disease; mD = Mild dementia; MMSE = Mini-mental state examination; NC = Normal controls; NE = Normal examination; NoD = Not demented; prAAMI = Age associated memory impairment; qD = Demented women; StAAMI = Age associated memory impairment; VmD = Very mild dementia

Contrast	Test(s)	SS	SP	LR+/–	Quality of study	Reviewers' comments
NC vs miAD	NYUdR GeoFigR (Comb 2 test)	0.96	0.91	10.7/0.04	1b	Plus: cog No cog speed No attention
NE vs AD	SRT: sum + del + 2	0.8	0.95	16.0/0.21	1a	Bronx AS Cross-sec Cut-off 2SD
StAAMI prAAMI	All SRT VR AL VeFluL VeFluC Bent	0.83	0.85	5.6/0.20		Kuopio Wide cog

References

1. Qizilbash Nea. Evidence-based dementia practice. Oxford: Blackwell Publishing; 2002.

2. Collie A, Maruff P. The neuropsychology of preclinical Alzheimer's disease and mild cognitive impairment. Neurosci Biobehav Rev 2000;24:365-74.

3. Tuokko H, Hadjistavropoulos T, Miller JA, Beattie BL. The Clock Test: a sensitive measure to differentiate normal elderly from those with Alzheimer disease. J Am Geriatr Soc 1992;40:579-84.

4. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1143-53.

5. Derrer DS, Howieson DB, Mueller EA, Camicioli RM, Sexton G, Kaye JA. Memory testing in dementia: how much is enough? J Geriatr Psychiatry Neurol 2001;14:1-6.

6. Storandt M, Hill RD. Very mild senile dementia of the Alzheimer type. II. Psychometric test performance. Arch Neurol 1989;46:383-6.

7. Swearer JM, O'Donnell BF, Kane KJ, Hoople NE, Lavoie M. Delayed recall in dementia: sensitivity and specificity in patients with higher than average general intellectual abilities. Neuropsychiatry Neuropsychol Behav Neurol 1998;11:200-6.

8. Albert MS, Moss MB, Tanzi R, Jones K. Preclinical prediction of AD using neuropsychological tests. J Int Neuropsychol Soc 2001;7:631-9.

9. Kluger A, Ferris SH, Golomb J, Mittelman MS, Reisberg B. Neuropsychological prediction of decline to dementia in nondemented elderly. J Geriatr Psychiatry Neurol 1999;12:168-79.

10. La Rue A. Patterns of performance on the Fuld Object Memory Evaluation in elderly inpatients with depression or dementia. J Clin Exp Neuropsychol 1989;11:409-22.

11. Locascio JJ, Growdon JH, Corkin S. Cognitive test performance in detecting, staging, and tracking Alzheimer's disease. Arch Neurol 1995;52:1087-99.

12. Masur DM, Fuld PA, Blau AD, Thal LJ, Levin HS, Aronson MK. Distinguishing normal and demented elderly with the selective reminding test. J Clin Exp Neuropsychol 1989;11:615-30.

13. Hanninen T, Hallikainen M, Koivisto K, Helkala EL, Reinikainen KJ, Soininen H, et al. A follow-up study of age-associated memory impairment: neuropsychological predictors of dementia. J Am Geriatr Soc 1995;43:1007-15.

15. **Evidence-based Evaluation of Single Cognitive Tests as a Diagnostic Marker of Dementia**

Conclusions

For Clock tests and CAMCOG, a sufficient number of studies could be included in order to summarize their effectiveness in diagnosing dementia and AD (Alzheimer's disease). For other tests, data are lacking and further studies are needed before a conclusion can be drawn.

There is moderately strong evidence that single cognitive tests such as CAMCOG contribute substantially to the diagnosis of dementia. There is also moderately strong evidence that Clock tests contribute substantially to the diagnosis of AD. There are no accepted studies on the diagnostic entity of MCI compared to dementia or AD and in relation to healthy individuals. Thus, no conclusions can be stated concerning this issue. There is no evidence and/or no accepted studies on other single cognitive tests (though many are in use) for diagnosing dementia, AD or MCI. Because there is only one study on MMSE that is of acceptable quality, no conclusion can be stated with regard to evidence.

Introduction

Previous studies regarding evidence-based evaluation of single cognitive tests as an aid in the diagnosis of dementia are presented in a chapter of "Evidence-based Dementia Practice" [1]. Single tests have been claimed to be useful in distinguishing between both specified and unspecified dementia and control subjects. However, the data are often based on a clinical setting where representative samples of patients with dementia

are compared to unrepresentative samples of normal, high-functioning controls. That may lead to an overestimate of likelihood ratios. The tests included in the present study were MMSE, various Clock tests, ADAS-Cog, CAMCOG, CERAD, and a single memory, fluency or other specific test of cognitive function. Before a final conclusion on the value of single cognitive tests in a dementia workup can be reached, future studies should be designed to include an appropriate spectrum of participants.

The aim was to review single cognitive tests in order 1) to predict dementia or a specific dementia disease and 2) to arrive at a differential diagnosis of dementia.

Search strategy

Single cognitive tests were specified as a prerequisite for the present study. A single cognitive test was defined as any task-based assessment of global cognitive function or specific single cognitive function. The search was performed on tests in the Medline database using a profile of [dementia AND (ADAS-Cog OR CERAD OR CAMCOG OR Clock test OR 7MS OR any of many other tests) AND (sensitivity AND specificity)] to identify research dated from 1966 through January 2005. A total of 549 articles were found. The articles underwent a two-step selection procedure. First, all abstracts were read and evaluated in terms of relevance to the aim. Studies were excluded from further evaluation because they dealt with a combination of various cognitive tests, used psychiatric or non-behavioral methods, or did not correspond to the intentions of the review for some other reason. This step left 130 studies. In the second step, studies were evaluated with regard to methodological quality as described above. The primary reasons for exclusion were an insufficient number of clinical examinations and inadequate data to calculate sensitivity and specificity. After the methodological evaluation, 52 studies remained for evidence-based analysis of the value of single cognitive tests in dementia workups.

The majority of accepted studies concerned a comparison between two or more levels of cognitive deterioration, from 1) unimpaired cognitive

function to 2) mild cognitive impairment (MCI) to 3) pronounced cognitive deficits in mild, moderate and severe dementia associated with certain disease (such as AD) or any type of cerebrovascular disorder. Most often (26 studies), groups of unspecified dementia patients were compared with controls. Another 19 studies compared specified dementia, such as AD with controls. Two studies investigated various stages in the course of the disease, such as the transition from unimpaired cognitive function to MCI. One study concerned the transition from MCI to mild dementia or from mild to more advance dementia. Finally, one study compared different dementia disorders, as exemplified by VaD and unspecified non-AD. Worth noting is that the certainty regarding unimpaired cognitive function varies considerably. Some studies included rigorous health screening, whereas others use a simple screening procedure or no clinical evaluation of health status, while stating that the participants had normal cognitive function. A couple of studies included more than one comparison.

The most frequently used single cognitive tests were MMSE [2], Clock tests (n = 11, including various formats of task and scoring), CAMCOG [3], Category fluency (n = 3), MIS [4] and 7MS [5]. Thirtynine different tests were used in only 1 or 2 studies. These tests concerned episodic memory (n = 12), any other specific cognitive function (n = 8) or a global measure of cognition (n = 19). Very high LR+ values (LR+ >20) were reported for some of the tests, the majority of which assess episodic memory. However, since the data were based on a single study, they are not presented in this review. Given that the instruments are common to clinical dementia research and clinical trials, neither ADAS-Cog nor CERAD appeared in the final set of studies to review. It was possible to obtain some information on the utility of various cut-off levels in MMSE and the scoring method for Clock tests.

Results

Below are data on sensitivity, specificity, LR+ and LR– for various contrasts between groups and in terms of three single cognitive tests: MMSE, Clock tests, and CAMCOG (see Table 15.1). MMSE is a test of limited evidence, particularly for assessing dementia compared to people

without dementia in similar age-groups. However, only one study on MMSE comparing Alzheimer to controls, corresponded to the criteria for inclusion. It is also obvious that a Clock test is valuable in diagnosing dementia. Both MMSE and Clock tests can be easily administered in a relatively short period of time by nurses, paramedical personnel, physicians, etc, without requiring extensive training. For CAMCOG, administration is more demanding and does not offer clear advantages in terms of utility, as documented by LR+.

Worth noting is that maximum LR+ and minimum LR– do not occur in the same study. Thus, LR+ or LR– must be prioritized before the test is chosen.

Furthermore, not only the specific test, but the way that it is to be administered, must be decided in advance, given the possible impact on LR+ and LR–. Some studies examined the effect on sensitivity and specificity by varying the cut-off level. These studies demonstrated greater sensitivity despite unchanged specificity when the cut-off level was increased [6,7].

Regarding the Clock test, considerable variation in terms of administration formats leads to varying degrees of difficulty (such as telling the time given the clock outline and hands, setting the hands given the time and clock outline, drawing clock outlines and hands given the time, etc). In addition, various scoring procedures have been suggested, and some studies have compared the effectiveness of different scoring procedures. According to these studies, the Wolf-Klein method [8] and the Sunderland method [9] are associated with the most favorable LR+ in diagnosing unspecified dementia.

Discussion

In summary, the results of the present review indicate that strict methodological requirements leave very few studies for our evidence-based evaluation. Furthermore, no study was found that used diagnostic criteria based on a neuropathological examination. Another striking discovery was that the overwhelming majority of studies were on dementia and

AD – only one was exclusively devoted to VaD. Moreover, no accepted study investigated MCI. These findings may serve as a reminder for future researchers when designing studies aimed at validating single cognitive tests for dementia. Finally, many excluded studies contained valuable information that largely agreed with the conclusion presented in this review.

Before stating a final conclusion, some critical points will be discussed. The typical age of patients and controls ranges from 70 to 90, whereas only few studies have examined younger people or a broader age range. Moreover, the stage of cognitive deterioration for people with and without dementia varies considerably among the studies, making a comparison difficult or even unjustified, given that large differences between contrast groups result in favorable LR+ values for the cognitive test under evaluation. This point is critical in the evidence-based evaluation of diagnostic procedures, since it can be influenced by increasing group contrasts. For instance, the dementia group may be biased by virtue of a conservative diagnosis and/or strict selection of people without dementia by health screening so as to avoid those on the borderline between cognitive intactness and pronounced impairment. As an example, in order to evaluate the utility of a Clock test, people with dementia who have MMSE <15 and people without dementia who have MMSE close to 30 are to be preferred, given that both the test and MMSE are associated with global cognitive function. As a result, there is not a clear correlation between the predictor in focus and the degree of cognitive deterioration in contrasting groups, but rather a confounding of the evidence-based evaluation.

In applications of single tests for screening purposes, there is no consensus concerning the cut-off level. In relation to the normal distribution of performance for control subjects, should the cut-off level be 2 SD below the mean for controls or something else, such as the 5th percentile? This choice will have a major impact on the specificity value and thereby on the LR+. Prioritizing a high specificity value may overstate the LR+. The challenge is to find a standard for the cut-off in various single tests. The solution might be to present the area under the curve (AUC).

A review of MMSE has pointed out that its performance is clearly related to both the age and education of the subject [10]. Thus, a universal cut-off point is inappropriate when diagnosing dementia – both age and education must be taken into account when making diagnostic decisions.

In the research reviewed, all test results for the patient group are compared to the control group (inter-individual comparison). That is based on the assumption that the two groups are similar in essential background factors. However, the true comparison should be between the premorbid and morbid value for the same person (intra-individual comparison). A second dilemma is that there is seldom any reliable knowledge about true premorbid functioning. This difference between an optimal and a possible comparison introduces an error in the prediction that is out of reach of present routines for assessing cognitive function. That suggests that future screening instruments should be based on intra-individual changes [11], be insensitive to demographic status, or take advantage of age-based and education-based norms.

Table 15.1 *Summary of accepted studies on single cognitive tests (MMSE, Clock tests, and CAMCOG) that fulfilled criteria of inclusion showing median SS and SP as well as mean LR+ and LR– and grade of evidence in comparison of groups varying in degree of cognitive dysfunction and diagnosis (D, AD, MCI, and C).*

Comparison group	No of studies	No of probands 1 vs 2	SS median
MMSE			
D vs C	5	321/1 167	0.86
AD vs C	1	68/114	0.85
Clock tests			
D vs C	2	128/62	0.86
AD vs C	4	237/116	0.89
CAMCOG			
D vs C	3	203/315	0.88

AD = Alzheimer's disease; C = Control; D = Dementia; LR = Likelihood ratio; SP = Specificity; SS = Sensitivity

	SP median	LR+ median	LR– median	Grade of evidence
	0.85	5.7	0.16	Limited
	0.98	42.5	0.15	No evidence. Only one study
	0.85	5.7	0.16	Limited
	0.94	14.8	0.12	Moderate
	0.91	9.8	0.13	Moderate

Table 15.2 *Single cognitive tests as markers of type and degree of dementia based on studies with clinical (A) and neuropathological verification (B) of diagnosis.*

Author Year Reference Country	**Sample (n) Follow-up (y)**	**Age (years)**	**Stage CDR/ MMSE/ GDS**	**Diagnostic criteria Clin/ neuropath**	**Indepen-dence**
Schramm et al 2002 [12] Germany	D, 79 C, 44	44–90	GDS	DSM-IV/no	No
Wolf-Klein et al 1989 [8] USA	AD, 105 NoD, x	76.8	$<15_{MMSE}$ 28_{MMSE}	NINCDS/no	Yes
Heinik et al 2003 [13] Israel	D, 88 Dep/anx, 26	78.3±6.0 74.7±6.6	18.5±4.8 27.3±2.2	DSM-IV/no	Yes
Hogervorst et al 2002 [14] United Kingdom	D, 82 C, 114 AD, 68 Follow-up: ?	75±7	20.0±4.6 28.5±1.5 25.3±5.2	DSM-IV/no NINCDS NINDS	Yes
de Koning et al 1998 [15] The Netherlands	D, 55 NoD, 229	73.0±7.3 68.2±8.0	19.9±5.2 26.7±2.7	DSM-III-R/no	Yes
Tuokko et al 1992 [16] USA	AD, 58 NE, 62	70.6±7.5 71.3±8.1	15.5±7.7	NINCDS/no DSM-III-R	Yes
Watson et al 1993 [17] USA	D, 40 NoD, 36	55–92	CDR	NINCDS/no	

Contrast	Test(s)	SS	SP	LR+/–	Quality of study	Reviewers comments
D-noD	$Clock_{Shullman}$	0.81	0.79	3.86	2a	Shulman meth
D-noD	$Clock_{Sunderland}$	0.56	0.91	6.22		recommended
D-noD	$Clock_{Wolf\text{-}Klein}$	0.39	0.95	7.80		
D-noD	$Clock_{Watson}$	0.56	0.80	2.80		
D-noD	$Clock_{Manos}$	0.67	0.86	4.79		
D-noD	$_{CDT+SKT}$	0.92	0.98	46		
D-noD	$_{CDT+MMSE}$	0.90	1.00	∞		
D-noD	$MMSE_{23/24}$	0.80	1.00	∞/0.20		
D-noD	$SKT_{8/9}$	0.75	0.98	37.5		
AD-noD	$CDT_{Wolf\text{-}Klein}$	0.867	0.927	11.9/14		Cross-sectional
D-noD	$MMSE_{23/24}$	0.96	0.81	5.05/0.05		Cross-sectional
	$CDT\text{-}Fr_{11/12}$	0.85	0.89	7.7/0.17		
	CDT+MMSE	1.00	0.91	11.1		
	CAMCOG	1.00	0.91	11.1/0.00		
D-noD	$HopVLTot/_{14.5}$	0.87	0.98	43.5		OPTIMA.
AD-noD	$HopVLMem/_{24.5}$	0.91	0.98	45.5		Cross-sectional
D-noD	$MMSE_{23/24}$	0.83	0.98	41.5/0.17		
AD-noD	$MMSE_{23/24}$	0.85	0.98	42.5/0.15		
D-noD	$CAMCOG_{69/70}$	0.85	0.90	8.5/0.17		Rott Stroke.
	$MMSE_{23/24}$	0.75	0.15	5		Cross-sectional
AD-NE	CDTdraw	0.92	0.86	6.6/0.09		Cut-off
AD-NE	CDTset	0.87	0.97	29.0/0.13		maximized.
AD-NE	CDTread	0.92	0.85	6.1/0.09		Cross-sectional
AD-NE	CDTcomb	0.94	0.93	13.4/0.06		
D-noD	CDT	0.87	0.82	4.8/0.16		Cross-sectional

The table continues on the next page

***Table 15.2** continued*

Author Year Reference Country	Sample (n) Follow-up (y)	Age (years)	Stage CDR/ MMSE/ GDS	Diagnostic criteria Clin/ Neuropath	Indepen-dence
Neri et al 1998 [18] Italy	D, 60 noD, 60 Follow-up: 1 year	~75 ~75	10–26 27–30	DSM-III-R/no	No
van Gorp et al 1999 [7] USA	AD, 22 VaD, 19 NC, 12	68.9±7.7 69.8±7.7 69.4±6.5	– – –	DSM-III-R/no	Yes
Mendez et al 1992 [19] USA	AD, 46 NE, 26	CDIS	13–21	NINCDS/no	
Cossa et al 1999 [20] Italy	D, 35 NoD, 733	60+ 60+	– –	DSM-III-R/no	Yes
Heun et al 1998 [21] Germany	D, 37 NoD, 250 Population based	89.1±6.2 74.7±10.0	19.4±5.5 27.9±1.7	ICD-10/no DSM-III-R	Yes
Brodaty et al 1997 [22] Australia	AD, 28 C, 28 Hospital based	73.1±8.9 69.5±7.7	19.5±5.3 28.7±1.4	DSM-III-R/no NINCDS	Yes

AD = Alzheimer's disease; C = Control; CDR = Clinical dementia rating scale; CDT = Clock drawing task; D = Dementia; GDS = Global deterioration scale; HopVLT = Hopkins verbal learning test; MMSE = Mini-mental state examination; MODA = Milan overall dementia assessment; NE = Normal examination; NoD = Not demented; SKT = Syndrom kurztest (or syndrom short test)

Contrast	Test(s)	SS	SP	LR+/–	Quality of study	Reviewers' comments
D-noD	$CAMCOG_{79/80}$	0.983	0.750	3.93		Cross-sectional
D-noD	$CAMCOGorg_{79/80}$	0.817	1.00	∞/0.18		
D-noD	CAMCOGshort	0.883	0.983	51.9/0.19		
D-noD	CAMCOGorgshort	0.933	1.000	∞/0.07		
D-NC	$MMSE_{25/26}$	0.71	1.00	∞		Cross-sectional
D-NC	$MMSE_{26/27}$	0.98	1.00	∞/0.02		
	$Mattis_{133/134}$	0.83	1.00	∞		
	NCSEtot	0.48	1.00	∞		
AD-NE	$CDT_{Shulman}$	0.91	1.00	∞/0.09		Cross-sectional
D-noD	MODA	1.00	0.716	3.52		Cross-sectional
D-noD	MMSE	0.857	0.9	8.57/0.16		
D-noD	$MMSE_{23/24}$	0.92	0.96	23.0/0.08	2a	
D-noD	$SIDAM_{42/43}$	0.97	0.91	10.8		
D-noD	$CatFlAn_{13/14}$	0.81	0.83	4.76		
D-noD	$WoRecIm_{12/3}$	0.82	0.77	3.57		
D-noD	$TMT_{39/40}$	0.81	0.71	2.79		
AD-C	$CDT_{Shulman\ 0.2/3}$	0.86	0.96	6.1/0.15	2a	Hospital
AD-C	$CDT_{Sunderland\ 0.8/9}$	0.79	0.93	11.3		
AD-C	$CDT_{Wolf\text{-}Klein\ 0.8/9}$	0.79	0.89	7.18		
AD-C	$MMSE_{23/24}$	0.71	1.00	∞		

References

1. Qizilbash N et al. Evidence-based dementia practice. Oxford: Blackwell Publishing Company; 2002.

2. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.

3. Roth M, Tym E, Mountjoy CQ, Huppert FA, Hendrie H, Verma S, et al. CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. Br J Psychiatry 1986;149:698-709.

4. Buschke H, Kuslansky G, Katz M, Stewart WF, Sliwinski MJ, Eckholdt HM, et al. Screening for dementia with the memory impairment screen. Neurology 1999;52:231-8.

5. Solomon PR, Hirschoff A, Kelly B, Relin M, Brush M, DeVeaux RD, et al. A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. Arch Neurol 1998;55:349-55.

6. Monsch AU, Foldi NS, Ermini-Funfschilling DE, Berres M, Taylor KI, Seifritz E, et al. Improving the diagnostic accuracy of the Mini-Mental State Examination. Acta Neurol Scand 1995;92:145-50.

7. van Gorp W, Marcotte TD, Sultzer D, Hinkin, C, Mahler, M, Cummings, JL. Screening for dementia: comparison of three commonly used instruments. J Clin Exp Neuropsychol 1999;21:29-38.

8. Wolf-Klein GP, Silverstone FA, Levy AP, Brod MS. Screening for Alzheimer's disease by clock drawing. J Am Geriatr Soc 1989;37:730-4.

9. Sunderland T, Hill JL, Mellow AM, Lawlor BA, Gundersheimer J, Newhouse PA, et al. Clock drawing in Alzheimer's disease. A novel measure of dementia severity. J Am Geriatr Soc 1989;37: 725-9.

10. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993; 269:2386-91.

11. Jorm AF. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. Int Psychogeriatr 2004;16:275-93.

12. Schramm U, Berger G, Muller R, Kratzsch T, Peters J, Frolich L. Psychometric properties of Clock Drawing Test and MMSE or Short Performance Test (SKT) in dementia screening in a memory clinic population. Int J Geriatr Psychiatry 2002;17:254-60.

13. Heinik J, Solomesh I, Bleich A, Berkman P. Are the clock-drawing test and the MMSE combined interchangeable with CAMCOG as a dementia evaluation instrument in a specialized outpatient setting? J Geriatr Psychiatry Neurol 2003;16:74-9.

14. Hogervorst E, Combrinck M, Lapuerta P, Rue J, Swales K, Budge M. The Hopkins

Verbal Learning Test and screening for dementia. Dement Geriatr Cogn Disord 2002;13:13-20.

15. de Koning I, van Kooten F, Dippel DW, van Harskamp F, Grobbee DE, Kluft C, et al. The CAMCOG: a useful screening instrument for dementia in stroke patients. Stroke 1998;29:2080-6.

16. Tuokko H, Hadjistavropoulos T, Miller JA, Beattie BL. The Clock Test: a sensitive measure to differentiate normal elderly from those with Alzheimer disease. J Am Geriatr Soc 1992;40:579-84.

17. Watson YI, Arfken CL, Birge SJ. Clock completion: an objective screening test for dementia. J Am Geriatr Soc 1993;41:1235-40.

18. Neri M, Rubichi S, DeVreese LP, Roth M, Cipolli C. Validation of the full and short forms of the CAMDEX interview for diagnosing dementia: evidence from a one-year follow-up study. Dement Geriatr Cogn Disord 1998;9:339-46.

19. Mendez MF, Ala T, Underwood KL. Development of scoring criteria for the clock drawing task in Alzheimer's disease. J Am Geriatr Soc 1992;40:1095-9.

20. Cossa FM, Sala SD, Musicco M, Spinnler H, Ubezio MC. The milan overall dementia assessment and the mini-mental state examination compared: an epidemiological investigation of dementia. Eur J Neurol 1999;6:289-94.

21. Heun R, Papassotiropoulos A, Jennssen F. The validity of psychometric instruments for detection of dementia in the elderly general population. Int J Geriatr Psychiatry 1998;13:368-80.

22. Brodaty H, Moore CM. The Clock Drawing Test for dementia of the Alzheimer's type: A comparison of three scoring methods in a memory disorders clinic. Int J Geriatr Psychiatry 1997;12:619-27.

16. Genetic Markers

Conclusion

ApoE genotyping has a small impact on the pretest probability of AD (Alzheimer's disease). It neither contributes significantly to the diagnosis of AD nor differentiates AD from other dementia disorders. No study in this review had a sensitivity of 80% or above and a LR+ of 5 or above. Thus, there is no evidence for the use of ApoE genotyping in the diagnostic and differential diagnostic of AD.

Causative genes for dementia disorders

Familial AD is rare, less than 1% of all patients with AD. Familial cases of VaD (cerebral autosomal arteriopathy with subcortical infarction and leucoencephalopathy = CADASIL), frontotemporal lobe dementia (FTLD) and dementia due to Creutzfeldt-Jakob disease (CJD) are even less frequent. For AD, mutations of three genes are known: presenilin genes 1 (Chromosome 14) and 2 (Chromosome 1) and the gene that codes for the amyloid precursor protein (Chromosome 21). For CADASIL, the only form of hereditary VaD, the Notch3 gene on chromosome 19 is identified. For FTLD, the tau gene on chromosome 17 and a yet unidentified gene on chromosome 3 is identified. For CJD, the prion gene on chromosome 20 is identified.

A search was conducted in Medline that included articles from 1975 to June 1, 2004. The keywords were "dementia/diagnosis", "dementia/genetics", "genetic counseling", "genetic testing", and "genetic screening". The search produced 207 titles of relevance. None of the abstracts contained information that disagreed with the findings and recommendations described in Chapter II.4.5 of "Evidence-based Dementia Practice" [1].

That chapter and consensus guidelines established in the United States and United Kingdom may be summarized as follows:

1. People who have a family history of AD with early onset are candidates for genetic testing.
2. A person who tests positive for pathogenic mutation has a chance of developing AD that is close to 100%.
3. A genetic test cannot predict age at onset of AD.
4. AD can still develop in people who test negative for a specific pathogenic mutation.
5. Tau mutation analysis can be used for the differential diagnosis of FTLD, but only patients with a family history of FTLD and typical symptoms are candidates for genetic testing.
6. Notch3 gene testing can be performed to confirm CADASIL in patients with a family history and typical symptoms of the disease.
7. Genetic counseling should be offered both before and after testing by a genetic specialist.

Apolipoprotein E ε4 as a diagnostic marker of AD

Background

The causes of sporadic AD, which is by far the most prevalent form, are not known. It is believed that genetic factors may interact with brain aging and various environmental factors, thus contributing to the development of AD. Apolipoprotein E (ApoE) gene on chromosome 19 is involved. It has three alleles: ε2, ε3 and ε4. The frequency of the three alleles varies across from continent to continent. In the Western world, where frequency is studied the most, the prevalence is about 15% for ε4, 75% for ε3 and 10% for ε2 [2].

According to several studies over the last ten years, people with the ApoE ε4 allele have an increased risk of developing AD and there is a dosage effect [3]. ApoE ε4 has also been shown to lead to earlier onset of AD, an effect that is dosage dependent. ApoE ε2 reduces the risk of

AD more than ε3 [4]. Consistent with this finding, healthy centenarians have a higher frequency of ε2 than the general population [5]. We also know that 40–50% of all people with at least one ApoE ε4 will eventually develop AD. But even among people who have the greatest risk, those with ε4/ε4 appear to have a 50% chance of escaping AD. The ApoE gene is a risk factor, not a cause of AD. We do not know exactly how the ApoE protein influences the pathophysiology of AD. One claim is that patients with AD who have ApoE ε4 deteriorate more rapidly than those without the allele, and that those with ε4 respond more poorly to acetylcholinesterase inhibitors, but the evidence for such assertions is not very good [6–10].

The use of ApoE as a diagnostic marker of AD has been addressed by several committees of experts, particularly in the United States and United Kingdom. The committees are from the American College of Medical Genetics, the Alzheimer's Disease Genetic Consortium, the United Kingdom Alzheimer's Disease Genetic Consortium, the National Institute of Aging, and Alzheimer's Disease International. So far, all consensus statements conclude that ApoE genotyping has no role in symptom-free people. This view is supported by a meta-analysis, which shows that with at least one ApoE ε4 allele, LR+ is 2.3, and that LR– of 0.55 separates AD patients from normal controls [4]. Using ε4/ε4 as a diagnostic marker in the same meta-analysis, LR+ rose to 8, whereas LR– was 0.87. A subcommittee of the American Academy of Neurology outlined guidelines and recommendations for the diagnostic workup of people with suspected dementia based on a literature review process [11]. The authors concluded that there is no evidence that Apo E genotyping is useful in the diagnostic workup of patients with suspected AD. Payami [1], the author of chapter II.4.5, "Genetic markers in differential diagnosis" in "Evidence-based Dementia Practice" came to the same conclusion after reviewing 69 case-control studies [1].

Some claims have been made that ApoE testing could be useful in differentiating AD from other dementia disorders. A study by Mayeux et al in 1998 on a large neuropathologically confirmed cohort of patients suggested that ApoE genotyping may be useful for this purpose in patients referred to a specialized assessment when the pre-test probability of AD

is very high [12]. The study demonstrated that the presence of at least one ε4 allele, along with clinical data, slightly increased the accuracy of a clinical diagnosis of AD, whereas the absence of an ApoE ε4 allele had little value in either confirming or refuting a clinical diagnosis of AD. Thus, ApoE testing seems to confer negligible diagnostic benefits. The groups in the United States and United Kingdom that have formulated consensus guidelines regarding ApoE genotyping do not recommend ApoE testing as part of the differential diagnostic assessment [13]. But Payami never concluded whether or not ApoE testing might be useful in the differential diagnostic workup [1]. He left the question open, pointing to a paper by Mayuex et al [12] and stated that "further research is needed to assess the applicability of this finding to the general population and to determine the predictive value of ApoE by gender, ethnicity and age".

The aim of this literature review was to further investigate new evidence for the clinical utility of ApoE testing to 1) differentiate people with AD from normal elderly, 2) differentiate AD from other dementia disorders, and 3) differentiate AD patients from people with mild cognitive impairment (MCI). We also searched for evidence that gender, age and ethnicity influence the predictive value of ApoE genotyping.

Literature search strategy

Searches were conducted in Medline among papers published between January 1, 1990 and June 1, 2004. The keywords were "dementia/genetics", "apolipoprotein", "comparative or control studies" and "cohort and family studies". Only papers written in English were requested. A thorough review of the references from "Evidence-based Dementia Practice" was also performed [14].

Results

There were 737 titles and abstracts found and reviewed for relevancy, 128 articles allowed calculation of the sensitivity, specificity and likelihood ratio (LR). Many high-quality papers reported only the frequency of the three alleles (ε2, ε3, ε4), making it impossible to calculate the sensitivity, specificity and likelihood ratio. Of the 128 papers, 28 more were

excluded because they did not use standardized criteria for the diagnosis of AD or other dementias, contain a description of a sufficient clinical diagnostic workup, include a comparison group, examine at least 20 + 20 individuals, or perform an independent blind evaluation of the test against the diagnosis. Some of these studies were significant [15–19].

Many studies have examined the utility of ApoE as a diagnostic marker both for AD and in the differential diagnosis of dementia. Thus, references appear in more than one table. To study age dependency, 80 was used as a cut-off. Early onset AD was compared with late onset AD. The results in Tables 16.1–5 are based on the assumption of at least one ApoE ε4 allele.

We found only one paper that included a sufficient number of patients and controls to permit calculation of sensitivity (19%), specificity (97%) and likelihood ratio (LR+ 5.7, LR– 0.84) for ε4/ε4 as a marker of AD [20]. No conclusions can be drawn from a single study.

ApoE ε4 allele as a marker of AD in comparison with controls

The results of the grade I and II studies are shown in Table 16.2. Polvikoski et al in Finland conducted the only grade Ia study [21]. It reported a LR+ of 2.07 and LR– of 0.69 and included a rather small number of AD patients. We found no association between LR and age in the five studies. All studies were conducted among Caucasians, so that the influence of ethnicity cannot be estimated. Sufficient information was not reported in order to analyze the influence of gender.

Table 16.3 shows the results from Population based studies and from studies with highly-selected patients for which clinical diagnosis was the gold standard. Most studies were conducted in the United States and Europe on Caucasians. The few Population based studies of African-Americans showed a somewhat lower LR+ than those among Caucasians, Asians and Hispanics. The only study of Arabs reported a very low prevalence of one ApoE ε4 allele: 5% in AD patients and 6% in elderly without dementia [22]. However, the differences for LR+ and

LR– among studies of different ethnicity, age and onset were not statistically significant (ANOVA and independent t-test). Gender-specific prevalence rates of ApoE ε4 were reported in only few studies, rendering statistical testing meaningless.

LR+ test was highest and LR– test was lowest among grade 2b studies (Table 16.1). But those studies are not representative of any clinical setting, because the controls are not representative of the cohort referred to clinical settings such as memory clinics or specialized outpatient clinics. Only three studies reported LR+ above 5, which is a significant predictive value for a diagnostic test, whereas none of these studies showed LR– below 0.4. All three were grade 2b studies with an extremely low prevalence of ApoE ε4 alleles among the controls [23–26].

ApoE ε4 allele as marker of AD compared to other dementia disorders

Table 16.4 shows the studies that compared ApoE ε4 allele as a marker for distinguishing AD from other dementias. Seventeen of the studies in Table 16.4 compared the presence of at least one ApoE ε4 allele in AD and VaD. The results of those studies averaged LR+ of 1.8 (1.4–2.2, 95% CI) and LR– of 0.74 (0.64–0.84, 95% CI), indicating that ApoE genotyping is a poor diagnostic method for differentiating AD from VaD. No differences in LR+ and LR– were found with regard to ethnicity and age. The information on gender and age at disease onset was not sufficient to allow for statistical testing.

Two grade Ib studies – one from the United States and one from the United Kingdom – were identified that contained reliable information regarding ApoE genotype in Diffuse Lewy Body Dementia (DLBD), with LR+ of 1.9 and LR– of 0.55 differentiating AD from DLBD in one study and LR+ of 1.0 and LR– of 1.0 differentiating AD from DLBD in the other study [27,28]. These results confirm that ApoE genotyping is not useful in the differential diagnostic workup of DLBD.

ApoE ε4 allele as marker of AD compared to MCI

Eight studies of sufficient quality were found that describe the discriminatory effect of having at least one ApoE ε4 allele between patients with AD and MCI. Four studies used the diagnostic term MCI, one used the term Age Associated Memory Impairment (AAMI) and one used the term Questionable Dementia (QD). As can be seen from Tables 16.1 and 16.5, LR+ varied between 0.7 and 2.4 and LR– varied between 0.64 and 1.1. This is not surprising given the suggestion that more than 50% of patients with MCI will develop AD. Comparisons of LR across ethnicity, gender and age at onset were not meaningful given the small number of patients and studies.

ApoE ε4 allele as marker of FTLD compared to normal controls

The search revealed 16 studies that compared the ApoE genotype between patients suffering from FTLD and elderly controls [29–45]. Two studies recruited their respondents from Population based studies, whereas the remaining 14 included highly-selected patients and controls. Most studies included very few patients and controls, and some did not report sufficient information in order to calculate sensitivity and specificity [29,33,35,37,41,43,45], leaving few studies with enough respondents to calculate sensitivity, specificity and LR+. Verpillat et al, 2002, who conducted the largest of these studies with 94 patients and 392 controls, reported a sensitivity of having at least one ApoE ε4 allele of 19.1% and a specificity of 69.1% [42]. A meta-analysis of seven case-control studies yielded a sensitivity of 26.7%, specificity of 73.8%, LR+ of 1.0 and LR– of 1.0 [42]. According to the meta-analysis, ApoE genotyping is not helpful in diagnosing FTLD.

Table 16.1 *ApoE ε4 as a diagnostic marker of Alzheimer's disease (AD). Summary of results.*

Comparison of groups	Number of studies	Number of people	Sensitivity Median (range)
AD vs controls	5	700 718	58% (43–65)
AD vs controls	32	3 860 23 749	45% (5–73)
AD vs controls	44	5 220 7 317	55% (19–87)
AD vs controls	81	9 780 31 784	49% (5–87)
AD vs OD	9	2 807 823	58% (32–83)
AD vs VaD	17	2 191 1 045	51% (32–65)
AD vs MCI	8	1 554 856	55% (5–62)

AD = Alzheimer's disease; MCI = Mild cognitive impairment; OD = Other dementias except VaD; VaD = Vascular dementia

	Specificity Median (range)	LR+ Median (range)	LR– Median (range)	Quality of study
	75% (70–79)	2.1 (2.0–2.7)	0.58 (0.37–0.72)	I/II a+b
	74% (60–94)	1.7 (0.8–5.6)	0.73 (0.38–1.0)	1a+b
	79% (64–95)	2.4 (1.7–5.7)	0.60 (0.16–0.9)	2a+b
	77% (60–95)	2.1 (0.8–5.7)	0.64 (0.16–1.0)	All grades
	67% (40–88)	1.9 (1.0–4.9)	0.77 (0.20–1.0)	All grades
	70% (50–88)	1.5 (0.8–3.6)	0.73 (0.46–1.2)	All grades
	57% (39–93)	1.2 (0.7–2.4)	0.84 (0.64–1.1)	All grades

Table 16.2 *ApoE ε4 (≥1 ε4) as a diagnostic marker. Alzheimer's disease vs non-demented controls. Quality of study I and II (neuropathologic diagnosis).*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	Path Criteria
Polvikoski et al 2001 [21] Finland	AD = 41 Co = 329	85+	NINCDS ADRDA DSM-III-R	CERAD
Tsuang et al 1999 [46] USA	AD = 94 Co = 38	80±7	NINCDS ADRDA DSM-III-R	CERAD
Singleton et al 2002 [28] United Kingdom	AD = 194 Co = 111 EOAD = 40 LOAD = 73	41+	NINCDS ADRDA	>5 SP >1 NFT
Bennett et al 2003 [47] USA	AD = 51 Co = 77		NINCDS ADRDA	CERAD
Nielsen et al 2003 [48] Denmark	AD = 320 Co = 163		DSM-III-R	CERAD Braak

AD = Alzheimer's disease; CERAD = Consortium to establish a registry for Alzheimer's disease; Co = Non-demented controls; EOAD = Early onset Alzheimer's disease; LOAD = Late onset Alzheimer's disease; LR+ = Likelihood ratio; NFT = Neurofibrillary tangles; SN = Senile plaques; SS = Sensitivity; SP = Specificity

	SS	SP	LR+	LR–	Quality of study	Comments
	0.47	0.77	2.07	0.69	Ia	
	0.59	0.71	2.03	0.58	Ib	
	0.58	0.75	2.3	0.56	Ib	
	0.53	0.74	2.1	0.64		EOAD
	0.59	0.72	2.1	0.57		LOAD
	0.43	0.79	2.1	0.72	Ib	
	0.65	0.7	2.7	0.37	IIb	

Table 16.3 *ApoE ε4 (≥1 ε4) as a diagnostic test. Alzheimer's disease (AD) vs non-demented controls. Quality of study 1 and 2 (clinical diagnosis).*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	SS
Lannfelt et al 1994 [49] Sweden	AD = 124 Co = 508	80+	NINCDS ADRDA DSM-III-R	0.73 0.38
van Duijn et al 1994 [50] The Netherlands	AD = 175 Co = 159	63±4	NINCDS ADRDA	0.53
Kukull et al 1996 [51] USA	AD = 234 Co = 304	80±7	DSM-III-R/IV	0.52
Myers et al 1996 [52] USA	AD = 43 Co = 962	80±6	NINCDS ADRDA	0.49
Tang et al 1996 [53] USA	AD = 305 Co = 485	65+	NINCDS ADRDA	0.36 0.47 0.34
Evans et al 1997 [54] USA	AD = 88 Co = 490	79±6	NINCDS ADRDA	0.23
Katzman et al 1997 [55] China	AD = 65 Co = 363	60–96	NINCDS ADRDA DSM-III-R	0.46
Sahota et al 1997 [56] USA	AD = 60 Co = 216	83±6	NINCDS ADRDA DSM-III-R ICD-10	0.50

	SP	LR+	LR–	Quality of study	Comments
	0.72 0.72	2.7 1.3	0.38 0.86	1a	Familial Sporadic
	0.73	1.96	0.64	1a	
	0.74	2.02	0.66	1a	
	0.79	2.37	0.65	1a	
	0.61 0.82 0.81	0.92 2.66 1.79	1.0 0.65 0.79	1a	Afro-American Caucasian Hispanic
	0.84	1.70	0.92	1a	
	0.80	2.62	0.68	1a	Asian
	0.61	1.27	0.82	1a	Afro-American

The table continues on the next page

Table 16.3 *continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	SS
Slooter et al 1997 [57] USA	AD = 70 Co = 507	80±7	NINCDS ADRDA DSMIV	0.39
Notkola et al 1998 [58] Finland	AD = 27 Co = 397	70–89	NINCDS ADRDA DSM-IV	0.45
Skoog et al 1998 [59] Sweden	AD = 52 Co = 303	85	NINCDS ADRDA	0.56
Slooter et al 1998 [60] The Netherlands	AD = 97 Co = 997	82±7	NINCDS ADRDA	0.53
Tang et al 1998 [61] USA	AD = 221 Co = 1 079	75±6	NINCDS ADRDA	0.34 0.30 0.27
Tilvis et al 1998 [62] Finland	AD = 41 Co = 474	75+	DSM-III-R	0.51
Devi et al 1999 [63] USA	AD = 106 Co = 220	78±7	NINCDS ADRDA	0.35
Tsuang et al 1999 [46] USA	AD = 94 Co = 38	80±7	NINCDS ADRDA DSM-III-R	0.49

	SP	LR+	LR–	Quality of study	Comments
	0.73	1.45	0.84	1a	
	0.74	1.73	0.74	1a	
	0.61	1.44	0.72	1a	
	0.72	1.90	0.65	1a	
	0.60 0.77 0.75	0.85 1.30 1.08	1.00 0.91 0.97	1a	Afro-American Caucasian Hispanic
	0.76	2.13	0.64	1a	
	0.73	1.30	0.89	1a	
	0.84	3.06	0.61	1a	

The table continues on the next page

Table 16.3 *continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	SS
Lilius et al 1999 [64] Sweden	AD = 94 Co = 176	80±5	DSM-III-R	0.47
Ganguli et al 2000 [65] USA/India	AD = 115 Co = 754 AD = 28 Co = 4 414	70+	NINCDS ADRDA DSM-III-R	0.28 0.29
Johnston et al 2000 [66] USA	AD = 102 Co = 375	80±5	NINCDS ADRDA DSM-III-R	0.28
Kardaun et al 2000 [67] USA/Honolulu	AD = 105 Co = 3 459	71–93	NINCDS ADRDA	0.31
Molero et al 2001 [68] Venezuela	AD = 121 Co = 1 165	78±9	NINCDS ADRDA	0.32
Bowirrat et al 2002 [22] Israel	AD = 98 Co = 173	60+	DSM-IV	0.05
Romas et al 2002 [69] Carribean	AD = 306 Co = 218		NINCDS ADRDA	0.53

	SP	LR+	LR–	Quality of study	Comments
	0.74	1.80	0.72	1a	
	0.80	1.36	0.98	1a	USA
	0.86	2.03	0.83		India
	0.79	1.39	0.91	1a	
	0.82	1.70	0.84	1a	Asian-American
	0.80	1.60	0.85	1a	Hispanic
	0.94	0.80	1.00	1a	Arab
	0.61	1.40	0.77	1a	

The table continues on the next page

Table 16.3 *continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	SS
Kukull et al 2002 [70] USA	AD = 151 Co = 215	65+	NINCDS ADRDA DSM-IV	0.41
Kim et al 2002 [26] Korea	AD = 104 Co = 52	76±6	NINCDS ADRDA	0.45
Chandak et al 2002 [71] India	AD = 49 Co = 100	40+	NINCDS ADRDA	0.35
Miech et al 2002 [72] USA	AD = 122 Co = 3 099	65+	NINCDS ADRDA DSM-III	0.43
Qui et al 2004 [73] Sweden	AD = 206 Co = 779	75+	DSM-III-R	0.35
Hsiung et al 2004 [74] Canada	AD = 140 Co = 582	82.7 75.6	NINCDS ADRDA DSM-III-R	0.36
Jobst et al 1997 [75] United Kingdom	AD = 80 Co = 105	57–100	NINCDS ADRDA DSM-III-R	0.70
Breitner et al 1998 [76] USA	AD = 37 Co = 344	62–73	NINCDS ADRDA	0.57

	SP	LR+	LR–	Quality of study	Comments
	0.67	1.30	0.88	1a	
	0.92	5.60	0.60	1a	Asian
	0.83	2.00	0.78	1a	Asian
	0.70	1.40	0.81	1a	
	0.83	2.10	0.50	1a	
	0.80	1.80	0.56	1a	
	0.60	1.75	0.50	1b	
	0.73	2.10	0.59	1b	

The table continues on the next page

Table 16.3 *continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	SS
Moceri et al 2001 [77] USA	AD = 200 Co = 237	60+	NINCDS ADRDA DSM-III-R/-IV	0.56
Stengard et al 1995 [78] Finland	AD = 27 Co = 353	70–89	DSM-III-R	0.44
Mullan et al 1996 [79] USA	AD = 107 Co = 248	74±10	NINCDS ADRDA	0.55
Bickeboller et al 1997 [80] France	AD = 417 Co = 1 030	50+	NINCDS ADRDA DSM-III-R	0.57
Quiroga et al 1999 [81] Chile	AD = 95 Co = 187	65+	NINCDS ADRDA DSM-IV ICD-10	0.62
Poirier et al 1993 [82] Canada	AD = 91 Co = 71	75±10	NINCDS ADRDA	0.63
Payami et al 1993 [83] USA	AD = 53 Co = 56	60+	NINCDS ADRDA	0.85
Ueki et al 1993 [23] Japan	AD = 42 Co = 96	76±8	DSM-III-R	0.60

	SP	LR+	LR–	Quality of study	Comments
	0.74	2.12	0.59	1b	
	0.74	1.72	0.76	2a	
	0.73	2.04	0.62	2a	
	0.72	2.04	0.60	2a	
	0.64	1.73	0.59	2a	Hispanic
	0.78	2.86	0.47	2b	
	0.71	2.93	0.21	2b	
	0.90	5.74	0.44	2b	Asian

The table continues on the next page

Table 16.3 *continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	SS
Dai et al 1994 [84] Japan	EOAD = 29 LOAD = 59 Co = 93	75±9	NINCDS ADRDA	0.72 0.49
Liddell et al 1994 [85] United Kingdom	AD = 86 Co = 77	74±10	NINCDS ADRDA	0.48
Tsai et al 1994 [86] USA	AD = 77 Co = 77	81±9	NINCDS ADRDA DSM-III-R	0.58
Nunomura et al 1996 [87] Japan	EOAD = 21 LOAD = 51 Co = 83	50–96	ICD-10	0.57 0.51
Tsuang et al 1996 [88] USA	AD = 55 Co = 99	71±7	NINCDS ADRDA	0.73
Yang et al 1996 [89] Australia	AD = 30 Co = 50		NINCDS ADRDA	0.87
Almeida et al 1997 [90] Brazil	AD = 55 Co = 56	45–89	NINCDS ADRDA	0.36
Kalman et al 1997 [91] Hungary	AD = 50 Co = 71	76±9	NINCDS ADRDA DSM-II-R	0.46

	SP	LR+	LR– of study	Quality	Comments
	0.82 0.82	4.00 2.73	0.34 0.62	2b	Asian
	0.78	2.16	0.67	2b	
	0.74	2.25	0.57	2b	
	0.85 0.85	3.94 3.53	0.51 0.58	2b	Asian
	0.70	2.40	0.39	2b	
	0.80	4.33	0.16	2b	
	0.82	2.03	0.78	2b	
	0.87	3.54	0.62	2b	

The table continues on the next page

Table 16.3 *continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	SS
Palumbo et al 1997 [24] Italy	EOAD = 32 LOAD = 64 Co = 40	50–88	NINCDS ADRDA	0.19 0.61
Wang et al 1997 [92] Taiwan	AD = 98 Co = 98	71±7	NINCDS ADRDA	0.34
Kowalska et al 1998 [25] Poland	EOAD = 25 LOAD = 39 Co = 43	30–94	NINCDS ADRDA	0.24 0.56
Lopez et al 1998 [93] USA Spain	AD = 66 Co = 49 AD = 209 Co = 58	75±9 73±8	NINCDS ADRDA	0.44 0.60
Bretsky et al 1999 [94] USA Canada	AD = 80 Co = 115	81±7	NINCDS ADRDA	0.71
Kim et al 1999 [95] Korea	AD = 110 Co = 226	50–85	NINCDS ADRDA	0.39
Lilius et al 1999 [64] Sweden	AD = 175 Co = 62	65±9	NINCDS ADRDA	0.74

	SP	LR+	LR–	Quality of study	Comments
	0.90 0.90	1.88 6.10	0.90 0.54	2b	
	0.88	2.93	0.75	2b	
	0.95 0.95	4.80 11.2	0.80 0.46	2b	
	0.76 0.64	1.83 1.67	0.74 0.63	2b	Caucasian Hispanic
	0.64	2.00	0.45	2b	
	0.82	2.22	0.74	2b	Asian
	0.69	2.42	0.38	2b	

The table continues on the next page

Table 16.3 *continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	SS
Nakayama et al 1999 [96] Japan	EOAD = 33 LOAD = 25 Co = 1 090	48±10 72±6	NINCDS ADRDA	0.44 0.61
Scacchi et al 1999 [97] Italy	AD = 83 Co = 152	86±4	NINCDS ADRDA DSM-III-R	0.3
Traykov et al 1999 [98] France	AD = 155 Co = 51	79±6	NINCDS ADRDA	0.56
Siest et al 2000 [99] Italy	AD = 489 Co = 429	75±9	NINCDS ADRDA DSM-IV	0.54
Kim et al 2001 [100] Korea	EOAD = 45 LOAD = 65 Co = 239		NINCDS ADRDA DSM-IV	0.44 0.35
Rigaud et al 2001 [101] France	AD = 42 Co = 98	68±5 67±5	NINCDS ADRDA	0.57
Zill et al 2001 [102] Germany	AD = 89 Co = 118	73±9	NINCDS ADRDA	0.57
Yang et al 2001 [103] China	AD = 191 Co = 218	65+	NINCDS ADRDA	0.48

	SP	LR+	LR–	Quality of study	Comments
	0.86 0.86	2.06 4.21	0.65 0.45	2b	Asian
	0.89	2.69	0.79	2b	
	0.86	4.05	0.51	2b	
	0.77	2.40	0.60	2b	
	0.82 0.82	2.52 1.44	0.68 0.92	2b	Asian
	0.71	2.00	0.61	2b	
	0.71	1.99	0.61	2b	
	0.79	2.31	0.66	2b	Asian

The table continues on the next page

Table 16.3 *continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	SS
Huang et al 2002 [104] Taiwan	AD = 99 Co = 96		NINCDS ADRDA	0.32
Graff-Radford et al 2002 [20] USA	AD = 338 Co = 301		NINCDS ADRDA	0.65
Frank et al 2002 [105] Spain	AD = 83 Co = 97		NINCDS ADRDA	0.54
Solfrizzi et al 2002 [106] Italy	AD = 61 Co = 63	68±7	NINCDS ADRDA	0.30
Panza et al 2003 [107] Italy	AD = 49 Co = 45	72±9	NINCDS ADRDA	0.31
Hawi et al 2003 [108] Ireland	AD = 110 Co = 217	65+	NINCDS ADRDA	0.65
Styczynska et al 2003 [109] Poland	AD = 100 Co = 100	70±7 74±7	NINCDS ADRDA	0.58

	SP	LR+	LR–	Quality of study	Comments
	0.84	2.00	0.81	2b	Asian
	0.67	2.00	0.52	2b	Afro-American
	0.87	4.20	0.53	2b	Hispanic
	0.87	2.40	0.80	2b	
	0.85	2.00	0.81	2b	
	0.65	1.90	0.54	2b	
	0.79	2.80	0.36	2b	

The table continues on the next page

Table 16.3 *continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	SS
Souza et al 2003 [110] Brazil	AD = 68 Co = 58	65–82	NINCDS ADRDA	0.46
Wehr et al 2003 [111] Poland	AD = 29 Co = 41	48–83	NINCDS ADRDA DSM-IV	0.48
Finckh et al 2003 [112] Germany	AD = 347 Co = 291	74±9 68±12	NINCDS ADRDA	0.60
Feldman et al 2003 [113] Canada	AD = 290 Co = 65	73.1+9 61.3+12	DSM-III-R	0.62
Borroni et al 2004 [114] Italy	AD = 157 Co = 134	72.2±8	NINCDS ADRDA	0.41
Luthra et al 2004 [115] India	AD = 29 Co = 76	66.6±9 63,2±10	NINCDS ADRDA	0.52

AD = Alzheimer's disease; Co = Non-demented controls; EOAD = Early onset Alzheimer's disease; LOAD = Late onset Alzheimer's disease; LR+ = Likelihood ratio; SP = Specificity; SS = Sensitivity

	SP	LR+	LR–	Quality of study	Comments
	0.79	2.20	0.45	2b	
	0.83	2.80	0.35	2b	
	0.75	2.40	0.42	2b	
	0.75	2.50	0.40	2b	
	0.84	2.60	0.70	2b	
	0.83	3.10	0.33	2b	Asian

Table 16.4 *ApoE ε4 (≥1 ε4) as a diagnostic marker. Alzheimer's disease vs other dementias.*

Author Year Reference Country	**Sample**	**Age (years)**	**Clinical criteria**	**Path criteria**
Polvikoski et al 2001 [21] Finland	AD = 41 OD = 47	85+	NINCDS ADRDA	CERAD
Welsh-Bohmer et al 1997 [116] USA	AD = 139 OD = 23	77±8	NINCDS ADRDA	CERAD
Mayeux et al 1998 [12] USA	AD = 1 770 OD = 418	72±10	NINCDS ADRDA DSM-III-R	CERAD Khachatu
Rosenberg et al 2001 [27] USA	AD = 181 LBD = 81	77 at death		CERAD Braak
Singleton et al 2002 [28] United Kingdom	AD = 194 LBD = 76	41+	NINCDS ADRDA Newcastle	>5 SP >1 NFT
Nielsen et al 2003 [48] Denmark	AD = 320 VaD = 163		DSM-III-R	CERAD Braak
Myers et al 1996 [52] USA	AD = 43 OD = 25	80±6	NINCDS ADRDA DSM-III	

	SS	SP	LR+	LR–	Quality of study	Comments
	0.47	0.59	1.16	0.90	Ia	
	0.83	0.83	4.88	0.20	Ib	
	0.65	0.68	2.03	0.51	IIb	CERAD used in some cases
	0.63	0.67	1.90	0.55	IIb	
	0.58	0.40	1.00	1.00	Ib	
	0.65	0.70	2.20	0.46	IIb	
	0.49	0.64	1.36	0.80	1a	

The table continues on the next page

***Table 16.4** continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	Path criteria
Katzman et al 1997 [55] China	AD = 65 VaD = 27	60–96	NINCDS ADRDA DSM-III-R	
Slooter et al 1997 [57] USA	AD = 70 VaD = 90	80±7	NINCDS ADRDA NINDS-AIREN	
Notkola et al 1998 [58] Finland	AD = 27 VaD = 20	70–89	DSM-III-R	
Skoog et al 1998 [59] Sweden	AD = 52 MID = 34	85	DSM-III-R	
Tilvis et al 1998 [62] Finland	AD = 41 VaD = 35	75+	DSM-III-R	
Molero et al 2001 [68] Venezuela	AD = 121 VaD = 34	78±9	NINCDS ADRDA ADDTC	
Hsiung et al 2004 [74] Canada	AD = 140 VaD = 51	82.7 77	NINCDS ADRDA DSM-III-R	
Kalman et al 1997 [91] Hungary	AD = 50 OD = 60	76±9	NINCDS ADRDA DSM-III-R	

	SS	SP	LR+	LR–	Quality of study	Comments
	0.46	0.67	1.38	0.81	1a	
	0.39	0.64	1.08	0.95	1a	
	0.45	0.65	1.35	0.85	1a	
	0.56	0.50	1.12	0.88	1a	
	0.51	0.66	1.50	0.74	1a	
	0.32	0.88	2.75	0.77	1a	
	0.36	0.57	0.80	1.20	1a	
	0.46	0.82	2.56	0.66	2b	

The table continues on the next page

***Table 16.4** continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	Path criteria
Nakayama et al 1999 [96] Japan	AD = 55 VaD = 45	72±10	NINCDS ADRDA NINDS-AIREN	
Traykov et al 1999 [98] France	AD = 155 VaD = 21	79±6	NINCDS ADRDA NINDS-AIREN	
Yang et al 2001 [103] China	AD = 191 VaD = 124	65+	NINCDS ADRDA NINDS-AIREN	
Traykov et al 2002 [117] France	AD = 219 VaD = 45	78±6	DSM-IV NINDS-AIREN	
Huang et al 2002 [104] Taiwan	AD = 99 VaD = 70		NINCDS ADRDA DSM-IV	
Huang et al 2002 [104] Taiwan	AD = 99 OD = 23		NINCDS ADRDA DSM-IV	
Frank et al 2002 [105] Spain	AD = 83 VaD = 26		NINCDS ADRDA ICD-10	
Wehr et al 2003 [111] Poland	AD = 29 VaD = 46	48–83	DSM-IV	

	SS	SP	LR+	LR–	Quality of study	Comments
	0.53	0.76	1.67	0.62	2b	
	0.56	0.76	2.33	0.58	2b	
	0.48	0.71	1.40	0.73	2b	
	0.54	0.80	2.70	0.58	2b	
	0.32	0.82	1.70	0.83	2b	
	0.32	0.88	2.70	0.77	2b	
	0.54	0.85	3.60	0.54	2b	
	0.48	0.78	2.20	0.46	2b	

The table continues on the next page

Table 16.4 *continued*

Author Year Reference Country	Sample	Age (years)	Clinical criteria	Path criteria
Engelborghs et al 2003 [118] Belgium	AD = 504 Co = 189	78.9±8 58.8±17	NINCDS ADRDA DSM-IV	
Feldman et al 2003 [113] Canada	AD = 290 OD = 70	73.1±9	DSM-III-R	
Luthra et al 2004 [115] India	AD = 29 VaD = 25	66.6±9 65.3±10	NINDS AIREN	

AD = Alzheimer's disease; LBD = Lewy body dementia; LR = Likelihood ratio; MID = Multiinfarct dementia; OD = Other dementias; SP = Specificity; SS = Sensitivity; VaD = Vascular dementia

	SS	SP	LR+	LR–	Quality of study	Comments
	0.56	0.57	1.30	0.77	2b	
	0.62	0.49	1.20	0.79	2b	
	0.52	0.56	1.20	0.85	2b	Asian

Table 16.5 *ApoE ε4 (≥1 ε4) as a diagnostic marker. Alzheimer's disease vs MCI.*

Author Year Reference Country	**Sample**	**Age (years)**	**Clinical criteria**
Katzman et al 1997 [55] China	AD = 65 QD = 72	60–96	NINCDS ADRDA DSM-III-R
Bowirrat et al 2002 [22] Israel	AD = 92 AAMI = 136	60+	DSM-IV
Hsiung et al 2004 [74] Canada	AD = 140 CIND = 337	82.7 75.6	NINCDS ADRDA DSM-III-R
Traykov et al 1999 [98] France	AD = 155 MCI = 45	79±6	NINCDS ADRDA Mayo
Zill et al 2001 [102] Germany	AD = 89 MCI = 32	73±9	NINCDS ADRDA Mayo
Traykov et al 2002 [117] France	AD = 219 MCI = 45	79±7	NINCDS ADRDA Mayo

	SS	SP	LR+	LR–	Quality of study
	0.46	0.80	2.36	0.68	1a
	0.05	0.93	0.70	1.00	1a
	0.36	0.77	1.60	0.64	1a
	0.56	0.49	1.14	0.90	2b
	0.57	0.44	1.02	0.98	2b
	0.54	0.61	1.40	0.75	2b

The table continues on the next page

Table 16.5 *continued*

Author Year Reference Country	**Sample**	**Age (years)**	**Clinical criteria**
Engelborghs et al 2003 [118] Belgium	AD = 504 MCI = 44	78.9±8 73.7±8	NINCDS ADRDA DSM-IV
Feldman et al 2003 [113] Canada	AD = 290 CIND = 145	73.1±9	DSM-III-R

AAMI = Age Associated Memory Impairment; AD = Alzheimer's disease; CIND = Cognitive impairment, no dementia; LR+ = Likelihood ratio; MCI = Mild cognitive impairment; QD = Questionable dementia; SP = Specificity; SS = Sensitivity

	SS	SP	LR+	LR–	Quality of study
	0.56	0.39	0.90	1.10	2b
	0.62	0.52	1.30	0.77	2b

References

1. Payami H. Genetic markers in differential diagnosis. In: Quizilbash N, Schneider L, Chui H, Tariot P, Brodaty H, Kaye J, et al, editors. Evidence-based dementia practice. Oxford: Blackwell Science; 2002. p 133-38.

2. St George-Hyslop PH. Genetic factors in the genesis of Alzheimer's disease. Ann N Y Acad Sci 2000;924:1-7.

3. Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993;43:1467-72.

4. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 1997;278:1349-56.

5. Kehoe P, Wavrant-De Vrieze F, Crook R, Wu WS, Holmans P, Fenton I, et al. A full genome scan for late onset Alzheimer's disease. Hum Mol Genet 1999;8:237-45.

6. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Jr, Rimmler JB, et al. Apolipoprotein E, survival in Alzheimer's disease patients, and the competing risks of death and Alzheimer's disease. Neurology 1995;45:1323-8.

7. Holmes C, Levy R, McLoughlin DM, Powell JF, Lovestone S. Apolipoprotein E: non-cognitive symptoms and cognitive decline in late onset Alzheimer's disease. J Neurol Neurosurg Psychiatry 1996;61:580-3.

8. Stern Y, Tang MX, Albert MS, Brandt J, Jacobs DM, Bell K, et al. Predicting time to nursing home care and death in individuals with Alzheimer disease. JAMA 1997;277:806-12.

9. Poirier J, Delisle MC, Quirion R, Aubert I, Farlow M, Lahiri D, et al. Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. Proc Natl Acad Sci U S A 1995;92:12260-4.

10. Farlow MR, Lahiri DK, Poirier J, Davignon J, Schneider L, Hui SL. Treatment outcome of tacrine therapy depends on apolipoprotein genotype and gender of the subjects with Alzheimer's disease. Neurology 1998;50:669-77.

11. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1143-53.

12. Mayeux R, Saunders AM, Shea S, Mirra S, Evans D, Roses AD, et al. Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. Alzheimer's Disease Centers Consortium on Apolipoprotein E and Alzheimer's Disease. N Engl J Med 1998;338:506-11.

13. Liddell MB, Lovestone S, Owen MJ. Genetic risk of Alzheimer's disease: advising relatives. Br J Psychiatry 2001;178:7-11.

14. Chui H, Zhang Q. Evaluation of dementia: a systematic study of the usefulness of the American Academy of Neurology's practice parameters. Neurology 1997;49:925-35.

15. Rebeck GW, Reiter JS, Strickland DK, Hyman BT. Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions. Neuron 1993;11:575-80.

16. Nalbantoglu J, Gilfix BM, Bertrand P, Robitaille Y, Gauthier S, Rosenblatt DS, et al. Predictive value of apolipoprotein E genotyping in Alzheimer's disease: results of an autopsy series and an analysis of several combined studies. Ann Neurol 1994;36:889-95.

17. Fabian VA, Jones TM, Wilton SD, Dench JE, Davis MR, Lim L, et al. Alzheimer's disease and apolipoprotein E genotype in Western Australia: an autopsy-verified series. Med J Aust 1996;165:77-80.

18. Benjamin R, Leake A, McArthur FK, Candy JM, Ince PG, Edwardson JA, et al. Apolipoprotein E genotype and Alzheimer's disease in an elderly Norwegian cohort. Neurodegeneration 1996;5:43-7.

19. Berg L, McKeel DW, Jr, Miller JP, Storandt M, Rubin EH, Morris JC, et al. Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. Arch Neurol 1998;55:326-35.

20. Graff-Radford NR, Green RC, Go RC, Hutton ML, Edeki T, Bachman D, et al. Association between apolipoprotein E genotype and Alzheimer disease in African American subjects. Arch Neurol 2002;59:594-600.

21. Polvikoski T, Sulkava R, Myllykangas L, Notkola IL, Niinisto L, Verkkoniemi A, et al. Prevalence of Alzheimer's disease in very elderly people: a prospective neuropathological study. Neurology 2001;56:1690-6.

22. Bowirrat A, Friedland RP, Farrer L, Baldwin C, Korczyn A. Genetic and environmental risk factors for Alzheimer's disease in Israeli Arabs. J Mol Neurosci 2002;19:239-45.

23. Ueki A, Kawano M, Namba Y, Kawakami M, Ikeda K. A high frequency of apolipoprotein E4 isoprotein in Japanese patients with late-onset nonfamilial Alzheimer's disease. Neurosci Lett 1993;163:166-8.

24. Palumbo B, Parnetti L, Nocentini G, Cardinali L, Brancorsini S, Riccardi C, et al. Apolipoprotein-E genotype in normal aging, age-associated memory impairment, Alzheimer's disease and vascular dementia patients. Neurosci Lett 1997;231:59-61.

25. Kowalska A, Florczak J, Pruchnik-Wolinska D, Kraszewski A, Wender M. Apolipoprotein E genotypes in sporadic early and late-onset Alzheimer's disease. Arch Immunol Ther Exp (Warsz) 1998; 46:177-81.

26. Kim JM, Shin IS, Yoon JS. Apolipoprotein E among Korean Alzheimer's disease patients in community-dwelling and hospitalized elderly samples. Dement Geriatr Cogn Disord 2002;13:119-24.

27. Rosenberg CK, Cummings TJ, Saunders AM, Widico C, McIntyre LM, Hulette CM. Dementia with Lewy bodies and Alzheimer's disease. Acta Neuropathol (Berl) 2001;102:621-6.

28. Singleton AB, Wharton A, O'Brien KK, Walker MP, McKeith IG, Ballard CG, et al. Clinical and neuropathological correlates of apolipoprotein E genotype in dementia with Lewy bodies. Dement Geriatr Cogn Disord 2002;14:167-75.

29. Frisoni GB, Calabresi L, Geroldi C, Bianchetti A, D'Acquarica AL, Govoni S, et al. Apolipoprotein E epsilon 4 allele in Alzheimer's disease and vascular dementia. Dementia 1994;5:240-2.

30. Geschwind D, Karrim J, Nelson SF, Miller B. The apolipoprotein E epsilon4 allele is not a significant risk factor for frontotemporal dementia. Ann Neurol 1998;44:134-8.

31. Gomez-Isla T, West HL, Rebeck GW, Harr SD, Growdon JH, Locascio JJ, et al. Clinical and pathological correlates of apolipoprotein E epsilon 4 in Alzheimer's disease. Ann Neurol 1996;39:62-70.

32. Gustafson L, Abrahamson M, Grubb A, Nilsson K, Fex G. Apolipoprotein-E genotyping in Alzheimer's disease and frontotemporal dementia. Dement Geriatr Cogn Disord 1997;8:240-3.

33. Helisalmi S, Linnaranta K, Lehtovirta M, Mannermaa A, Heinonen O, Ryynanen M, et al. Apolipoprotein E polymorphism in patients with different neurodegenerative disorders. Neurosci Lett 1996;205:61-4.

34. Kalman J, Juhasz A, Majtenyi K, Rimanoczy A, Jakab K, Gardian G, et al. Apolipoprotein E polymorphism in Pick's disease and in Huntington's disease. Neurobiol Aging 2000;21:555-8.

35. Lehmann DJ, Smith AD, Combrinck M, Barnetson L, Joachim C. Apolipoprotein E epsilon2 may be a risk factor for sporadic frontotemporal dementia. J Neurol Neurosurg Psychiatry 2000;69:404-5.

36. Masullo C, Daniele A, Fazio VM, Seripa D, Gravina C, Filippini V, et al. The Apolipoprotein E genotype in patients affected by syndromes with focal cortical atrophy. Neurosci Lett 2001;303:87-90.

37. Mesulam MM, Johnson N, Grujic Z, Weintraub S. Apolipoprotein E genotypes in primary progressive aphasia. Neurology 1997;49:51-5.

38. Minthon L, Hesse C, Sjogren M, Englund E, Gustafson L, Blennow K. The apolipoprotein E epsilon4 allele frequency is normal in fronto-temporal dementia, but correlates with age at onset of disease. Neurosci Lett 1997;226:65-7.

39. Pickering-Brown SM, Siddons M, Mann DM, Owen F, Neary D, Snowden JS. Apolipoprotein E allelic frequencies in patients with lobar atrophy. Neurosci Lett 1995;188:205-7.

40. Pickering-Brown SM, Owen F, Isaacs A, Snowden J, Varma A, Neary D, et al. Apolipoprotein E epsilon4 allele has no effect on age at onset or duration of disease in cases of frontotemporal dementia with pick- or microvacuolar-type histology. Exp Neurol 2000;163:452-6.

41. Short RA, Graff-Radford NR, Adamson J, Baker M, Hutton M. Differences in tau and apolipoprotein E polymorphism frequencies in sporadic frontotemporal lobar degeneration syndromes. Arch Neurol 2002;59:611-5.

42. Verpillat P, Camuzat A, Hannequin D, Thomas-Anterion C, Puel M, Belliard S, et al. Apolipoprotein E gene in fronto-

temporal dementia: an association study and meta-analysis. Eur J Hum Genet 2002;10:399-405.

43. Schneider JA, Gearing M, Robbins RS, de l'Aune W, Mirra SS. Apolipoprotein E genotype in diverse neurodegenerative disorders. Ann Neurol 1995;38:131-5.

44. Stevens M, van Duijn CM, de Knijff P, van Broeckhoven C, Heutink P, Oostra BA, et al. Apolipoprotein E gene and sporadic frontal lobe dementia. Neurology 1997;48:1526-9.

45. Farrer LA, Abraham CR, Volicer L, Foley EJ, Kowall NW, McKee AC, et al. Allele epsilon 4 of apolipoprotein E shows a dose effect on age at onset of Pick disease. Exp Neurol 1995;136:162-70.

46. Tsuang D, Larson EB, Bowen J, McCormick W, Teri L, Nochlin D, et al. The utility of apolipoprotein E genotyping in the diagnosis of Alzheimer disease in a community-based case series. Arch Neurol 1999;56:1489-95.

47. Bennett DA, Wilson RS, Schneider JA, Evans DA, Aggarwal NT, Arnold SE, et al. Apolipoprotein E epsilon4 allele, AD pathology, and the clinical expression of Alzheimer's disease. Neurology 2003;60:246-52.

48. Nielsen AS, Ravid R, Kamphorst W, Jorgensen OS. Apolipoprotein E epsilon 4 in an autopsy series of various dementing disorders. J Alzheimers Dis 2003;5:119-25.

49. Lannfelt L, Lilius L, Nastase M, Viitanen M, Fratiglioni L, Eggertsen G, et al. Lack of association between apolipoprotein E allele epsilon 4 and sporadic Alzheimer's disease. Neurosci Lett 1994;169:175-8.

50. van Duijn CM, de Knijff P, Cruts M, Wehnert A, Havekes LM, Hofman A, et al. Apolipoprotein E4 allele in a Population based study of early-onset Alzheimer's disease. Nat Genet 1994;7:74-8.

51. Kukull WA, Schellenberg GD, Bowen JD, McCormick WC, Yu CE, Teri L, et al. Apolipoprotein E in Alzheimer's disease risk and case detection: a case-control study. J Clin Epidemiol 1996;49:1143-8.

52. Myers RH, Schaefer EJ, Wilson PW, D'Agostino R, Ordovas JM, Espino A, et al. Apolipoprotein E epsilon4 association with dementia in a Population based study: The Framingham study. Neurology 1996;46:673-7.

53. Tang MX, Maestre G, Tsai WY, Liu XH, Feng L, Chung WY, et al. Relative risk of Alzheimer disease and age-at-onset distributions, based on APOE genotypes among elderly African Americans, Caucasians, and Hispanics in New York City. Am J Hum Genet 1996;58:574-84.

54. Evans DA, Beckett LA, Field TS, Feng L, Albert MS, Bennett DA, et al. Apolipoprotein E epsilon4 and incidence of Alzheimer disease in a community population of older people. JAMA 1997;277:822-4.

55. Katzman R, Zhang MY, Chen PJ, Gu N, Jiang S, Saitoh T, et al. Effects of apolipoprotein E on dementia and aging in the Shanghai Survey of Dementia. Neurology 1997;49:779-85.

56. Sahota A, Yang M, Gao S, Hui SL, Baiyewu O, Gureje O, et al. Apolipoprotein E-associated risk for Alzheimer's disease in the African-American population is genotype dependent. Ann Neurol 1997;42:659-61.

57. Slooter AJ, Tang MX, van Duijn CM, Stern Y, Ott A, Bell K, et al. Apolipoprotein E epsilon4 and the risk of dementia with stroke. A Population based investigation. JAMA 1997;277:818-21.

58. Notkola IL, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, Kivinen P, et al. Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. Neuroepidemiology 1998;17:14-20.

59. Skoog I, Hesse C, Aevarsson O, Landahl S, Wahlstrom J, Fredman P, et al. A population study of apoE genotype at the age of 85: relation to dementia, cerebrovascular disease, and mortality. J Neurol Neurosurg Psychiatry 1998;64:37-43.

60. Slooter AJ, Cruts M, Kalmijn S, Hofman A, Breteler MM, Van Broeckhoven C, et al. Risk estimates of dementia by apolipoprotein E genotypes from a Population based incidence study: the Rotterdam Study. Arch Neurol 1998;55:964-8.

61. Tang MX, Stern Y, Marder K, Bell K, Gurland B, Lantigua R, et al. The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. JAMA 1998;279:751-5.

62. Tilvis RS, Strandberg TE, Juva K. Apolipoprotein E phenotypes, dementia and mortality in a prospective population sample. J Am Geriatr Soc 1998;46:712-5.

63. Devi G, Ottman R, Tang M, Marder K, Stern Y, Tycko B, et al. Influence of APOE genotype on familial aggregation of AD in an urban population. Neurology 1999;53:789-94.

64. Lilius L, Froelich Fabre S, Basun H, Forsell C, Axelman K, Mattila K, et al. Tau gene polymorphisms and apolipoprotein E epsilon4 may interact to increase risk for Alzheimer's disease. Neurosci Lett 1999;277:29-32.

65. Ganguli M, Chandra V, Kamboh MI, Johnston JM, Dodge HH, Thelma BK, et al. Apolipoprotein E polymorphism and Alzheimer disease: The Indo-US Cross-National Dementia Study. Arch Neurol 2000;57:824-30.

66. Johnston JM, Nazar-Stewart V, Kelsey SF, Kamboh MI, Ganguli M. Relationships between cerebrovascular events, APOE polymorphism and Alzheimer's disease in a community sample. Neuroepidemiology 2000;19:320-6.

67. Kardaun JW, White L, Resnick HE, Petrovitch H, Marcovina SM, Saunders AM, et al. Genotypes and phenotypes for apolipoprotein E and Alzheimer disease in the Honolulu-Asia aging study. Clin Chem 2000;46:1548-54.

68. Molero AE, Pino-Ramirez G, Maestre GE. Modulation by age and gender of risk for Alzheimer's disease and vascular dementia associated with the apolipoprotein E-epsilon4 allele in Latin Americans: findings from the Maracaibo Aging Study. Neurosci Lett 2001;307:5-8.

69. Romas SN, Santana V, Williamson J, Ciappa A, Lee JH, Rondon HZ, et al. Familial Alzheimer disease among Caribbean Hispanics: a reexamination of its association with APOE. Arch Neurol 2002;59: 87-91.

70. Kukull WA, Higdon R, Bowen JD, McCormick WC, Teri L, Schellenberg GD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. Arch Neurol 2002;59:1737-46.

71. Chandak GR, Sridevi MU, Vas CJ, Panikker DM, Singh L. Apolipoprotein E and presenilin-1 allelic variation and Alzheimer's disease in India. Hum Biol 2002;74:683-93.

72. Miech RA, Breitner JC, Zandi PP, Khachaturian AS, Anthony JC, Mayer L. Incidence of AD may decline in the early 90s for men, later for women: The Cache County study. Neurology 2002;58:209-18.

73. Qiu C, Kivipelto M, Aguero-Torres H, Winblad B, Fratiglioni L. Risk and protective effects of the APOE gene towards Alzheimer's disease in the Kungsholmen project: variation by age and sex. J Neurol Neurosurg Psychiatry 2004;75:828-33.

74. Hsiung GY, Sadovnick AD, Feldman H. Apolipoprotein E epsilon4 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging. CMAJ 2004;171:863-7.

75. Jobst KA, Barnetson LP, Shepstone BJ. Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: the use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, X-ray CT, and APO E4 medial temporal lobe dementias. The Oxford Project to Investigate Memory and Aging. Int Psychogeriatr 1997;9 Suppl 1:191-222; discussion 247-52.

76. Breitner JC, Jarvik GP, Plassman BL, Saunders AM, Welsh KA. Risk of Alzheimer disease with the epsilon4 allele for apolipoprotein E in a Population based study of men aged 62–73 years. Alzheimer Dis Assoc Disord 1998;12:40-4.

77. Moceri VM, Kukull WA, Emanual I, van Belle G, Starr JR, Schellenberg GD, et al. Using census data and birth certificates to reconstruct the early-life socioeconomic environment and the relation to the development of Alzheimer's disease. Epidemiology 2001;12:383-9.

78. Stengard JH, Pekkanen J, Sulkava R, Ehnholm C, Erkinjuntti T, Nissinen A. Apolipoprotein E polymorphism, Alzheimer's disease and vascular dementia among elderly Finnish men. Acta Neurol Scand 1995;92:297-8.

79. Mullan M, Scibelli P, Duara R, Fallin D, Gold M, Schinka J, et al. Familial and Population based studies of apolipoprotein E and Alzheimer's disease. Ann N Y Acad Sci 1996;802:16-26.

80. Bickeboller H, Campion D, Brice A, Amouyel P, Hannequin D, Didierjean O, et al. Apolipoprotein E and Alzheimer disease: genotype-specific risks by age and sex. Am J Hum Genet 1997;60:439-46.

81. Quiroga P, Calvo C, Albala C, Urquidi J, Santos JL, Perez H, et al. Apolipoprotein E polymorphism in elderly Chilean people with Alzheimer's disease. Neuroepidemiology 1999;18: 48-52.

82. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. Apolipoprotein E polymorphism and Alzheimer's disease. Lancet 1993;342:697-9.

83. Payami H, Kaye J, Heston LL, Bird TD, Schellenberg GD. Apolipoprotein E genotype and Alzheimer's disease. Lancet 1993;342:738.

84. Dai XY, Nanko S, Hattori M, Fukuda R, Nagata K, Isse K, et al. Association of apolipoprotein E4 with sporadic Alzheimer's disease is more pronounced in early onset type. Neurosci Lett 1994;175:74-6.

85. Liddell M, Williams J, Bayer A, Kaiser F, Owen M. Confirmation of association between the e4 allele of apolipoprotein E and Alzheimer's disease. J Med Genet 1994;31:197-200.

86. Tsai MS, Tangalos EG, Petersen RC, Smith GE, Schaid DJ, Kokmen E, et al. Apolipoprotein E: risk factor for Alzheimer disease. Am J Hum Genet 1994;54:643-9.

87. Nunomura A, Chiba S, Eto M, Saito M, Makino I, Miyagishi T. Apolipoprotein E polymorphism and susceptibility to early- and late-onset sporadic Alzheimer's disease in Hokkaido, the northern part of Japan. Neurosci Lett 1996;206:17-20.

88. Tsuang D, Kukull W, Sheppard L, Barnhart RL, Peskind E, Edland SD, et al. Impact of sample selection on APOE epsilon 4 allele frequency: a comparison of two Alzheimer's disease samples. J Am Geriatr Soc 1996;44:704-7.

89. Yang JG, Poropat RA, Brooks WS, Broe GA, Nicholson GA. Apolipoprotein E genotyping in Alzheimer's disease in an Australian sample. Aust N Z J Med 1996;26:658-61.

90. Almeida OP, Shimokomaki CM. Apolipoprotein E4 and Alzheimer's disease in Sao Paulo-Brazil. Arq Neuropsiquiatr 1997;55:1-7.

91. Kalman J, Juhasz A, Csaszar A, Kanka A, Magloczky E, Bencsik K, et al. Apolipoprotein E allele frequencies in patients with late-onset sporadic Alzheimer's dementia in Hungary. Acta Neurol Scand 1997;95:56-9.

92. Wang PN, Wang SJ, Hong CJ, Liu TT, Fuh JL, Chi CW, et al. Risk factors for Alzheimer's disease: a case-control study. Neuroepidemiology 1997;16:234-40.

93. Lopez OL, Lopez-Pousa S, Kamboh MI, Adroer R, Oliva R, Lozano-Gallego M, et al. Apolipoprotein E polymorphism in Alzheimer's disease: a comparative study of two research populations from Spain and the United States. Eur Neurol 1998;39:229-33.

94. Bretsky PM, Buckwalter JG, Seeman TE, Miller CA, Poirier J, Schellenberg GD, et al. Evidence for an interaction between apolipoprotein E genotype, gender, and Alzheimer disease. Alzheimer Dis Assoc Disord 1999;13:216-21.

95. Kim KW, Jhoo JH, Lee KU, Lee DY, Lee JH, Youn JY, et al. Association between apolipoprotein E polymorphism and Alzheimer's disease in Koreans. Neurosci Lett 1999;277:145-8.

96. Nakayama S, Kuzuhara S. Apolipoprotein E phenotypes in healthy normal controls and demented subjects with Alzheimer's disease and vascular dementia in Mie Prefecture of Japan. Psychiatry Clin Neurosci 1999;53:643-8.

97. Scacchi R, Gambina G, Ruggeri M, Martini MC, Ferrari G, Silvestri M, et al. Plasma levels of apolipoprotein E and genetic markers in elderly patients with Alzheimer's disease. Neurosci Lett 1999;259:33-6.

98. Traykov L, Rigaud AS, Caputo L, Couderc R, Coste J, Michot JL, et al. Apolipoprotein E phenotypes in demented and cognitively impaired patients with and without cerebrovascular disease. Eur J Neurol 1999;6:415-21.

99. Siest G, Bertrand P, Qin B, Herbeth B, Serot JM, Masana L, et al. Apolipoprotein E polymorphism and serum concentration in Alzheimer's disease in nine European

centres: the ApoEurope study. ApoEurope group. Clin Chem Lab Med 2000;38:721-30.

100. Kim KW, Jhoo JH, Lee JH, Lee DY, Lee KU, Youn JY, et al. Transferrin C2 variant does not confer a risk for Alzheimer's disease in Koreans. Neurosci Lett 2001;308:45-8.

101. Rigaud AS, Traykov L, Caputo L, Coste J, Latour F, Couderc R, et al. Association of the apolipoprotein E epsilon4 allele with late-onset depression. Neuroepidemiology 2001;20:268-72.

102. Zill P, Engel R, Hampel H, Behrens S, Burger K, Padberg F, et al. Polymorphisms in the apolipoprotein E (APOE) gene in gerontopsychiatric patients. Eur Arch Psychiatry Clin Neurosci 2001; 251:24-8.

103. Yang J, Feng G, Zhang J, Hui Z, Breen G, St Clair D, et al. Is ApoE gene a risk factor for vascular dementia in Han Chinese? Int J Mol Med 2001;7:217-9.

104. Huang HM, Kuo YM, Ou HC, Lin CC, Chuo LJ. Apolipoprotein E polymorphism in various dementias in Taiwan Chinese population. J Neural Transm 2002;109:1415-21.

105. Frank A, Diez-Tejedor E, Bullido MJ, Valdivieso F, Barreiro P. APOE genotype in cerebrovascular disease and vascular dementia. J Neurol Sci 2002;203-204:173-6.

106. Solfrizzi V, Panza F, D'Introno A, Colacicco AM, Capurso C, Basile AM, et al. Lipoprotein(a), apolipoprotein E genotype, and risk of Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002;72:732-6.

107. Panza F, Solfrizzi V, Colacicco AM, Basile AM, D'Introno A, Capurso C, et al. Apolipoprotein E (APOE) polymorphism influences serum APOE levels in Alzheimer's disease patients and centenarians. Neuroreport 2003;14:605-8.

108. Hawi Z, Sheehan K, Lynch A, Evans I, Lowe N, Lawlor B, et al. Late onset Alzheimer's disease and apolipoprotein association in the Irish population: relative risk and attributable fraction. Ir J Med Sci 2003;172:74-6.

109. Styczynska M, Religa D, Pfeffer A, Luczywek E, Wasiak B, Styczynski G, et al. Simultaneous analysis of five genetic risk factors in Polish patients with Alzheimer's disease. Neurosci Lett 2003;344: 99-102.

110. Souza DR, de Godoy HR, Hotta J, Tajara EH, Brandao AC, Pinheiro Junior S, Tognola WA, Dos Santos JE. Association of apolipoprotein E polymorphism in late-onset Alzheimer's disease and vascular dementia in Brazilians. Braz J Med Biol Res 2003;36:919-923.

111. Wehr H, Bednarska-Makaruk M, Graban A, Kunicki PK, Lojkowska W, Rodo M, et al. Apolipoprotein E polymorphism and low density lipoprotein (LDL) oxidation in patients with dementia. Folia Neuropathol 2003;41:65-8.

112. Finckh U, van Hadeln K, Muller-Thomsen T, Alberici A, Binetti G, Hock C, et al. Association of late-onset Alzheimer disease with a genotype of PLAU, the gene encoding urokinase-type plasminogen activator on chromosome 10q22.2. Neurogenetics 2003;4: 213-7.

113. Feldman H, Levy AR, Hsiung GY, Peters KR, Donald A, Black SE, et al. A Canadian cohort study of cognitive impairment and related dementias (ACCORD): study methods and baseline results. Neuroepidemiology 2003;22:265-74.

114. Borroni B, Archetti S, Agosti C, Akkawi N, Brambilla C, Caimi L, et al. Intronic CYP46 polymorphiosm along with ApoE genotype in sporadic Alzheimer Disease: from risk factors to disease modulators. Neurobiol Aging 2004;25:747-51.

115. Luthra K, Tripathi M, Grover R, Dwivedi M, Kumar A, Dey AB. Apolipoprotein E gene polymorphism in Indian patients with Alzheimer's disease and vas-cular dementia. Dement Geriatr Cogn Disord 2004;17:132-5.

116. Welsh-Bohmer KA, Gearing M, Saunders AM, Roses AD, Mirra S. Apolipoprotein E genotypes in a neuropathological series from the Consortium to Establish a Registry for Alzheimer's Disease. Ann Neurol 1997;42:319-25.

117. Traykov L, Rigaud AS, Baudic S, Smagghe A, Boller F, Forette F. Apolipoprotein E epsilon 4 allele frequency in demented and cognitively impaired patients with and without cerebrovascular disease. J Neurol Sci 2002;203-204:177-81.

118. Engelborghs S, Dermaut B, Goeman J, Saerens J, Marien P, Pickut BA, et al. Prospective Belgian study of neurodegenerative and vascular dementia: APOE genotype effects. J Neurol Neurosurg Psychiatry 2003;74:1148-51.

17. Structural and Functional Imaging of the Brain in Dementia Workup

Conclusions

There is strong evidence (Evidence Grade 1) that atrophy of the medial temporal lobe structures (whole medial temporal lobe, hippocampus, enthorinal cortex), estimated by means of MRI/CT, contributes to a diagnostic workup that differentiates AD (Alzheimer's disease) patients from controls and AD from other dementia disorders (Tables 17.1–17.2).

The conclusion is based on studies that used clinical diagnosis as the gold standard. No studies were included that used histopathology as the gold standard.

The majority of studies were based on degree of quality 2b, reflecting populations at memory clinics, usually at university hospitals. There were no studies that could be referred to a general practitioner setting – of the 3 studies of quality 1a [1–3], 1 was population based [3] and the other 2 were at university hospitals with heterogeneous study populations. Two of these studies investigated AD patients vs controls and 2 investigated patients with other dementia disorders vs controls. Both comparisons resulted in high LR+ values.

We cannot generalize these findings into a general practice setting, given that we found no studies that used medial temporal lobe atrophy or any other brain structure as a diagnostic method in such a setting.

For diagnostic workups performed in specialized settings, evaluating atrophy of medial temporal lobe structures contributed to diagnostic reliability.

Although we included more recent high-quality studies, our results do not differ from EBDP [4,5].

Introduction

This evaluation has investigated Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single Photon Computed Tomography (SPECT), Positron Emission Tomography (PET) and Electro Encephalography (EEG) as diagnostic methods for the detection and differentiation of dementia disorders. The structural imaging methods (CT and MRI) are used to find secondary disorders, such as tumors, subdural hematomas and normal pressure hydrocephalus. That has not been addressed in the evaluation, since it is obvious that CT and MRI are effective in detecting those diseases and are recommended by the American Association of Neurology.

Search strategy

Medline 1980–2004 (July)

Dementia/radionuclide imaging
Dementia AND Diagnostic Imaging
Dementia AND Electroencephalography
AND
Comparative Study
Sensitivity and Specificity
Sensitivity [Text Word]
Specificity [Text Word]
Accuracy [Text Word]
AND Human
>18 years

NOT Case Report
Editorial [Publication Type]
Letter [Publication Type]
Review [Publication Type]
HIV [Text Word]
434 hits were found.

Structural imaging

Results

After the screening procedure, we selected 36 articles concerning MRI or CT. Papers were excluded due to:

- inclusion of too few subjects
- insufficient description of the investigation procedure or diagnostic criteria
- insufficient description of statistical methods or
- irrelevance.

Generally, the papers presented a limited number of cases and focused largely on AD patients versus controls. Few studies proceeded from a longitudinal prospective. Most of the brain structures studied were part of the medial temporal lobe. That is most evident starting in 1990, probably reflecting the increased use of MRI, which allows for better visualization of the medial temporal lobes than computer tomography. During the "CT era" the size of lateral ventricles and other CSF spaces were most common studied structure. Diagnostic parameters are clustered around the medial temporal lobe.

No paper was found that addressed white matter changes or infarcts as diagnostic tools.

Studies on very early cases of AD, such as "mild cognitive impairment", have been published recently [6–14]. The main focus in those papers is on studying the accuracy of imaging for detecting AD cases in the large

heterogeneous group of mild cognitive impairment subjects (conversion to dementia).

The majority of papers investigated hospital populations, and only two studies took a Population based approach [15,16].

As mentioned earlier, many of the papers compared AD patients with controls. That is a limitation in clinical practice. A method designed to differentiate between common dementia disorders (such as frontotemporal dementia, Lewy Body Dementia LBD or VaD) and AD is more valuable. Several studies addressed this issue [17–25].

However, only a limited number of research groups contributed to the scientific literature, and several authors presented more than one paper. Whether or not the same population was used in the different studies is unknown.

One paper concerned diseases other than AD – Zidler et al studied Creutzfeldt-Jakob disease and a variant of Creutzfeldt-Jakob disease and the pulvinar sign [26]. This sign is found on MRI and yields a specificity value of 1.0 with an infinite positive likelihood ratio. One study used magnetic resonance spectroscopy as a diagnostic tool [25].

The question of workup bias (unreliable results due to the results of the imaging method having influenced the diagnostic procedure) was taken into consideration. Very few studies explicitly stated that the method was evaluated independently of the imaging results [14,17]. Given that a structural image is used routinely in clinical workup, we assumed a high risk of dependence between study results and diagnostic procedure.

We calculated the mean LR+ and LR– values and tabulated LR+ according to degree of quality (Table 17.1).

One problem with LR+ values is the dependency on sensitivity and specificity figures yielded by the test's cut-off values. Cut-off values were rarely stated along with sensitivity and specificity values. Thus, the influence of various cut-off values is not known.

Table 17.1 *MR-CT. Distribution of articles according to degree of quality.*

Degree of quality	Not fulfilling basal evidence criteria	Reference	Fulfilling basal evidence criteria*	Reference
Ia	2	[15,16]	–	
Ib	–		1	[27]
IIa	–		–	
IIb	–		1	[26+]
1a	–		3	[14,17,28]
1b	2	[8,21]	3	[6,7,29++]
2a	5	[19,20,22,23,25]	3	[18,25,30]
2b	5	[9,10,12,24,31]	11	[11,32–41]

* Sensitivity >80%; specificity >80% LR+ ≥5.
+ CJD (Creutzfeldt-Jakob disease) – "pulvinal sign".
++ Magnetic resonance spectroscopy.

Table 17.2 *CT/MRI studies of brain morphology.*

Author Year Reference Country	Method	Sample (n)	Age	Population/ selection	Diagnostic criteria	Global cognitive function
Barber et al 1999 [23] United Kingdom	MRI	26 DLB 28 AD 24 VaD 26 C	76 77 77 76	Hospital referrals	DSM-IV NINDS-AIREN NINCDS LBD	13 15 18 28
Bigler et al 2001 [28] USA	MRI	175 mixed dementia 375 controls	65–99 68–87	Population based, random selection "Cache County"		– –
Bottino et al 2002 [13] Brazil	MRI	39 AD 21 MCI 20 C	73 69 69	Hospital referrals	DSM-III-R ICD-10	20 26 29
de Leon et al 1993 [7] USA	MRI	54 C 32 MCI	70 71	Research, longi-tudinal prospective Follow-up: 4 years	NINCDS	– –
DeCarli et al 1995 [37] USA	MRI	31 AD 29 C	69 68	Hospital referrals	NINCDS	20 – ESD
Denihan et al 2000 [20] Ireland	MRI	60 AD 17 VaD 14 depression 9 paraphrenia	74 78 73 74	Referrals from psychiatric and memory clinics	NINCDS (AD) ADDTC (VaD) DSM-IV (Depression and paraphrenia)	19 20 25 25
Du et al 2003 [40] USA	MRI	21 AD 23 C	74 76	Hospital referrals Follow-up: 2 years	NINCDS ADRDA	22 29

Work up bias	SS	SP	LR+	LR–	Comparison	Structure	Quality of study
No info	0.38 0.28	1.00 0.88	– 2.3	0.62 0.81	DLB-AD DLB-VaD	Visual MTA rating	2a
No info	0.95 0.91 0.91 0.86	0.96 0.94 0.90 0.87	23 11 10 6.6	0.05 0.09 0.09 0.16	OD-C OD-C OD-C OD-C	Whole brainvolume Ventricle/brain Temporalhorn/brain Hippocampus/brain	1a
No info	0.90 0.83 0.81	0.85 0.71 0.80	6 3 4	0.11 0.24 0.23	AD-C AD-MCI MCI-C	Hippocampus Amygdala	2b
No info	0.91	0.89	8.3	0.10	AD-C	Visual rating of hippocampal formation	1b
No info	0.87	0.83	5.1	0.16	AD-C	Temporal lobes Visually rated atrophy	2b 2b
No info	0.75 0.61	0.90 0.91	7.5 6.7	0.28 0.42	AD-other Mild AD-other	Minimal distance of MTL	2a
No info	0.78 0.86	0.76 0.76	3.3 3.6	0.28 0.18	AD-C	Entorhinal cortex Rate of atrophy	2a

The table continues on the next page

Table 17.2 *continued*

Author Year Reference Country	Method	Sample (n)	Age	Population/ selection	Diagnostic criteria	Global cognitive function
El Fakhri et al 2003 [11] USA	MRI	56 MCI 26 AD	72 73	Longitudinal prospective 2–3 years	NINCDS ADRDA	CDR 0.5 MMSE 29 CDR 5.25
Erkinjuntti et al 1993 [31] Finland	MRI	34 AD 39 C	70 70	Hospital referrals	NINCDS DSM-III-R	193 245
Frisoni et al 1996 [35] Italy	MRI	44 AD 31 C	71 70	Hospital referrals spouses	NINCDS	18 29
Frisoni et al 2002 [38] Italy	MRI	42 AD 29 C	76 70	Hospital referrals	NINCDS Path	21 27
Gao et al 2004 [41] Canada	MRI	41 C 49 AD	71 70	Hospital referred	NINCDS-ADRDA	28 18
Golebiowski et al 1999 [36] Poland	MRI	50 AD 25 C	67 65	Hospital referrals	NINCDS	20 25
Gosche et al 2002 [27] USA	MRI	24 AD 32 C	90 88	"Nun study"	Khachaturian	MMSE 10 25

Work up bias	SS	SP	LR+	LR–	Comparison	Structure	Quality of study
No info	0.80	0.90	8	0.22	MCI-AD predictiv value	Combinded of atrophy in limbic system	1b
No info	0.60 0.80 0.60 0.35	0.96 0.82 0.87 0.92	20 4 4.6 4.4	0.41 0.24 0.46 0.70	AD-C	EC TH HC	
No info	0.86 0.81	0.95 0.95	20 16	0.15 0.20	Mild AD-C AD-C	Combinded measure of linear measure-ments of medial temporal lobe	2b
No info	0.93	0.97	13	0.07	AD-C	Radial width of the temporal horn	2b
No info	0.86 0.84 0.84	0.93 0.81 0.76	11.7 4.3 3.4	0.15 0.19 0.21	TMTL HC AD-C		2b
No info	0.95	0.92	12	0.05	AD-C	Hippocampus volume	2b
No info	0.83	0.80	6.3	0.21	AD-C	Hippocampus	Ib

The table continues on the next page

Table 17.2 *continued*

Author Year Reference Country	Method	Sample (n)	Age	Population/ selection	Diagnostic criteria	Global cognitive function
Jobst et al 1998 [15] United Kingdom	CT	44 AD and 10 non-AD drawn from 167 patients and 75 C	57–94	General practitioners and hospital referrals OPTIMA study	Khachaturian criteria	–
Juottonen et al 1998 [34] Finland	MRI	30 AD 32 C	70 72	Hospital referrals	NINCDS-ADRDA	20 28
Kantarci et al 2002 [12] USA	MRI	61 C 24 MCI 22 AD	80 82 79	Hospital referred	DSM-III-R NINCDS ADRDA	MMSE 29 28 26
Killiany et al 2002 [6] USA		136 16 mild AD 21 converters to AD 73 questionable (MCI) 28 controls	70 74 72 72	Prospective, longitudinal study. Follow-up: 3 years. Recruited thorough advertisement	DSM-IV NINCDS	MMSE 24 29 29 –
Kitagaki et al 1997 [24] Japan	MRI	22 FTD 22 AD 16 NC	65.3 65 63.5	Hospital referrals	NINCDS Lund-Manchester	17 18
Koslow et al 1992 [39] France	CT	58 AD 59 C	68	Clinic/research	NINCDS	MMSE 19 29
Laakso et al 2000 [32] Finland	MRI	57 AD 34 C	70 72	Hospital referrals	NINCDS	MMSE 22 28

Work up bias	SS	SP	LR+	LR–	Comparison	Structure	Quality of study
No info	0.85	0.78	4	0.19	AD-C	Min dist of MTL cut-off 0.79	Ia
No info	0.80 0.80	0.91 0.94	13 9	0.21 0.21	AD-C	EC Hippocampus	2b
No info	0.79 0.86 0.75	0.80 0.80 0.80	4 4.3 2.5	0.26 0.17 0.27	AD-C MCI-C MCI-AD	Hippocampus	2b
No info	0.82 0.76	0.94 0.76	13 3	0.50 0.91	C-"MCI" C-AD	Entohrinal cortex Hippocampus	1b
No info	0.86 0.86 0.64 0.64	0.94 0.73 1.00 0.96	– – 16	0.26 0.38	FTD-C FTD-AD FTD-C FTD-AD	T2-frontal WMH T2-frontal WMH Frontal atrophy Frontal atrophy	2b
No info	0.83	0.30	5.9	0.22	AD-C	Combination of CT measurement	2b
No info	0.86 0.83	0.85 0.94	6 13	0.16 0.18	AD-C	Right Hippocampus Left Hippocampus	2b

The table continues on the next page

***Table 17.2** continued*

Author Year Reference Country	Method	Sample (n)	Age	Population/ selection	Diagnostic criteria	Global cognitive function
Laakso et al 1998 [30] Finland	MRI	55 AD 44 AAMI 42 C	70 70 72	Hospital referrals. Random selection from population based study	NINCDS	22 28 28
Laakso et al 1995 [9] Finland	MRI	54 AD 40 AAMI 27 C	70 70 71	Hospital referrals	NINCSD NIH-criteria Spouses	22 27 28
Laakso et al 1995 [10] Finland	1995	54 AD 38 AAMI (MCI) 34 C old 20 C young	70 70 72 29	Clinic, research	NINCDS-ADRDA	22 23 28
Lavenu et al 1997 [19] France	MRI	77 AD 48 other dementias	72 71	Hospital referrals	NINCDS	19 22
O'Brien et al 2001 [29] United Kingdom	MRI SPECT	30 AD 22 C	71 72	Hospital referrals Follow-up: 3 years spouses	NINCDS	8 28
O'Brien et al 2000 [22] United Kingdom	MRI	69 AD 25 VaD 9 DLB 13 depression	80 77 81 76	Hospital referrals	NINCDS NINDS-AIREN DLB DSM-IV	16 20 13 26
O'Brien et al 1997 [18] United Kingdom	MRI	77 AD 61 major depression 44 other 40 C	71 71 69 ?	Consecutive referrals/research Mixed controls	NINCDS	MMSE 17 25 24 28

Work up bias	SS	SP	LR+	LR–	Comparison	Structure	Quality of study
	0.84	0.90	12	0.17	AD-C AD-OD	Hippocampus	2a
No info	0.37	0.72	1.3	0.90	AD-OD	Interunctal distance	2b
No info	0.76	0.72	2.7	0.33	AD-C	Amygdala	2b
No info	0.77 0.34	0.93 0.93	11 6	0.24 0.68	MMT <18 MMT >18	Combination of medial temp lobe atrophy and reduced rCBFin par/temp area	2a
No info	0.93 0.77	0.86 0.82	7 4	0.08 0.28	AD-C	SPECT+MR SPECT	1b
No info	0.51 0.56 0.54	0.72 0.32 0.72	2 1 1	0.68 1.37 0.64	AD-Depr AD-DLB AD-VaD	Minimal of MTL width	2a
No info	0.83 0.83 0.83	0.88 0.97 0.98	7 27 41.5	0.19 0.17 0.17	AD-C AD-MD AD-OD	Visual rating of different temp lobe structures	2a

The table continues on the next page

Table 17.2 *continued*

Author Year Reference Country	Method	Sample (n)	Age	Population/ selection	Diagnostic criteria	Global cognitive function
O'Brien et al 1994 [33] United Kingdom	MRI	43 AD 32 major depression	70 71	Consecutive referrals	DSM-III-R	MMSE 15 26 MMSE
Pennanen et al 2004 [14] Finland	MRI	48 AD 65 MCI 59 C	71 72 72	Population based cohort	DSM-IV NINCDS-ADRDA Petersen criteria for MCI	21 24 27
Rossi et al 2004 [16] United Kingdom/Italy	CT	20 AD 23 C	75 35	OPTIMA study	CERAD	15 28
Shonk et al 1995 [25] USA	MRS	65 AD 39 OD 20 C	73 75 71	Research, recruited from a clinical trial	NINCDS-NINDS-AIREN OD research crit	– – –
Varma et al 2002 [21] United Kingdom	MRI	23 AD 21 FTD 20 VaD	63 63 60	Hospital referrals Follow-up: 3 years	NINCDS NINDS-AIREN Lund-Manchester	18 21 21
Wahlund et al 2000 [17] Sweden	MRI	41 AD 35 OD 66 C	63 69 68	Hospital referrals Follow-up: 6 months	DSM-IV-R NINCDS NINDS-AIREN Lund-Manchester	MMSE 18 21 28

Work up bias	SS	SP	LR+	LR–	Comparison	Structure	Quality of study
No info	0.93	0.84	3.5	0.08	AD-MD	Visually rated:	2b
No info	0.81	0.94	13.5	0.20		Ant HC	
	0.81	0.94	13.5	0.20		Amygdala	
	0.67	0.94	20	0.35		EC	
						Cerebr cortex	
No	0.60	0.71	2	0.84	MCI-C	EC	1a
bias	0.88	0.93	17	0.13	AD-C	HC + EC	
	0.81	0.83	5	0.23	AD-MCI	HC	
No info	0.80	0.83	4.7	0.24	AD-C	rWTH	Ia
No info	0.83	0.95	16.6	0.18	AD-C	MRS	2a
	0.82	0.64	2.3	0.28	AD-OD	MI/Cr	
No info	0.71	0.93	10	0.31	FTD-non-FTD	Frontal atrophy or	1b
	0.71	0.76	3	0.38	FTD-non-FTD	Asymetry.	
						Parietal atrophy	
						and rCBF	
No bias	0.88	0.96	22	0.13	AD-C	Volumetry MTL	2b
	0.93	0.98	46	0.07	OD-C	Visual rating MTA	
	0.78	0.96	19	0.22	OD-AD	Volumetry MTL	
	0.82	0.95	16	0.19		Visual rating MTA	
	0.68	0.53	1.5	0.60		Volumetry MTL	
	0.78	0.64	2.5	0.34		Visual rating MTA	

The table continues on the next page

Table 17.2 *continued*

Author Year Reference Country	Method	Sample (n)	Age	Population/ selection	Diagnostic criteria	Global cognitive function
Xu et al 2000 [8] USA	MRI	30 C 30 MCI 30 AD	79 78 79	Recruited from prospective study, MCI	DSM-III-R NINCDS Peterson criteria	MMSE 28 25 20
Zeidler et al 2000 [26] Germany	MR	CJD	30	Hospital referrals	Criteria for CJD and Variant CJD	–

AAMI = Age Associated Memory Impairment; AD = Alzheimer's disease; C = Control; CDR = Clinical dementia rating; CJD = Creutzfeldt-Jakob disease; CR = Creatinine; CT = Computerized tomography; DLB = Dementia with Lewy body; EC = Entorhinal cortex; FTD = Frontotemporal dementia; HC = Hippocampus; MCI = Mild cognitive impairment; MD = Manic-depressiv disorder; MI = Myo-innositol; MMSE = Mini-mental state examination; MMT = Mini mental test; MRI = Magnetic resonance imaging; MRS = Magnetic resonance spectroscopy; MTA = Medral temporal lobe atrophy; MTL = Medral temporal lobe; NC = Normal controls; OD = Other dementias; rCBF = Regional cerebral blood flow; rWTH = Radical width of temporal horn; TH = Temporal horn; TMTL = Total medral temporal lobe; VaD = Vascular dementia; WMH = White matter MR

Work up bias	SS	SP	LR+	LR–	Comparison	Structure	Quality of study
No info	0.63	0.8	3	0.46	C-MCI	Hippocampus	1b
	0.8	0.8	4	0.25			
	0.6	0.8	3	0.46	C-AD		
	0.6	0.8	3	0.50	AD-MCI		
	0.76	0.8	4	0.30			
	0.6	0.8	3	0.50			
					C-MCI	Entorhinal cortex	
					C-AD		
					AD-MCI		
	0.78	1	0	0.78	Variant CJD-C	"Pulvinal sign"	IIb

References

1. Herholz K, Salmon E, Perani D, Baron JC, Holthoff V, Frolich L, et al. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. Neuroimage 2002;17:302-16.

2. Talbot PR, Lloyd JJ, Snowden JS, Neary D, Testa HJ. A clinical role for 99mTc-HMPAO SPECT in the investigation of dementia? J Neurol Neurosurg Psychiatry 1998;64:306-13.

3. Hoffman JM, Welsh-Bohmer KA, Hanson M, Crain B, Hulette C, Earl N, et al. FDG PET imaging in patients with pathologically verified dementia. J Nucl Med 2000;41:1920-8.

4. Silverman DH, Truong CT, Kim SK, Chang CY, Chen W, Kowell AP, et al. Prognostic value of regional cerebral metabolism in patients undergoing dementia evaluation: comparison to a quantifying parameter of subsequent cognitive performance and to prognostic assessment without PET. Mol Genet Metab 2003; 80:350-5.

5. Pasquier J, Michel BF, Brenot-Rossi I, Hassan-Sebbag N, Sauvan R, Gastaut JL. Value of (99m)Tc-ECD SPET for the diagnosis of dementia with Lewy bodies. Eur J Nucl Med Mol Imaging 2002;29:1342-8.

6. Killiany RJ, Hyman BT, Gomez-Isla T, Moss MB, Kikinis R, Jolesz F, et al. MRI measures of entorhinal cortex vs hippocampus in preclinical AD. Neurology 2002;58:1188-96.

7. de Leon MJ, Golomb J, George AE, Convit A, Tarshish CY, McRae T, et al. The radiologic prediction of Alzheimer disease: the atrophic hippocampal formation. AJNR Am J Neuroradiol 1993;14:897-906.

8. Xu Y, Jack CR, Jr O'Brien PC, Kokmen E, Smith GE, Ivnik RJ, et al. Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD. Neurology 2000;54:1760-7.

9. Laakso M, Soininen H, Partanen K, Hallikainen M, Lehtovirta M, Hanninen T, et al. The interuncal distance in Alzheimer disease and age-associated memory impairment. AJNR Am J Neuroradiol 1995;16:727-34.

10. Laakso MP, Partanen K, Lehtovirta M, Hallikainen M, Hanninen T, Vainio P, et al. MRI of amygdala fails to diagnose early Alzheimer's disease. Neuroreport 1995;6:2414-8.

11. El Fakhri G, Kijewski MF, Johnson KA, Syrkin G, Killiany RJ, Becker JA, et al. MRI-guided SPECT perfusion measures and volumetric MRI in prodromal Alzheimer disease. Arch Neurol 2003;60:1066-72.

12. Kantarci K, Xu Y, Shiung MM, O'Brien PC, Cha RH, Smith GE, et al. Comparative diagnostic utility of different MR modalities in mild cognitive impairment and Alzheimer's disease. Dement Geriatr Cogn Disord 2002;14:198-207.

13. Bottino CM, Castro CC, Gomes RL, Buchpiguel CA, Marchetti RL, Neto MR. Volumetric MRI measurements can differentiate Alzheimer's disease, mild cognitive impairment, and normal aging. Int Psychogeriatr 2002;14:59-72.

14. Pennanen C, Kivipelto M, Tuomainen S, Hartikainen P, Hanninen T, Laakso MP, et al. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. Neurobiol Aging 2004;25: 303-10.

15. Jobst KA, Barnetson LP, Shepstone BJ. Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: the use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, X-ray CT, and Apo E4 in medial temporal lobe dementias. Oxford Project to Investigate Memory and Aging. Int Psychogeriatr 1998;10: 271-302.

16. Rossi R, Joachim C, Smith AD, Frisoni GB. The CT-based radial width of the temporal horn: pathological validation in AD without cerebrovascular disease. Int J Geriatr Psychiatry 2004;19:570-4.

17. Wahlund LO, Julin P, Johansson SE, Scheltens P. Visual rating and volumetry of the medial temporal lobe on magnetic resonance imaging in dementia: a comparative study. J Neurol Neurosurg Psychiatry 2000;69:630-5.

18. O'Brien JT, Desmond P, Ames D, Schweitzer I, Chiu E, Tress B. Temporal lobe magnetic resonance imaging can differentiate Alzheimer's disease from normal ageing, depression, vascular dementia and other causes of cognitive impairment. Psychol Med 1997;27:1267-75.

19. Lavenu I, Pasquier F, Lebert F, Jacob B, Petit H. Association between medial temporal lobe atrophy on CT and parietotemporal uptake decrease on SPECT in Alzheimer's disease. J Neurol Neurosurg Psychiatry 1997;63:441-5.

20. Denihan A, Wilson G, Cunningham C, Coakley D, Lawlor BA. CT measurement of medial temporal lobe atrophy in Alzheimer's disease, vascular dementia, depression and paraphrenia. Int J Geriatr Psychiatry 2000;15:306-12.

21. Varma AR, Adams W, Lloyd JJ, Carson KJ, Snowden JS, Testa HJ, et al. Diagnostic patterns of regional atrophy on MRI and regional cerebral blood flow change on SPECT in young onset patients with Alzheimer's disease, frontotemporal dementia and vascular dementia. Acta Neurol Scand 2002;105:261-9.

22. O'Brien JT, Metcalfe S, Swann A, Hobson J, Jobst K, Ballard C, et al. Medial temporal lobe width on CT scanning in Alzheimer's disease: comparison with vascular dementia, depression and dementia with Lewy bodies. Dement Geriatr Cogn Disord 2000;11:114-8.

23. Barber R, Gholkar A, Scheltens P, Ballard C, McKeith IG, O'Brien JT. Medial temporal lobe atrophy on MRI in dementia with Lewy bodies. Neurology 1999;52:1153-8.

24. Kitagaki H, Mori E, Hirono N, Ikejiri Y, Ishii K, Imamura T, et al. Alteration of white matter MR signal intensity in frontotemporal dementia. AJNR Am J Neuroradiol 1997;18:367-78.

25. Shonk TK, Moats RA, Gifford P, Michaelis T, Mandigo JC, Izumi J, et al. Probable Alzheimer disease: diagnosis with proton MR spectroscopy. Radiology 1995;195:65-72.

26. Zeidler M, Sellar RJ, Collie DA, Knight R, Stewart G, Macleod MA, et al. The pulvinar sign on magnetic resonance

imaging in variant Creutzfeldt-Jakob disease. Lancet 2000;355:1412-8.

27. Gosche KM, Mortimer JA, Smith CD, Markesbery WR, Snowdon DA. Hippocampal volume as an index of Alzheimer neuropathology: findings from the Nun Study. Neurology 2002; 58:1476-82.

28. Bigler ED, Tate DF. Brain volume, intracranial volume, and dementia. Invest Radiol 2001;36:539-46.

29. O'Brien JT, Ames D, Desmond P, Lichtenstein M, Binns D, Schweitzer I, et al. Combined magnetic resonance imaging and single-photon emission tomography scanning in the discrimination of Alzheimer's disease from age-matched controls. Int Psychogeriatr 2001;13:149-61.

30. Laakso MP, Soininen H, Partanen K, Lehtovirta M, Hallikainen M, Hanninen T, et al. MRI of the hippocampus in Alzheimer's disease: sensitivity, specificity, and analysis of the incorrectly classified subjects. Neurobiol Aging 1998;19:23-31.

31. Erkinjuntti T, Lee DH, Gao F, Steenhuis R, Eliasziw M, Fry R, et al. Temporal lobe atrophy on magnetic resonance imaging in the diagnosis of early Alzheimer's disease. Arch Neurol 1993;50:305-10.

32. Laakso MP, Hallikainen M, Hanninen T, Partanen K, Soininen H. Diagnosis of Alzheimer's disease: MRI of the hippocampus vs delayed recall. Neuropsychologia 2000;38:579-84.

33. O'Brien JT, Desmond P, Ames D, Schweitzer I, Tuckwell V, Tress B. The differentiation of depression from dementia by temporal lobe magnetic resonance imaging. Psychol Med 1994;24:633-40.

34. Juottonen K, Laakso MP, Insausti R, Lehtovirta M, Pitkanen A, Partanen K, et al. Volumes of the entorhinal and perirhinal cortices in Alzheimer's disease. Neurobiol Aging 1998;19:15-22.

35. Frisoni GB, Beltramello A, Geroldi C, Weiss C, Bianchetti A, Trabucchi M. Brain atrophy in frontotemporal dementia. J Neurol Neurosurg Psychiatry 1996;61:157-65.

36. Golebiowski M, Barcikowska M, Pfeffer A. Magnetic resonance imaging-based hippocampal volumetry in patients with dementia of the Alzheimer type. Dement Geriatr Cogn Disord 1999;10: 284-8.

37. DeCarli C, Murphy DG, McIntosh AR, Teichberg D, Schapiro MB, Horwitz B. Discriminant analysis of MRI measures as a method to determine the presence of dementia of the Alzheimer type. Psychiatry Res 1995;57:119-30.

38. Frisoni GB, Geroldi C, Beltramello A, Bianchetti A, Binetti G, Bordiga G, et al. Radial width of the temporal horn: a sensitive measure in Alzheimer disease. AJNR Am J Neuroradiol 2002;23:35-47.

39. Koslow SA, Swihart AA, Latchaw RE, Hirsch WL, Belle SH, Shim YK, et al. Quantitative computer tomography in Alzheimer's disease: a re-evaluation. Gerontology 1992;38:174-84.

40. Du AT, Schuff N, Zhu XP, Jagust WJ, Miller BL, Reed BR, et al. Atrophy rates of entorhinal cortex in AD and normal aging. Neurology 2003;60:481-6.

41. Gao FQ, Black SE, Leibovitch FS, Callen DJ, Rockel CP, Szalai JP. Linear width of the medial temporal lobe can discriminate Alzheimer's disease from normal aging: the Sunnybrook dementia study. Neurobiol Aging 2004;25:441-8.

18. **Functional Imaging's Diagnostic Tool in Dementia Workup Search Strategies**

Conclusions

There is moderately strong evidence that SPECT/PET helps the diagnostic workup differentiate AD (Alzheimer's disease) patients from controls and AD from non-AD dementia (Evidence Grade 2).

From this evaluation, it is not obvious that PET is superior to SPECT in differentiating AD patients from controls or AD from other dementia disorders. The likelihood ratios were similar regardless of whether PET (using glucose metabolism) or SPECT was employed.

Our results are in agreement with those in AAN's guidelines, as well as Jagust et al in "Evidence–Based Dementia Practice" [1].

Moreover, a systematic review by Dougall et al calculated the LR+ as 7 for the comparison of AD patients to controls using SPECT and reduction of blood flow in parietotemporal areas. Our results are in the same neighborhood.

Introduction

The American Academy of Neurology has suggested that the use of functional imaging (SPECT and PET in this evaluation) in dementia workup is not to be recommended as part of routine evaluation (guideline). Nevertheless, it is often used, particularly in specialized memory clinics and as a complement to structural imaging in difficult differential diagnostic evaluations.

From the original 434 articles, 24 were selected. The reasons for exclusion were:

- too few subjects
- lack of information concerning diagnostic procedure or selection of the population or
- lack of information concerning ratio calculations.

By functional imaging we mean regional blood flow (rCBF) and glucose metabolism (GLU met) performed with either SPECT (HMPAO) Xenon SPECT or PET. Several areas of the brain were studied, mainly rCBF and GLU met in the temporal and parietal cortex. Sometimes other areas, such as posterior gyrus cinguli, were reported. A reduction in blood flow or glucose metabolism in parietotemporal areas was the most common diagnostic criterion. A cut-off value of 2 or 3 standard deviations below the age norm was usually presented. The most common comparisons between diagnostic groups were: AD patients vs controls and AD vs non-AD dementia. For the sake of simplicity, the following diagnostic groups comprised non-AD dementia: VaD, Lewy Body dementia, frontotemporal dementia and certain other rare diseases.

Search strategy

Medline 1980–2004 (July)

Dementia/radionuclide imaging
Dementia AND Diagnostic Imaging
Dementia AND Electroencephalography
AND
Comparative Study
Sensitivity and Specificity
Sensitivity [Text Word]
Specificity [Text Word]
Accuracy [Text Word]

AND	Human
	>18 years
NOT	Case Report
	Editorial [Publication Type]
	Letter [Publication Type]
	Review [Publication Type]
	HIV [Text Word]

434 hits were found.

Results

Ten studies compared AD patients to controls [2–11] and 12 studies compared AD to non-AD dementia [5,12–22]. Two studies with a likelihood ratio of 2.6 [15,16] compared AD to MCI and 1 study with a likelihood ratio of 4 compared patients with frontotemporal dementia to controls. The majority of studies were classified as having a quality of 2b. Five studies were reported with histopathological verification Ia, IIb. There were no major difference in the likelihood ratio between studies with histopathological verification and those with clinical diagnosis as the gold standard. The evidence is based on studies with quality 2b from memory clinic settings. Only 1 study reported results from a Population based setting [19]. There were no studies from general practice settings. As is the case with structural imaging, caution must be exercised when interpreting LR+ values. Workup bias: 6 studies stated explicitly that there was no workup bias [3,6,11,20,22,24]. The other studies did not provide any information in that regard.

Table 18.1 *SPECT/PET. Distribution of articles according to degree of quality.*

Study quality	Not fulfilling	Reference	Fulfilling basal evidence criteria*	Reference
Ia	–		1	[19]
Ib	1	[24]	–	
IIa	–		–	
IIb	3	[4,21,23]	–	
1a	3	[3,13,16]	–	
1b	–		2	[8,9]
2a	1	[20]	3	[7,12,22]
2b	5	[5,14,15,18,25]	5	[2,6,10,11,17]

* Specificity >0.8, Sensitivity >0.8, LR+ ≥5.

Table 18.2 *Functional imaging (SPECT/PET).*

Author Year Reference Country	Type of functional imaging	Population/ selection	Sample (n)	Age	Clinical criteria	Path criteria
Azari et al 1993 [2] USA	PET	Referred to university hospital	19 probable AD 22 controls	52–81 53–75	NINCDS-ADRDA	
Bergman et al 1997 [16] Canada	SPECT	Referred to university hospital Follow-up 6–2 months	58 AD 17 VaD 25 CIND/MCI 20 controls	76 79 73 68	NINCDS-ADRDA	
Bonte et al 1997 [4] Belgium	SPECT	Referred to university hospital	54 AD 29 controls	58–80 55–87	–	Yes (54 patients) Histo-pathology
Claus et al 1994 [7] The Netherlands	SPECT	Referred to hospital	48 AD 60 controls	72 74	NINCDS-ADRDA	
El Fakhri et al 2003 [9] USA	SPECT	Prospective long hospital based	83 MCI 27 AD	72 73	NINCDS-ADRDA	

Global cognitive function	Study design	Workup bias	SS	SP	LR+	LR–	Comments	Quality of study
AD: MMSE = 20 Subject at risk: MMSE = 28	Cross-sectional for AD and controls	No info	0.89 0.80 –	0.86 0.81	6.3 4.2	0.13 0.25	AD vs controls: – Frontal-parietal – Other areas	2b
MMSE = 22 MMSE = 22.4 MMSE = 27 Controls: MMSE = 29	Cross-sectional	No info	0.21 0.29 0.55	0.80 0.75 0.65	1.0 1.1 1.2		AD vs controls: B pattern as positive B or C as positive B or C or D as positive (B: lateral posterior temporal and/or parietal cortex defects. C: bilateral posterior temporal and/or parietal cortex defects with additional defects. D: unilateral posterior temporal and/or parietal cortex defects with or without additional defects)	1a
	Cross-sectional	No info	0.86	0.73	3.1	0.19	AD vs controls Posterior regions	IIb
AD: MMSE = 20 Controls: MMSE = 28	Cross-sectional	No info	0.42 0.56 0.79	0.9 0.9 0.9	4.2 5.6 7.9	0.64 0.48 0.23	Temporal rCBF Mild AD Moderate AD-C Severe AD-C	2a
MMSE 29 CDR 0.5 5.25		No info	0.8	0.8	5.0	0.25	AD-nAD comb of areas	1b

The table continues on the next page

***Table 18.2** continued*

Author Year Reference Country	Type of functional imaging	Population/ selection	Sample (n)	Age	Clinical criteria	Path criteria
Hanyu et al 1993 [12] Japan	SPECT	Referred to university hospital	56 AD 81 VaD 165 OD 25 normal	75 73 ~70 74 –	NINCDS-ADRDA for AD diagnosis DSM-III-R for other dementia diagnosis	
Herholz et al 2002 [10] Germany/ USA	PET	Hospital based	110 C 395 AD	57 69	NINCDS-ADRDA	
Hoffman et al 2000 [23] USA	PET	Referred to university hospital	22 patients with memory loss or dementia 15 AD 6 non AD	65	NINCDS-ADRDA	Yes (all patients) (CERAD)
Ishii et al 1996 [5] Japan	SPECT	Referred to university hospital	42 AD 51 non AD	68	NINCDS-ADRDA for AD	
Jobst et al 1998 [19] United Kingdom	SPECT	General practitioners and hospital-based service. Referred to university hospital	200 dementia (104 autopsy) 80 AD 14 controls 24 OD		NINCDS-ADRDA DSM-III-R	118 dementia (CERAD)
Johnson et al 1993 [6] USA	SPECT	Referred to university hospital	29 AD 78 controls	73 70	NINCDS-ADRDA	

Global cognitive function	Study design	Workup bias	SS	SP	LR+	LR–	Comments	Quality of study
	Cross-sectional	No info	0.82	0.89	7.4	0.2	AD vs non-AD: Parieto-temporal Hypoperfusion	2a
>24 19	–	No info	0.93 0.84	0.93 0.93	13 12	0.07 0.17	AD-C Post cing temporo/ parietal glucose metabol	2b
	Cross-sectional	No info	0.93	0.63 0.37	2.5	0.11	AD vs non-AD Bilateral temporo-parietal hypometabolism	IIb
	Cross-sectional	No info	0.95	0.57	2.1	0.08	AD vs non-AD Temporoparietal deficits	2b
AD: CAMCOG = 45 Other dementia: CAMCOG = 57	Cross-sectional Longi-tudinal		0.89 0.85 0.8	0.8 0.78 0.93	4.5 3.9 8.5	0.14 0.19 0.21	AD vs controls Parietal temporal lobe CT MTL atrophy Komb CT/SPECT	Ia
AD: (BDS) = 24.7	Cross-sectional	No bias	0.91	0.86	6.5	0.1	AD vs controls	2b

The table continues on the next page

***Table 18.2** continued*

Author Year Reference Country	Type of functional imaging	Population/ selection	Sample (n)	Age	Clinical criteria	Path criteria
Lobotesis et al 2001 [18] United Kingdom	SPECT	Community-dwelling population of patients referred to local old-age psychiatry services	50 AD 23 DLB 20 controls	82 79 78	NINCDS-ADRDA DLB consensus criteria	6 patients
Mattman et al 1997 [15] Canada	SPECT	Referred to university hospital	128 AD 54 not demented MCI Obs	70 65	NINCDS-ADRDA DSM-III-R	
O'Brien et al 2004 [22] United Kingdom		Hospital	33 C 34 AD 23 DLB 38 PD	75 79 76 76	NINCDS "consensus för DLB"	
Pasquier et al 2002 [25] France	SPECT	Hospital based	34 LBD 28 AD	74 76	Mackeith NINCDS-ADRDA	
Sackeim et al 1993 [14] USA	^{133}Xe technique	Referred to university hospital	30 AD 30 major depression 30 controls	67 66 64	DSM-III-R NINCDS-ADRDA HRSD	

Global cognitive function	Study design	Workup bias	SS	SP	LR+	LR–	Comments	Quality of study
MMSE = 17 MMSE = 16 MMSE = 28	Cross-sectional	No info	0.63	0.95	13	0.39	Visual rating Occ+medial+ temporal (AD+DLB) vs controls	2b
FRS	Cross-sectional	No info	0.6 0.53	0.66 0.75	2.6 1.17	0.59 0.62	AD vs not demented. Left temporal lobe Temp/or parietal bilateral	2b
28 17 16 26		No bias	0.78 0.84 0.78 0.82	0.94 0.94 0.94 0.94	15 16 12 14		C-DLB C-PD AD-KLB AD-PD R01 measurement of uptake in basal ganglia	2a
MMSE 16 17	–	No info	0.70	0.70	2.0	0.43	AD-nAD Occipital/temporal rCBF	2b
AD: Modified MMSE = 30.80	Cross-sectional	No info	0.97 0.78	0.7 0.84	3.2 5.0	0.04 0.26	AD-C AD-Depression	2b

The table continues on the next page

***Table 18.2** continued*

Author Year Reference Country	Type of functional imaging	Population/ selection	Sample (n)	Age	Clinical criteria	Path criteria
Silverman et al 2001 [21] USA	PET	Hospital	97 AD 23 non AD	– –	Histo-pathology	
Silverman et al 2003 [24] USA	PET	Hospital Follow-up 10 years	167 pat with cogn deficit		Histo-pathology	
Sjögren et al 2000 [17] Sweden	SPECT	Mölndal prospective dementia study in the Dept of Neuropsychiatry at Sahlgrenska university hospital	16 FTD 52 AD 19 SWD (subcortical white matter dementia)	62 67 71	Lund-Manchester criteria NINCDS-ADRDA History, CT risk factors, NINDS-AIREN	
Smith et al 1992 [8] USA	PET	Aging and Dementia Research Center of the New York university medical center	45 AD 20 controls	68 69	NINCDS-ADRDA	

Global cognitive function	Study design	Workup bias	SS	SP	LR+	LR–	Comments	Quality of study
AD/nonAD MMSE 53% 26–30 25% 20–25 18% <20		–	0.94 0.94	0.73 0.78	3.5 4.3	0.08 0.08	AD-nAD Dem-nDem "PET pattern"	IIB
24		No work up bias	0.95	0.79	5.0		Predictive value for PET to forecast progression	Ib
No degree of dementia reported	Cross-sectional	No info	0.875F TD-C 0.875F TD-AD 0.875F TD-SWD	0.786 0.85 0.78	4.0 6.0 4.0	0.15 0.14 0.15	FTD-C FTD-AD FTD-SWD	2b
Incipient + mild AD: GDS = 3.6 Moderate + severe AD: GDS = 5.3 Controls: GDS = 1.7	Cross-sectional Longitudinal	No info	0.955 0.886 0.886 0.864 0.818 0.773	0.762 0.810 0.524 0.857 0.81 0.667	4.0 4.7 1.8 6.1 4.3 1.8	0.05 0.15 0.21 0.16 0.21 0.34	Controls vs AD: Temporal lobe metabolic rate Parietal lobe metabolic rate Linear ventricular measure Controls vs mild AD: metabolic rate Temporal lobe Parietal lobe metabolic rate Linear ventricular measure	1b

The table continues on the next page

***Table 18.2** continued*

Author Year Reference Country	Type of functional imaging	Population/ selection	Sample (n)	Age	Clinical criteria	Path criteria
Talbot et al 1998 [13] United Kingdom	SPECT	Referred to university hospital. Follow-up 3 years	132 AD 78 VaD 24 LBD 58 FTD 81 OD	64 64 68 59 65	NINCDS-ADRDA + according to established criteria	Yes: 8 AD: 1 VaD: 3 LBD: 4 FTD: 2 progressive aphasia
Van Gool et al 1995 [3] The Netherlands	SPECTS	Controls: Amsterdam study of elderly (AMSTEL) + referred to university hospital	110 demented (68) AD 18 controls	79 76	DSM-III-R NINCDS-ADRDA	
Warkentin et al 2004 [11] Sweden		Hospital based	132 AD 92 C	74 39	NINCDS-ADRDA	
Varma et al 2002 [20] United Kingdom	SPECT	Hospital based	21 FTD 23 AD 20 VaD	63 63 86	Lund-M NINCDS NINDS	

AD = Alzheimer's disease; BDS = Blessed dementia scale; C = Control; CAMCOG = Cambridge cognitive examination; CDR = Clinical dementia rating scale; CERAD = Consortium to establish a registry for Alzheimer's disease; CIND = Cognitive impairment, no dementia; CT = Computerized tomography; DLB = Dementia with Lewy bodies; FTD = Frontotemporal dementia; KLB = Klotho with Lewy bodies; LBD = Lewy body dementia; LR = Likelihood ratio; MCI = Mild cognitive impairment; MMSE = Mini-mental state examination; MTL = Medral temporal lobe; OD = Other dementias; PD = Parkinson's disease; PET = Positron emission tomography; rCBF = Regional cerebral blood flow; SP = Specificity; SPECT = Single photon emission computed tomography; SS = Sensitivity; SWD = Subcortical white matter dementia; VaD = Vascular dementia

Global cognitive function	Study design	Workup bias	SS	SP	LR+	LR–	Comments	Quality of study
	Cross-sectional	No info	No info	No info	Likeli-hood ratios See ref for details on LR+:s		AD-non AD	1a
Dementia: MMSE = 16 Controls: MMSE = 27	Longi-tudinal follow-up 6 months	No bias	0.43 0.56 <80 0.29 >80 years	0.89 0.89 0.89	4.0 5.0 2.6	0.64 0.49 0.79	AD vs controls: Temporoparietal perfusion	1a
21 –	–	No bias	0.86	0.9	9.0	0.15	AD-C Combination of rCBF pattern "neuronal network"	2b
21 18 21	–	No work-up bias	0.77 0.52	0.63 0.93	2.3 7.8	0.36 0.51	AD-nAD FTD-nFTD	2a

References

1. Jagust W, Chui H, Lee A-Y. Functional Imaging in Dementia. Evidence-based Dementia Practice. Oxford: Blackwell Publishing Company, UK; 2002. p 162-170.

2. Azari NP, Pettigrew KD, Schapiro MB, Haxby JV, Grady CL, Pietrini P, et al. Early detection of Alzheimer's disease: a statistical approach using positron emission tomographic data. J Cereb Blood Flow Metab 1993;13:438-47.

3. Van Gool WA, Walstra GJ, Teunisse S, Van der Zant FM, Weinstein HC, Van Royen EA. Diagnosing Alzheimer's disease in elderly, mildly demented patients: the impact of routine single photon emission computed tomography. J Neurol 1995;242:401-5.

4. Bonte FJ, Weiner MF, Bigio EH, White CL, 3rd. Brain blood flow in the dementias: SPECT with histopathologic correlation in 54 patients. Radiology 1997;202:793-7.

5. Ishii K, Mori E, Kitagaki H, Sakamoto S, Yamaji S, Imamura T, et al. The clinical utility of visual evaluation of scintigraphic perfusion patterns for Alzheimer's disease using I-123 IMP SPECT. Clin Nucl Med 1996;21:106-10.

6. Johnson KA, Kijewski MF, Becker JA, Garada B, Satlin A, Holman BL. Quantitative brain SPECT in Alzheimer's disease and normal aging. J Nucl Med 1993;34:2044-8.

7. Claus JJ, van Harskamp F, Breteler MM, Krenning EP, de Koning I, van der Cammen TJ, et al. The diagnostic value of SPECT with Tc 99m HMPAO in Alzheimer's disease: a Population based study. Neurology 1994;44:454-61.

8. Smith GS, de Leon MJ, George AE, Kluger A, Volkow ND, McRae T, et al. Topography of cross-sectional and longitudinal glucose metabolic deficits in Alzheimer's disease. Pathophysiologic implications. Arch Neurol 1992;49:1142-50.

9. El Fakhri G, Kijewski MF, Johnson KA, Syrkin G, Killiany RJ, Becker JA, et al. MRI-guided SPECT perfusion measures and volumetric MRI in prodromal Alzheimer disease. Arch Neurol 2003;60:1066-72.

10. Herholz K, Salmon E, Perani D, Baron JC, Holthoff V, Frolich L, et al. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. Neuroimage 2002;17:302-16.

11. Warkentin S, Ohlsson M, Wollmer P, Edenbrandt L, Minthon L. Regional cerebral blood flow in Alzheimer's disease: classification and analysis of heterogeneity. Dement Geriatr Cogn Disord 2004;17:207-14.

12. Hanyu H, Abe S, Arai H, Asano T, Iwamoto T, Takasaki M. Diagnostic accuracy of single photon emission computed tomography in Alzheimer's disease. Gerontology 1993;39:260-6.

13. Talbot PR, Lloyd JJ, Snowden JS, Neary D, Testa HJ. A clinical role for 99mTc-HMPAO SPECT in the investigation of dementia? J Neurol Neurosurg Psychiatry 1998;64:306-13.

14. Sackeim HA, Prohovnik I, Moeller JR, Mayeux R, Stern Y, Devanand DP.

Regional cerebral blood flow in mood disorders. II. Comparison of major depression and Alzheimer's disease. J Nucl Med 1993;34:1090-101.

15. Mattman A, Feldman H, Forster B, Li D, Szasz I, Beattie BL, et al. Regional HmPAO SPECT and CT measurements in the diagnosis of Alzheimer's disease. Can J Neurol Sci 1997;24:22-8.

16. Bergman H, Chertkow H, Wolfson C, Stern J, Rush C, Whitehead V, et al. HM-PAO (CERETEC) SPECT brain scanning in the diagnosis of Alzheimer's disease. J Am Geriatr Soc 1997;45:15-20.

17. Sjogren M, Gustafson L, Wikkelso C, Wallin A. Frontotemporal dementia can be distinguished from Alzheimer's disease and subcortical white matter dementia by an anterior-to-posterior rCBF-SPET ratio. Dement Geriatr Cogn Disord 2000;11: 275-85.

18. Lobotesis K, Fenwick JD, Phipps A, Ryman A, Swann A, Ballard C, et al. Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. Neurology 2001;56:643-9.

19. Jobst KA, Barnetson LP, Shepstone BJ. Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: the use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, X-ray CT, and Apo E4 in medial temporal lobe dementias. Oxford Project to Investigate Memory and Aging. Int Psychogeriatr 1998;10:271-302.

20. Varma AR, Adams W, Lloyd JJ, Carson KJ, Snowden JS, Testa HJ, et al. Diagnostic patterns of regional atrophy on MRI and regional cerebral blood flow change on SPECT in young onset patients with Alzheimer's disease, frontotemporal dementia and vascular dementia. Acta Neurol Scand 2002;105:261-9.

21. Silverman DH, Small GW, Chang CY, Lu CS, Kung De Aburto MA, Chen W, et al. Positron emission tomography in evaluation of dementia: Regional brain metabolism and long-term outcome. JAMA 2001;286:2120-7.

22. O'Brien JT, Colloby S, Fenwick J, Williams ED, Firbank M, Burn D, et al. Dopamine transporter loss visualized with FP-CIT SPECT in the differential diagnosis of dementia with Lewy bodies. Arch Neurol 2004;61:919-25.

23. Hoffman JM, Welsh-Bohmer KA, Hanson M, Crain B, Hulette C, Earl N, et al. FDG PET imaging in patients with pathologically verified dementia. J Nucl Med 2000;41:1920-8.

24. Silverman DH, Truong CT, Kim SK, Chang CY, Chen W, Kowell AP, et al. Prognostic value of regional cerebral metabolism in patients undergoing dementia evaluation: comparison to a quantifying parameter of subsequent cognitive performance and to prognostic assessment without PET. Mol Genet Metab 2003;80:350-5.

25. Pasquier J, Michel BF, Brenot-Rossi I, Hassan-Sebbag N, Sauvan R, Gastaut JL. Value of (99m)Tc-ECD SPET for the diagnosis of dementia with Lewy bodies. Eur J Nucl Med Mol Imaging 2002;29:1342-8.

19. Evidence Based Evaluation of EEG (Quantitative EEG and Visual Rated EEG)

Conclusions

There is limited evidence that either visually rated EEG or qEEG helps the diagnostic workup differentiate AD (Alzheimer's Disease) patients from controls or AD from other dementia disorders (Evidence Grade 3).

Introduction

EEG and qEEG have been used in dementia workup for many years. The frequency varies, but generally they are associated with lower costs and less discomfort for patients than methods such as MRI, CT, SPECT and PET.

The American Academy of Neurology did not address EEG or qEEG in its Practice Parameter of 2001.

Search strategy

Medline 1980–2004 (July)

Dementia/radionuclide imaging
Dementia AND Diagnostic Imaging
Dementia AND Electroencephalography
AND
Comparative Study
Sensitivity and Specificity
Sensitivity [Text Word]

Specificity [Text Word]
Accuracy [Text Word]
AND Human
>18 years
NOT Case Report
Editorial [Publication Type]
Letter [Publication Type]
Review [Publication Type]
HIV [Text Word]
434 hits were found.

Twentyone articles were selected that contained information about sensitivity and specificity, eight of them were of high enough quality to be included.

The majority of the papers presented data on AD patients vs controls or patients with other dementia disorders vs controls. AD vs depression and Creutzfeldt-Jakob disease vs other dementia were also found. Two of the studies presented visually rated EEG, and the remaining presented quantitative EEG calculations [1,2]. The most common qEEG parameters were relative power alfa, beta, teta and delta power. One study presented evoked response potentials (EVP) [3] and one study presented data from EEG registrations during sleep [4].

The only Creutzfeldt-Jakob disease study included histopathological evaluation and was performed on a large population. However, the basal criteria for evidence (sensitivity, specificity >80%, LR+ >5) were not met. Another limitation is that there are no studies that present data on discriminating between AD and other dementia disorders.

Table 19.1 *EEG/qEEG. Distribution of articles according to degree of quality.*

Degree of quality	Not fulfilling	Reference	Fulfilling basal evidence criteria*	Reference
Ia	–		–	
Ib	1	[1]	–	
IIa	–		–	
IIb	–		–	
1a	–		–	
1b	–		–	
2a	1	[2]	2	[3**]
2b	5	[4–8]	–	

* Sensitivity >80%; Specificity >80%; LR+≥5.
** Combination of CT and P200.

Table 19.2 *Quantitative EEG (qEEG) and visual rated EEG.*

Author Year Reference Country	Settings	Sample (n)	Age	Clinical criteria	Path criteria	Global cognitive function
Anderer et al 1994 [5] Austria/ Germany EEG	No info	111 dementia (Study I) 96 dementia (Study II) 56 controls	82 82 68	DSM-III		
Engedal et al 1989 [3] Norway EEG	Population based	20 AD 10 MID 11 other dementia 38 controls	81.7 (median) 81 (median)	NINCDS-ADRDA & DSM-III	7 dementia 2 controls	Dementia: MMS = 19.8 Controls: MMS = 28.8
Houck et al 1991 [4] USA EEG	University based	61 AD 77 elderly depressed patients	73.6 70.8	DSM-III SADS/RDC		Blessed Dementia: Rating Scale AD = 9.9 Depressed patients = 2.7
Poser et al 1999 [1] Germany EEG	Population based	364 suspected CJD (6 was excluded later)	?	Probable CJD: dementia, EEG periodic sharp waves, two of the following findings: myoclonus, visual/cerebellar symptoms, pyramidal/extrapyramidal signs Possible CJD: fulfill above criteria, but did not have typical EEG	Probable CJD: 95 Possible CJD: 21 Other disease: 20	

Study design	Workup bias	SS	SP	LR+	LR–	Comments	Quality ot study
Cross-sectional	No info	Optimal selection 0.78 0.74 0.83	 0.8 0.9 0.9	 3.9 7.4 8.3	 0.22 0.28 0.19	Dementia vs controls: The absolute delta+ theta power *(qEEG)*	2b
Cross-sectional Longitudinal	No info	0.92 0.96	0.75 0.83	3.68 5.6	0.1 0.05	AD vs controls: Cortical atrophy on CAT & FVER P200 latency *(EVP)*	2a
Cross-sectional	No info	0.80 5.0	0.77	3.5	0.25	AD vs depressed patients: EEG sleep data: The area under ROC curve is 0.86 *(qEEG: sleep)*	2b
Cross-sectional Longitudinal	No info	0.65	0.86	4.64	0.4	CJD vs others: Periodic sharp wave complexes in the EEG *(Visual EEG)*	Ib

The table continues on the next page

***Table 19.2** continued*

Author Year Reference Country	Settings	Sample (n)	Age	Clinical criteria	Path criteria	Global cognitive function
Prinz et al 1989 [7] USA EEG	Community based	41 AD 22 depression 50 controls	70.9 62.3 67.5	NINCDS-ADRDA & DSM-III RDC		AD: MMS = 22.8 Depression: MMS = 29.2 Controls: MMS = 29.7
Reynolds et al 1988 [8] USA EEG	University based	49 AD 67 depressed 42 mixed dementia & depression 77 controls	72.8 70.3 72.6 69.3	DSM-III RDC		AD: MMSE = 16.5 Depressed: MMSE = 28.3 Mixed: MMSE = 19.2 Controls: MMSE = 29.4
Robinson et al 1994 [2] Canada EEG	Population based	86 AD 17 mixed AD & MID 56 controls	73.4 8.0 75.9 4.0	DSM-III-R ischemic score	105 patients	AD: ESD = 56.69 Mixed AD & MID: ESD = 97.88 Controls 1: ESD = 237.42 Controls 2: ESD = 242.71
Stevens et al 1998 [6] Germany/ United Kingdom EEG	Hospital based. Controls are from newspaper advertise-ment	31 elderly patients (cogni-tivelyimpaired/ demented 30 elderly controls 35 young controls	69.6 68.6 31.1	DSM-III-R ICD-10 SIDAM		MMSE was done, but no mean scores were reported

AD = Alzheimer's disease; CAT = Computer aided tomography; CJD = Creutzfeldt-Jakob disease; ESD = Extended scale for dementia; EVP = Electroencephalography, visual, evalued potentials; FVER = Functional verification; LR+ = Likelihood ratio; MID = Multiinfarct dementia; MMSE = Mini-mental state examination

Study design	Workup bias	SS	SP	LR+	LR–	Comments	Quality of study
Cross-sectional	No info	0.71 0.66	0.82 0.83	3.94 3.88	0.35 0.40	AD vs controls: Dominant occipital alpha rhythm AD vs depression: Dominant occipital alpha rhythm *(qEEG)*	2b
Cross-sectional Longitudinal	No info	0.8	0.8	4.0	0.25	AD vs depressed *(qEEG: sleep)*	2b
Cross-sectional Longitudinal	No info	0.87 0.50	0.63 3.0 0.95	2.38 12.2	0.20 0.52	AD vs controls AD subgroup (4 years illness) vs controls *(Visual EEG)*	2a
Cross-sectional	No info	0.84	0.60	2.1	0.27	Dementia vs healthy elderly: Microstate duration & number of single peak segments during the resting state with eyes closed *(qEEG)*	2b

References

1. Poser S, Mollenhauer B, Kraubeta A, Zerr I, Steinhoff BJ, Schroeter A, et al. How to improve the clinical diagnosis of Creutzfeldt-Jakob disease. Brain 1999;122:2345-51.

2. Robinson DJ, Merskey H, Blume WT, Fry R, Williamson PC, Hachinski VC. Electroencephalography as an aid in the exclusion of Alzheimer's disease. Arch Neurol 1994;51:280-4.

3. Engedal K, Oftedal SI, Lilleaas F, Laake P. Electroencephalography, visual evoked potentials, and cerebral CAT-scan as diagnostic tools in senile dementia of Alzheimer type. Aging (Milano) 1989;1:139-45.

4. Houck PR, Reynolds CF, 3rd, Mazumdar S, Kupfer DJ. Receiver operating characteristic analysis for validating EEG sleep discrimination of elderly depressed and demented patients. J Geriatr Psychiatry Neurol 1991;4:30-3.

5. Anderer P, Saletu B, Kloppel B, Semlitsch HV, Werner H. Discrimination between demented patients and normals based on topographic EEG slow wave activity: comparison between z statistics, discriminant analysis and artificial neural network classifiers. Electroencephalogr Clin Neurophysiol 1994;91:108-17.

6. Stevens A, Kircher T. Cognitive decline unlike normal aging is associated with alterations of EEG temporo-spatial characteristics. Eur Arch Psychiatry Clin Neurosci 1998;248:259-66.

7. Prinz PN, Vitiello MV. Dominant occipital (alpha) rhythm frequency in early stage Alzheimer's disease and depression. Electroencephalogr Clin Neurophysiol 1989;73:427-32.

8. Reynolds CF, 3rd, Kupfer DJ, Houck PR, Hoch CC, Stack JA, Berman SR, et al. Reliable discrimination of elderly depressed and demented patients by electroencephalographic sleep data. Arch Gen Psychiatry 1988;45:258-64.

20. Cerebrospinal Fluid Biomarkers in AD

Conclusion

There is strong evidence (Evidence Grade 1) that CSF T-tau, CSF Aß42 and the combination of CSF T-tau and Aß42 contribute, and moderately strong evidence (Evidence Grade 2) that CSF P-tau contributes, to the diagnostic workup in differentiating AD (Alzheimer's disease) patients from controls and from other dementia disorders.

Background

The CSF is in direct contact with the extracellular space of the brain and thus reflects biochemical changes in the brain. Because AD pathology is restricted to the brain, CSF is an obvious source of biomarkers for AD. Various studies have evaluated numerous potential CSF biomarkers for AD, but this review will focus on tau and ß-amyloid only, for reasons outlined below.

Tau protein is a microtubule-associated protein located in the neuronal axons. Due to alternative splicing of tau mRNA, there are 6 isoforms ranging from 352 to 441 amino acids, with molecular weights of ≈50–65 kDa (for review, see Buée et al, 2000 [1]). In AD, an abnormally hyperphosphorylated form of tau is the principal component of the paired helical filaments (PHFs), which make up the neurofibrillary tangles, neuropil threads and senile plaque neurites (for review, see Buée et al, 2000 [1]). Using different techniques, more than 30 phosphorylation sites have been described on tau in the brain (for review, see Buée et al, 2000 [1]). The CSF level of Total tau (T-tau) probably reflects the intensity of neuronal degeneration, while indirect evidence suggests that CSF P-tau (Phosphorylated tau) may specifically reflect the phosphorylation state of tau (for review, see Blennow and Hampel, 2003 [2]).

ß-amyloid (Aß) is the main protein constituent of plaques and is generated by proteolytic cleavage of its precursor, the amyloid precursor protein (APP) (for review see Andreasen and Blennow, 2002 [3]). There are several C-terminal forms of Aß. The longest form, ending at Ala42 (Aß42), has been found to aggregate more rapidly than shorter Aß variants and to be the initial form of Aß deposited in diffuse plaques (for review, see Andreasen and Blennow, 2002 [3]). The reduced CSF level of Aß42 in AD was initially hypothesized to be caused by deposition of Aß42 in plaques, with lower levels diffusing to CSF, while subsequent studies have questioned this explanation (for review, see Blennow and Hampel, 2003 [2]).

Search strategy

Studies were identified by searches on Medline and from references in relevant articles. Numerous papers on potential CSF markers for AD have been published. For example, the terms "Alzheimer" and "cerebrospinal fluid" yielded 1 230 hits. This review considered only CSF biomarkers that have been evaluated in more than 10 publications by independent research groups. The biomarkers must also have been evaluated using different methods available to the research community. Thus, this review is restricted to the CSF markers T-tau, P-tau and the 42 amino-acid form of ß-amyloid (Aß42). Thus, the Medline searches used "Alzheimer", "CSF", and either "tau" or "amyloid".

Selection criteria

To be evaluated in this review, papers had to include a sufficient number of patients and controls. For studies on AD patients versus controls, the papers had to include more than 20 AD patients and 20 controls – or if the number of controls was insufficient, at least 30 cases total. For studies on early AD, the papers had to include more than 10 AD patients with an MMSE score of 25 or higher. For studies on MCI, the papers had to include more than 10 MCI patients that were followed clinically in order to verify progression to AD with dementia. For studies on other

dementia, psychiatric or neurological disorders, the papers had to include more than 10 patients.

Papers also had to contain an adequate description of the clinical investigation procedure and diagnostic criteria for both patients and controls, analytical methods and statistical methods. All papers had to be in English. Papers were excluded if they did not present sensitivity and specificity figures, if such figures could not be calculated from graphs, or if they included control groups consisting of patients with neurological or psychiatric symptoms.

The definition of Evidence Grade, which is also the basis for the subdivision of the papers in the tables, is outlined by Chui H in chapter II:1 of "Evidence-based Dementia Practice" [4].

Around half of the papers focused on the differentiation between AD patients and controls, while the other half also included other differential diagnoses. The majority of papers investigated hospital populations, while only a few were based on Population based materials or longitudinal prospective studies.

Analytical principles for CSF T-tau, P-tau and Aß42

The following section presents a short description of the analytical methods, along with a summary of protein level changes in CSF in AD.

CSF total tau (T-tau)

The first report on CSF T-tau as a biomarker for AD was published in 1993. This paper used an ELISA with a polyclonal reporter antibody [5]. Subsequent studies used ELISA methods based on monoclonal antibodies that detect all isoforms of tau, independent of the phosphorylation state of tau [6–8]. Thus, they measure the total tau level in CSF.

Using all of these different ELISA methods, more than 80 studies consistently found a moderate to marked increase in CSF T-tau in AD. For the 2 most commonly used ELISA methods, the Innogenetics ELISA [6] and the Athena ELISA [8], the mean CSF T-tau level in the 36 evaluated studies was around 300% of that in controls (Table 20.1).

CSF ß-amyloid (Aß42)

Eleven different methods have been published for quantification of Aß42 in CSF (Table 20.2). These include 6 different ELISA methods [9–14]. Other methods include variants of SDS-PAGE combined with Western blot [15–17], and SELDI-TOF [18].

Using these different methods, the majority of studies found a moderate to marked decrease in CSF Aß42 in AD, but 1 study found a 161% increase [12]. For the 2 most commonly used ELISA methods, the Innogenetics ELISA [9] and the Athena ELISA [10], the mean CSF Aß42 level in the 15 evaluated studies was around 50% of that in controls (Table 20.2).

CSF phosphorylated tau (P-tau)

Several ELISA methods have been developed for the measurement of P-tau phosphorylated on different epitopes. These include threonine 181+231 ($Thr_{181+231}$) [6], Thr_{181}, [19], Thr_{231} and serine 235 (Thr_{231}+Ser_{235}) [20], Ser_{199} [20], Thr_{231} [21], and $Ser_{396+404}$ [22].

Using all these different ELISA methods, 25 studies have consistently found a moderate to marked increase in CSF P-tau in AD. For the 6 different ELISA methods in the 14 evaluated studies, the mean CSF P-tau level was around 430% of that in controls (Table 20.3).

Whether there is a difference in the diagnostic performance among ELISA methods for different P-tau epitopes has been discussed. However, a study that directly compared P-Tau_{181}, P-Tau_{199} and P-Tau_{231} in the same patient material found strong correlations among the ELISA methods [23].

Diagnostic performance of CSF markers for AD

The diagnostic performance of T-tau, Aß42 and P-tau is reviewed below. In general, one important factor for the variation in sensitivity, specificity, LR+ and LR– among studies is that several different principles were used to set the cut-off level. The International Federation of Clinical Chemistry (IFCC) recommends the use of a rank-based method, the 0.95 fractile, for reference values [24]. In the papers of CSF biomarkers for AD, the principles for setting the cut-off included variants of "best separation", ROC curves, and the highest or lowest value in controls. If the highest or lowest value in controls was used, i e as specificity of 100%, it yielded an infinite LR+ value and an LR– value of 0. In these instances, the LR+ value was set to 40 and the LR– value to 0.025.

Results on sensitivity, specificity, LR+ and LR– for the differentiation between AD patients and controls are shown in Tables 20.1–20.4, for the performance of the CSF markers in early AD and MCI in Table 20.5, and for specificity vs other cognitive, psychiatric and neurological disorders in Table 20.6. A summary of the diagnostic validity of the CSF markers appears in Table 20.7.

CSF T-tau

The majority of studies used the Innogenetics ELISA method for CSF T-tau [6], which is also part of the clinical routine in Sweden, while two studies used the Athena ELISA method [8]. Sensitivity and specificity figures are available from 36 studies for CSF T-tau (Table 20.1). The mean sensitivity to differentiate AD patients from controls was 77.1%, while the specificity was 90%, resulting in an LR+ of 16.4 and an LR– of 0.16 (Table 20.1).

In the 9 class 1a studies (Table 20.1), the mean sensitivity to differentiate AD patients from controls was 83% at a specificity of 92%, yielding an LR+ of 16.0 and an LR– of 0.11. Thus, there is strong evidence that CSF T-tau is useful in the clinical diagnosis of AD.

Aß42

The majority of studies used the Innogenetics ELISA method for CSF Aß42 [9] (Table 20.2). This method is part of clinical routine in Sweden. Two studies used the Athena ELISA method for Aß42 [10]. Sensitivity and specificity figures for CSF Aß42 are available from 15 studies (Table 20.2). The mean sensitivity to differentiate AD patients from controls was 87%, while the specificity was also 87%, resulting in an LR+ of 11.7 and an LR– of 0.16 (Table 20.2).

In the 5 class 1a studies (Table 20.2), the mean sensitivity was 88% at a specificity of 89%, yielding an LR+ of 10.5 and an LR– of 0.13. Thus, there is strong evidence that CSF Aß42 is useful in the clinical diagnosis of AD.

CSF P-tau

Although 14 papers presented sensitivity and specificity figures for CSF P-tau, there are few studies on each ELISA method or the P-tau epitope (Table 20.3). The 3 class 1a studies (Table 20.3) had a mean sensitivity of 62% at a specificity of 91%, yielding an LR+ of 7.9 and an LR– of 0.14. In the 14 studies, including 8 other class 2a studies, the mean sensitivity was 80.5% at a specificity of 91.7%, yielding an LR+ of 16.3 and an LR– of 0.12 (Table 20.3). Thus, there is moderately strong evidence that CSF T-tau is useful in the clinical diagnosis of AD.

In a specific comparison of the diagnostic performance of P-Tau$_{181}$, P-Tau$_{199}$ and P-Tau$_{231}$ in the same patient material, all three performed equally well in discriminating AD patients from controls without dementia [23].

Combination of CSF markers

Eighteen studies evaluated the diagnostic potential of combining CSF T-tau and Aß42, P-tau and Aß42, and T-tau and P-tau (Table 20.4). The most common combination was CSF T-tau and Aß42 (Table 20.4). Several different methods of combining results, such as discrimination lines or quadrants in plots of T-tau and Aß42, and cut-off levels were

used. The mean sensitivity to differentiate AD patients from controls was 85%, while the specificity was 92%, resulting in an LR+ of 18.1 and an LR– of 0.14 (Table 20.4).

Six class 1a studies examined the combination of CSF T-tau and Aß42 (Table 20.2), with a mean sensitivity of 90% at a specificity of 89%, yielding an LR+ of 14.8 and an LR– of 0.17. Thus, there is strong evidence that the combination of CSF T-tau and Aß42 is useful in the clinical diagnosis of AD.

Another diagnostic application for the combination of CSF markers is the identification of Creutzfeldt-Jakob disease (CJD). Several papers found a highly pronounced increase in CSF T-tau in CJD [25–31]. In contrast, there was only a mild to moderate increase in the CSF level of P-tau [27,30,31]. Thus, there is a significantly higher ratio of T-tau/P-tau in CSF in CJD, which has been found to discriminate CJD from AD and other dementia disorders with 100% accuracy [31,32].

CFS markers in early Alzheimer's disease and MCI

Nineteen studies examined CSF markers in early AD (with MMSE scores above 25) and MCI cases with progression to AD (Table 20.5). Only studies in which the CSF tap was taken at baseline and patients were monitored clinically to verify progression to AD with dementia were included in the present evaluation.

The mean sensitivity in these studies was 80% for CSF T-tau, 71% for CSF Aß42, 79% for CSF P-tau and 78% for the combination of CSF T-tau and Aß42 (Table 20.5).

CFS markers in other cognitive, psychiatric and neurological disorders

Fourtysix papers including a total of 1 116 cases evaluated the specificity of the CSF markers in other cognitive, psychiatric and neurological disorders (Table 20.6).

The specificity figures varied among different papers – both the number of cases with high or low CSF levels for the markers, depending on the cut-off level, and the degree of increase or decrease.

The data are summarized below. For Lewy body dementia, there is a mild to moderate increase in both CSF T-tau and P-tau in about 25% of cases, while CSF Aß42 decreases in the majority of cases (Table 20.6). That may be due to the large overlap in pathology between AD and Lewy body dementia [33].

For VaD, about half of the studies found a clear increase in CSF T-tau in the majority of cases, while the other half found normal levels (Table 20.6). The three studies on CSF Aß42 found a mild to moderate decrease in the majority of cases, while most of the 6 studies on CSF P-tau found a mild increase in around 25% of cases. These divergent results may reflect difficulties in making a clinical diagnosis of "pure" VaD. Indeed, neuropathological studies have shown that a high percentage (40–80%) of patients clinically diagnosed with VaD have notable concomitant AD pathology [34,35].

For frontotemporal dementia, most studies found a mild increase in CSF T-tau and P-tau and a mild decrease in Aß42 (Table 20.6).

Normal levels of CSF T-tau, or a mild increase in a minority of cases, have been found in cerebrovascular disease without dementia, amyotrophic lateral sclerosis, Parkinson's disease without dementia, progressive supranuclear palsy, corticobasal degeneration, depression and alcoholism with dementia (Table 20.6).

In general, the specificity of CSF P-tau to differentiate AD from other dementias, as well as from other neurological and psychiatric disorders, seems to be higher than for T-tau and Aß42 (Table 20.6). However, the sensitivity and specificity figures of P-tau vary among different studies. Thus, additional large studies are needed to determine whether there is a difference in sensitivity and specificity figures for the various ELISA methods for P-tau. However, group separation was maximized between AD and FTD using P-Tau$_{231}$ and between AD and DLB using P-Tau$_{181}$ [23]. Thus, differences in the phosphorylation of specific tau epitopes among various dementia disorders may be reflected in the CSF level of the corresponding P-tau variant.

As mentioned above, for sporadic CJD, there is a very pronounced increase in CSF T-tau but normal or only mildly to moderately increased CSF P-tau levels, resulting in a markedly higher ratio of T-tau/P-tau, which has been found to discriminate CJD from AD and other dementia disorders with 100% accuracy [31,32].

The systematic review on CSF-tau, as part of the dementia-project, was one of the first to be finished (Februari 2004). An updated search of the literature reveals that addictional studies have been published, and that these studies give support to the evidence that CSF p-tau can differentiate Alzheimer's disease from other forms of dementia (see [92–97]).

Table 20.1 *CSF-total tau in Alzheimer's disease and controls.*

Author Year Reference	Method	AD (n)	Controls (n)	Change in AD (% of controls)
Andreasen et al 1998 [36]	Innog	43	18	419
Sjögren et al 2000 [37]	Innog	60	32	242
Sjögren et al 2001 [38]	Innog	41	17	145
Sjögren et al 2001 [39]	Innog	47	12	237
Riemenschneider et al 2002 [40]	Innog	74	40	355
Sjögren et al 2002 [41]	Innog	19	17	269
Gomez-Tortosa et al 2003 [42]	Innog	33	46	250
Kapaki et al 2003 [43]	Innog	49	49	360
Wallin et al 2003 [44]	Innog	39	12	237

Sensitivity	Specificity	LR+	LR–	Quality of study	Comments
95	94	15.8	0.06	1a	Community-based patient sample
79	82	4.4	0.23	1a	Prospective, consecutive cases
85	95	17.1	0.06	1a	Prospective, consecutive cases
77	92	9.6	0.10	1a	Prospective, consecutive cases
95	98	47.5	0.02	1a	Consecutive cases
84	94	14.0	0.07	1a	Prospective, consecutive cases
73	80	3.7	0.27	1a	Prospective study
88	96	22.0	0.05	1a	Clinical practice, 3-year follow-up
72	93	10.3	0.10	1a	Prospective study

The table continues on the next page

Table 20.1 *continued*

Author Year Reference	Method	AD (n)	Controls (n)	Change in AD (% of controls)
Andreasen et al 1999 [45]	Innog	407	93	304
Arai et al 1995 [46]	Innog	70	19	858
Blennow et al 1995 [6]	Innog	44	31	283
Vigo-Pelfrey et al 1995 [8]	Athena	71	59	190
Arai et al 1998 [47]	Innog	69	17	443
Galasko et al 1998 [48]	Athena	82	60	171
Kanai et al 1998 [49]	Innog	93	41	226
Mecocci et al 1998 [50]	Innog	29	23	205
Shoji et al 1998 [51]	Innog	55	34	214
Vanderstichele et al 1998 [9]	Innog	81	15	178

Sensitivity	Specificity	LR+	LR–	Quality of study	Comments
93	86	6.6	0.15	1b	Community-based patient sample
100	100	40.0	0.025	2a	
84	97	28	0.04	2a	
39	100	40	0.025	2a	
89	100	40	0.025	2a	"Old" tau standard*
57	83	3.4	0.30	2a	Multicenter study
40	100	40	0.025	2a	Multicenter study
59	83	3.5	0.29	2a	
49	97	16.3	0.06	2a	Adjusted IFCC cut-off from graph
90	67	2.7	0.37	2a	

The table continues on the next page

Table 20.1 *continued*

Author Year Reference	Method	AD (n)	Controls (n)	Change in AD (% of controls)
Nishimura et al 1998 [52]	Innog	163	65	227
Hulstaert et al 1999 [53]	Innog	150	100	218
Kahle et al 2000 [54]	Innog	30	16	247
Kanemaru et al 2000 [55]	Innog	24	19	400
Sjögren et al 2000 [56]	Innog	21	18	200
Sjögren et al 2000 [56]	Innog	21	18	186
Kapaki et al 2001 [28]	Innog	38	47	358
Rösler et al 2001 [57]	Innog	27	49	320
Buerger et al 2002 [58]	Innog	80	21	N g
Hu et al 2002 [22]	Innog	52	56	226

Sensitivity	Specificity	LR+	LR–	Quality of study	Comments
66	83	3.9	0.26	2a	Multicenter study
79	70	2.6	0.38	2a	Multicenter study
63	75	2.5	0.40	2a	
83	95	16.6	0.06	2a	
76	85	5.1	0.20	2a	Early onset AD
57	85	3.8	0.26	2a	Late onset AD
90	92	11.3	0.09	2a	
89	100	40	0.025	2a	
81	91	8.6	0.12	2a	
79	100	40	0.025	2a	

The table continues on the next page

Table 20.1 *continued*

Author Year Reference	Method	AD (n)	Controls (n)	Change in AD (% of controls)
Shoji et al 2002 [59]	Innog	366	316	290
Motter et al 1995 [10]	Athena	37	20	192
Kurz et al 1998 [60]	Innog	40	36	442
Burger née Buch et al 1999 [61]	Innog	38	47	212
Hampel et al 1999 [62]	Innog	25	19	231
Morikawa et al 1999 [63]	Innog	36	23	505
Mulder et al 2002 [64]	Innog	20	20	223
Maruyama et al 2001 [65]	Innog	54	15	351
Sum		**2 628**	**1 540**	
Mean				**289.3**

* The "old" standard gave lower CSF tau levels.

AD = Alzheimer's disease; Athena = Athena ELISA method [8]; IFCC = International Federation of Clinical chemistry; Innog = Innogenetics ELISA method [6]; LR = Likelihood ratio; N g = Not given

Sensitivity	Specificity	LR+	LR–	Quality of study	Comments
59	97	19.7	0.05	2a	Multicenter study
59	95	11.8	0.08	2b	Multicenter study
89	97	29.7	0.03	2b	
84	62	2.20	0.45	2b	
80	85	5.3	0.19	2b	
92	95	18.4	0.05	2b	
90	90	9	0.11	2b	
87	93	12.4	0.08	2b	Prospective follow-up
77.1	**89.9**	**16.4**	**0.16**		

Table 20.2 *CSF-Aß42 in Alzheimer's disease and controls.*

Author Year Reference	Variant of Aß42	Method	AD (n)	Controls (n)	Change in AD (% of controls)
Maddalena et al 2003 [66]	Aß 1–42	Innog	51	31	57
Riemenschneider et al 2002 [40]	Aß 1–42	Innog	74	40	37
Sjögren et al 2000 [37]	Aß 1–42	Innog	60	32	49
Sjögren et al 2002 [41]	Aß 1–42	Innog	19	17	42
Kapaki et al 2003 [43]	Aß 1–42	Innog	49	49	49
Andreasen et al 1999 [67]	Aß 1–42	Innog	53	21	42
Hulstaert et al 1999 [53]	Aß 1–42	Innog	150	100	57
Vanderstichele et al 1998 [9]	Aß 1–42	Innog	81	51	75
Galasko et al 1998 [48]	Aß X–42	Athena	82	60	56

Sensitivity	Specificity	LR+	LR–	Quality of study	Comments
78	90	7.8	0.13	1a	Consecutive cases
89	95	17.8	0.06	1a	Consecutive cases
93	85	6.2	0.16	1a	Prospective, consecutive cases
100	94	16.7	0.06	1a	Prospective, consecutive cases
82	80	4.1	0.24	1a	Clinical practice, 3-year follow-up
92	95	18.4	0.05	1b	Community-based sample
78	81	4.1	0.24	2a	Multicenter study
81	80	4.1	0.25	2a	
78	83	4.6	0.22	2a	Multicenter study

The table continues on the next page

***Table 20.2** continued*

Author Year Reference	Variant of Aß42	Method	AD (n)	Controls (n)	Change in AD (% of controls)
Kanemaru et al 2000 [55]	Aß 1–42	Innog	24	19	40
Kapaki et al 2001 [28]	Aß 1–42	Innog	38	47	51
Rösler et al 2001 [57]	Aß 1–42	Innog	27	49	48
Motter et al 1995 [10]	Aß X–42	Athena	37	20	61
Mulder et al 2002 [64]	Aß 1–42	Innog	20	20	46
Maruyama et al 2001 [65]	Aß 1–42	Innog	54	15	71
Sum			**819**	**571**	
Mean					**52.1**

AD = Alzheimer's disease; Athena = Athena ELISA method [10]; Innog = Innogenetics ELISA method [9]; LR = Likelihood ratio

Sensitivity	Specificity	LR+	LR–	Quality of study	Comments
96	95	19.2	0.05	2a	
76	85	5.1	0.2	2a	
78	100	40	0.025	2a	
100	80	5	0.2	2b	Multicenter study
100	95	20	0.05	2b	
89	67	2.7	0.37	2b	Prospective follow-up
87.3	**87**	**11.7**	**0.16**		

Table 20.3 *CSF-phospho tau in Alzheimer's disease and controls.*

Author Year Reference	P-tau epitope	AD (n)	Controls (n)	Change in AD (% of controls)
Sjögren et al 2001 [38]	Thr_{181}	41	17	145
Sjögren et al 2002 [41]	Thr_{181}	19	17	164
Maddalena et al 2003 [66]	Thr_{181}	51	31	193
Parnetti et al 2001 [68]	Thr_{181}	80	40	N g
Hampel et al 2004 [23]	Thr_{181}	108	23	186
Riemenschneider et al 2003 [31]	Thr_{181}	42	43	359
Hampel et al 2004 [23]	Ser_{199}	108	23	212
Ishiguro et al 1999 [20]	Ser_{199}	36	20	N g

Sensitivity	Specificity	LR+	LR–	Quality of study	Comments
44	95	8.8	0.11	1a	Prospective, consecutive cases
58	94	9.7	0.1	1a	Prospective, consecutive cases
84	84	5.3	0.19	1a	Consecutive cases
84	88	7	0.14	2a	
85	91	9.4	0.11	2a	Two-center study
88	100	40	0.025	2a	
85	82	4.7	0.21	2a	Two-center study
94	80	4.7	0.21	2b	"Non-AD" controls

The table continues on the next page

Table 20.3 *continued*

Author Year Reference	P-tau epitope	AD (n)	Controls (n)	Change in AD (% of controls)
Buerger et al 2002 [58]	Thr_{231}	82	21	N g
Hampel et al 2004 [23]	Thr_{231}	108	23	1 906
Kohnken et al 2000 [21]	Thr_{231}	27	31	N g
Hu et al 2002 [22]	$Ser_{396+404}$	52	56	346
Ishiguro et al 1999 [20]	Thr_{231} + Ser_{235}	36	20	N g
Blennow et al 1995 [6]	Thr_{181} + Thr_{231}	40	31	348
Sum **Mean**		**830**	**396**	**428.8**

AD = Alzheimer's disease; LR = Likelihood ratio; N g = Not given

Sensitivity	Specificity	LR+	LR–	Quality of study	Comments
100	91	10.5	0.1	2a	Multicenter study
85	96	21.3	0.05	2a	Two-center study
85	97	28.3	0.04	2b	"Non-AD" controls
94	89	8.5	0.12	2a	Cut-off P-tau >100 pg/mL
53	100	40	0.025	2b	"Non-AD" controls
88	97	29.3	0.03	2a	
80.5	**91.7**	**16.3**	**0.12**		

Table 20.4 *Combination of CSF markers in Alzheimer's disease and controls.*

Author Year Reference	Marker and method	AD (n)	Controls (n)	Sensitivity
Sjögren et al 2000 [37]	Tau + Aß42 (Innog)	60	32	73
Andreasen et al 2001 [39]	Tau + Aß42 (Innog)	105	N a	94
Riemenschneider et al 2002 [40]	Tau + Aß42 (Innog)	74	40	92
Sjögren et al 2002 [41]	Tau + Aß42 (Innog)	19	17	100
Gomez-Tortosa et al 2003 [42]	Tau + Aß42 (Innog)	33	46	84
Kapaki et al 2003 [43]	Tau + Aß42 (Innog)	49	49	96
Andreasen et al 2001 [69]	Tau + Aß42 (Innog)	35	19	92
Galasko et al 1998 [48]	Tau + Aß42 (Athena)	82	60	90
Vanderstichele et al 1998 [9]	Tau + Aß42 (Innog)	81	15	74

Specificity	LR+	LR–	Quality of study	Comments
84	4.6	0.22	1a	Prospective, consecutive cases
N a	N a	N a	1a	Community-based sample
95	18.4	0.05	1a	Consecutive cases
100	40	0.025	1a	Prospective, consecutive cases
79	4	0.25	1a	Prospective study
86	6.9	0.15	1a	Clinical practice, 3-year follow-up
90	9.2	0.11	1b	
80	4.1	0.22	2a	Multicenter study
93	10.6	0.09	2a	

The table continues on the next page

***Table 20.4** continued*

Author Year Reference	Marker and method	AD (n)	Controls (n)	Sensitivity
Hulstaert et al 1999 [53]	Tau + Aß42 (Innog)	150	100	85
Rösler et al 2001 [57]	Tau + Aß42 (Innog)	27	49	85
Takeda et al 2001 [70]	Tau + Aß42 (Innog)	189	27	80
Motter et al 1995 [10]	Tau + Aß42 (Athena)	37	20	59
Mulder et al 2002 [64]	Tau + Aß42 (Innog)	20	20	100
Sunderland et al 2003 [14]	Tau (Innog) + AßX-42 (IGEN)	131	72	92
Kanai et al 1998 [49]	Tau + Aß42 (Innog + Jap)	93	54	40
Maddalena et al 2003 [66]	P-Tau181 + Aß42 (Innog)	51	31	86
Hu et al 2002 [22]	T-tau + P-tau$_{396/404}$	52	56	96
Sum		**1 228**	**675**	
Mean				**85**

AD = Alzheimer's disease; Athena = Athena ELISA method [8]; Innog = Innogenetics ELISA method [6]; LR = Likelihood ratio; N a = Not applicable

Specificity	LR+	LR–	Quality of study	Comments
87	6.5	0.15	2a	Multicenter study
100	40.0	0.025	2a	
100	40	0.025	2a	Multicenter study
95	7.4	0.08	2b	Multicenter study
95	20	0.05	2b	
82	5.1	0.2	2b	31 AD with neuropathological diagnosis
90	9.3	0.25	2a	Multicenter study
97	28.7	0.03	1a	Consecutive cases
100	40	0.025	2a	
91.8	**18.1**	**0.14**		

Table 20.5 *CSF markers in early Alzheimer's disease and MCI.*

Author, year, reference	Marker	Criteria	n
Andreasen et al, 1999 [45]	T-tau	AD et al, MMSE >23	205
Galasko et al, 1997 [71]	T-tau	AD et al, MMSE >25	12
Riemenschneider et al, 1996 [72]	T-tau	AD et al, MMSE >25	11
Kurz et al, 1998 [60]	T-tau	AD et al, MMSE >25	19
Arai et al, 2000 [73]	T-tau	MCI with progr to AD	20
Andreasen et al, 2003 [74]	T-tau	MCI with progr to AD	44
Maruyama et al, 2001 [65]	T-tau	MCI et al, 70% with progr to AD	19
Gottfries et al, 2001 [75]	T-tau	MCI with progr to AD	32
Arai et al, 1997 [76]	T-tau	MCI with progr to AD	10
Sum **Mean**			**372**
Andreasen et al, 1999 [67]	Aß42	AD et al, MMSE >25	24
Andreasen et al, 2003 [74]	Aß42	MCI with progr to AD	44
Maruyama et al, 2001 [65]	Aß42	MCI 70% with progr to AD	19
Sum **Mean**			**87**

Change in AD (% of controls)	Sensitivity	Quality of study	Comments
288	94	1b	Community-based patient sample
N g	75	2a	
284	91	2b	
384	84	2b	
N a	80	1b	Consecutive cases
212	80	1b	Community-based patient sample
291	68	2a	
267	60	2a	
N a	90	2b	
287.7	**80.2**		
N g	88	1b	Community-based sample
57	77	1b	Community-based sample
94	47	2b	
75.5	**70.7**		

The table continues on the next page

Table 20.5 *continued*

Author, year, reference	Marker	Criteria	n
Galasko et al, 1998 [48]	T-tau + Abß42	AD et al, MMSE >23	24
Hulstaert et al, 1999 [53]	T-tau + Abß42	AD et al, MMSE >23	23
Andreasen et al, 1999 [77]	T-tau + Abß42	MCI with progr to AD	16
Riemenschneider et al, 2002 [78]	T-tau + Abß42	MCI with progr to AD	10
Sum **Mean**			**73**
Riemenschneider et al, 2003 [31]	P-Thr_{181}	AD et al, MMSE >25	29
Arai et al, 2000 [73]	P-Thr_{231} + P-Ser_{235}	MCI with progr to AD	20
Andreasen et al, 2003 [74]	P-Thr_{181}	MCI with progr to AD	44
Sum **Mean**			**93**

AD = Alzheimer's disease; MCI = Mild cognitive impairment; MMSE = Mini-mental state examination; N a = Not applicable; N g = Not given

	Change in AD (% of controls)	Sensitivity	Quality of study	Comments
	N a	62	2a	Multicenter study
	N a	70	2a	Multicenter
	N a	88	1b	Community-based patient sample
	N a	90	2a	
		77.5		
	303	97	2a	
	N a	70	1b	Consecutive cases
	202	70	1b	Community-based patient sample
		79.0		

Table 20.6 *CFS markers in other brain disorders.*

Author Year Reference	Number of cases	CSF total tau Percent with increase	Degree of increase	Number of cases	CSF Aß42 Percent with decrease
Lewy body dementia					
Kanemaru et al 2000 [55]	11	18	Normal-mild	11	73
Itoh et al 2001 [27]	13	15	Normal-mild		
Saez-Valero et al 2003 [79]	19	16	Normal-mild	19	74
Shoji et al 2002 [59]	14	7	Mild-moderate		
Buerger et al 2002 [58]	17	53	Moderate		
Hampel et al 2004 [23]					
Hampel et al 2004 [23]					
Hampel et al 2004 [23]					

Degree of decrease	Number of cases	CSF phospho tau Percent with increase	Degree of increase	Quality of study	Comments
Mild-moderate				2a	
	13	15	Normal-mild	2a	P-Ser_{199}
Moderate	19	11	Normal	2a	P-Thr_{181}
				2a	
	17	59		2a	P-Thr_{231}
	22	36	Mild-moderate	2a	P-Thr_{231}
	22	32	Mild-moderate	2a	P-Thr_{181}
	22	50	Mild-moderate	2a	P-Ser_{199}

The table continues on the next page

Table 20.6 *continued*

Author Year Reference	Number of cases	CSF total tau Percent with increase	Degree of increase	Number of cases	CSF Aß42 Percent with decrease
Riemenschneider et al 2003 [31]					
Sum	74			**30**	
Mean		21.8			73.5
Fronto-temporal dementia					
Sjögren et al 2000 [37]	17	24	Normal-mild	17	41
Sjögren et al 2001 [38]	18	0	Normal		
Sjögren et al 2001 [39]	14	14	Normal-mild		
Sjögren et al 2002 [41]	14	14	Mild	14	50
Wallin et al 2003 [44]	14	21	Normal-mild		
Blennow et al 1995 [6]	11	36	Mild		
Mecocci et al 1998 [50]	10	0	Normal		

Degree of decrease	Number of cases	CSF phos-pho tau Percent with increase	Degree of increase	Quality of study	Comments
	18	N g	Mild	2a	15 with mild, 3 high P-tau
	133	33.8			
Mild				1a	
	18	0	Normal	1a	P-Thr$_{181}$
				1a	
Moderate	14	0	Normal	1a	P-Thr$_{181}$
				1a	
	11	55	Mild incr	2a	P-Thr$_{181+231}$
				2a	

The table continues on the next page

Table 20.6 *continued*

Author Year Reference	Number of cases	CSF total tau Percent with increase	Degree of increase	Number of cases	CSF Aß42 Percent with decrease
Green et al 1999 [80]	23	69	Moderate		
Hulstaert et al 1999 [53]	11	27	Mild-moderate	11	45
Vanmechelen et al 2000 [19]	18	0	Normal		
Sjögren et al 2000 [56]	18	11	Normal-mild		
Itoh et al 2001 [27]	16	25	Normal-mild		
Shoji et al 2002 [59]	14	36	Mild		
Buerger et al 2002 [58]	26	38	Mild		
Rosso et al 2003 [81]	17	35	Moderate	17	12
Hampel et al 2004 [23]					

	Degree of decrease	Number of cases	CSF phospho tau Percent with increase	Degree of increase	Quality of study	Comments
					2a	
	Mild-moderate				2a	
		18	0	Normal	2a	P-Thr$_{181}$ Low P-tau in FTD
					2a	
		16	37	Mild-moderate	2a	P-Ser$_{199}$
					2a	
		26	12	Mild	2a	P-Thr$_{231}$
	Mild	17	29	Mild-moderate	2a	
		24	8	Normal-mild	2a	P-Thr$_{231}$

The table continues on the next page

Table 20.6 *continued*

Author Year Reference	Number of cases	CSF total tau Percent with increase	Degree of increase	Number of cases	CSF Aß42 Percent with decrease
Hampel et al 2004 [23]					
Hampel et al 2004 [23]					
Fabre et al 2001 [82]	47	49	Mild-moderate		
Sum	**288**			**59**	
Mean		**24.9**			**37**
Vascular dementia					
Andreasen et al 1998 [36]	21	86	Moderate		
Sjögren et al 2000 [37]	25	52	Mild-moderate	25	68
Sjögren et al 2001 [38]	17	0	Normal		
Sjögren et al 2001 [39]	16	50	Mild		
Wallin et al 2003 [44]	17	47	Normal-mild		

	Degree of decrease	Number of cases	CSF phospho tau Percent with increase	Degree of increase	Quality of study	Comments
		24	29	Mild	2a	P-Thr$_{181}$
		24	58	Mild-moderate	2a	P-Ser$_{199}$
					2b	
		192	**22.8**			
					1a	
	Mild-moderate				1a	
		17	6	Mild	1a	P-Thr$_{181}$
					1a	2 cases with marked increase
					1a	

The table continues on the next page

Table 20.6 *continued*

Author Year Reference	Number of cases	CSF total tau Percent with increase	Degree of increase	Number of cases	CSF Aß42 Percent with decrease
Blennow et al 1995 [6]	17	76	Moderate		
Mori et al 1995 [7]	12	0	Normal		
Arai et al 1998 [47]	21	5	Normal		
Mecocci et al 1998 [50]	10	20	Normal-mild		
Hulstaert et al 1999 [53]	33	27	Moderate	33	67
Itoh et al 2001 [27]	23	39	Mild-moderate		
Gottfries et al 2001 [75]	14	44	Mild-moderate		
Shoji et al 2002 [59]	63	13	Normal		
Buerger et al 2002 [58]	20	40	Moderate		

	Degree of decrease	Number of cases	CSF phos-pho tau Percent with increase	Degree of increase	Quality of study	Comments
		17	65	Moderate incr	2a	P-Thr$_{181+231}$
					2a	
					2a	
					2a	
	Mild-moderate				2a	
		23	17	Mild	2a	P-Ser$_{199}$
					2a	
					2a	
		20	35	Moderate	2a	P-Thr$_{231}$

The table continues on the next page

Table 20.6 *continued*

Author Year Reference	Number of cases	CSF total tau Percent with increase	Degree of increase	Number of cases	CSF Aß42 Percent with decrease
Hu et al 2002 [22]	46	50	Mild-moderate		
Saez-Valero et al 2003 [79]	12	17	Normal-mild	12	58
Sum	**367**			**70**	
Mean		**35.4**			**64.3**
Cerebrovascular disease without dementia					
Vigo-Pelfrey et al 1995 [8]	16	0	Normal		
Arai et al 1995 [46]	19	16	Normal		
Nishimura et al 1998 [52]	38	13	Normal-mild		
Sum	**73**				
Mean		**9.7**			
Normal pressure hydrocephalus					
Hulstaert et al 1999 [53]	20	20	Mild-moderate	20	50

	Degree of decrease	Number of cases	CSF phospho tau Percent with increase	Degree of increase	Quality of study	Comments
		46	7	Mild	2a	P-$Ser_{396+404}$
	Mild-moderate	7	14	Normal-mild	2a	P-Thr_{181}
		130	**24**			
					2a	
					2a	16/19 normal tau
					2a	
	Mild-moderate				2a	

The table continues on the next page

Table 20.6 *continued*

Author Year Reference	Number of cases	CSF total tau Percent with increase	Degree of increase	Number of cases	CSF Aß42 Percent with decrease
Kudo et al 2000 [83]	20	55	Mild-moderate		
Tullberg et al 2000 [84]	43	N g	Normal-mild		
Sum	**83**			**20**	**50**
Mean		**37.5**			
Amyotrophic lateral sclerosis					
Sjögren et al 2002 [41]	19	45	Mild-moderate	19	100
Vigo-Pelfrey et al 1995 [8]	20	10	Normal-mild		
Kanai et al 1998 [49]	12	0	Normal		
Kapaki et al 2000 [85]	17	0	Normal		
Sum	**68**			**19**	
Mean		**13.8**			**100**

	Degree of decrease	Number of cases	CSF phospho tau Percent with increase	Degree of increase	Quality of study	Comments
					2b	
					2b	
	Moderate-severe	19	9	Mild	1a	P-Thr$_{181}$
					2a	
					2a	
					2a	
		19	**9**			

The table continues on the next page

Table 20.6 *continued*

Author Year Reference	Number of cases	CSF total tau Percent with increase	Degree of increase	Number of cases	CSF Aß42 Percent with decrease
Parkinson's disease without dementia					
Sjögren et al 2000 [37]	23	22	Mild	23	26
Sjögren et al 2001 [38]	15	0	Normal		
Sjögren et al 2002 [41]	15	0	Normal	15	27
Blennow et al 1995 [6]	15	27	Mild		
Holmberg et al 2003 [86]				48	4
Sum	**68**			**86**	
Mean		**12.3**			**19**
Parkinson's disease without dementia					
Holmberg et al 2003 [86]				15	0
Itoh et al 2001 [27]	21	0	Normal		

Degree of decrease	Number of cases	CSF phos-pho tau Percent with increase	Degree of increase	Quality of study	Comments
Mild				1a	
	15	0	Normal	1a	P-Thr_{181}
Mild	15	0	Normal	1a	P-Thr_{181}
	15	27	Mild	2a	P-$Thr_{181+231}$
Normal				2a	
	45	**9**			
Normal				2a	
	21	19	Mild	2a	P-Ser_{199}

The table continues on the next page

***Table 20.6** continued*

Author Year Reference	Number of cases	CSF total tau Percent with increase	Degree of increase	Number of cases	CSF Aß42 Percent with decrease
Shoji et al 2002 [59]	14	7	Normal		
Urakami et al 2001 [87]	30	0	Normal		
Sum	**65**			**15**	
Mean		**2.3**			**0**
Corticobasal degeneration					
Itoh et al 2001 [27]	15	33	Normal-mild		
Shoji et al 2002 [59]	14	14	Normal-mild		
Sum	**29**				
Mean		**23.5**			
Depression					
Sjögren et al 2000 [37]	19	10	Normal-mild	19	0
Andreasen et al 1999 [45]	28	18	Normal-mild		
Blennow et al 1995 [6]	10	0	Normal		

	Degree of decrease	Number of cases	CSF phospho tau Percent with increase	Degree of increase	Quality of study	Comments
					2a	
					2b	
		15	47	Mild-moderate	2a	P-Ser_{199}
					2a	
		15	**47**			
	Normal				1a	
					1b	
		10	0		2a	P-$Thr_{181+231}$

The table continues on the next page

Table 20.6 *continued*

Author Year Reference	Number of cases	CSF total tau Percent with increase	Degree of increase	Number of cases	CSF Aß42 Percent with decrease
Rösler et al 1996 [88]	11	9	Normal-mild		
Burger née Buch et al 1999 [61]	19	26	Normal-mild		
Buerger et al 2003 [89]					
Schonknecht et al 2003 [90]	25	0	Normal		
Sum **Mean**	**112**	**10.5**		**19**	
Alcoholism					
Morikawa et al 1999 [63]	20	5	Normal		
Sum **Mean**	**20**	**5**			
Creutzfeldt-Jakob disease					
Otto et al 1997 [25]	21	100	Very high		
Otto et al 2000 [91]				27	89

	Degree of decrease	Number of cases	CSF phos-pho tau Percent with increase	Degree of increase	Quality of study	Comments
					2a	
					2b	
		34	N g	Normal-mild	2a	
					2a	
		44	**0**			
					2b	With dementia
					IIB	Tau cut-off = 1 530 pg/mL
	Moderate				IIB	

The table continues on the next page

Table 20.6 *continued*

Author Year Reference	**Number of cases**	**CSF total tau Percent with increase**	**Degree of increase**	**Number of cases**	**CSF Aß42 Percent with decrease**
Kapaki et al 2001 [28]	14	100	Very high	14	64
Otto et al 2002 [29]	109	96	Very high		89
van Everbroeck et al 1999 [26]	29	74	Very high	29	N g
Itoh et al 2001 [27]	11	100	Very high		
van Everbroeck et al 2002 [30]	75	92	Very high		
Riemenschneider et al 2003 [31]	20	100	Very high		
Sum	**279**			**70**	
Mean		**94.6**			**80.7**

N g = Not given

	Degree of decrease	Number of cases	CSF phospho tau Percent with increase	Degree of increase	Quality of study	Comments
	Moderate-marked				IIB	Tau cut-off = 2 131 pg/mL
					IIB	Tau cut-off = 1 300 pg/mL
	Moderate				2a	Tau cut-off = 1 530 pg/mL
		11	36	Mild	2a	P-Ser_{199}
		75	Ng	Mild-moderate	2a	Tau cut-off = 1 350 pg/mL
		20	85	Mild	2a	P-Thr_{181}
		106	**60.5**			

Table 20.7 *Summary of diagnostic validity of CSF markers.*

CSF marker	Degree of quality	Studies (n)	AD (n)	Controls (n)
T-tau	1-a	9	405	243
	1-a, 1b, 2a, 2b	36	2 628	1 540
Aß1-42	1-a	5	253	169
	1-a, 1b, 2a, 2b	15	819	571
P-tau	1-a	3	111	65
	1-a, 1b, 2a, 2b	14	830	396
Combination of T-tau, P-tau or Aß1-42	1-a	6	340	184
	1-a, 1b, 2a, 2b	18	1 228	675

AD = Alzheimer's disease; LR = Likelihood ratio

Sensitivity	Specificity	LR+	LR–	Grade of evidence
83.2 77.1	91.6 89.9	16 16.4	0.11 0.16	Grade 1 (strong)
88.4 87.3	88.8 87	10.5 11.7	0.13 0.16	Grade 1 (strong)
62 80.5	91 91.7	7.9 16.3	0.14 0.12	Grade 2 (moderately strong)
89.8 85	88.8 91.8	14.8 18.1	0.17 0.14	Grade 1 (strong)

References

1. Buee L, Bussiere T, Buee-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. Brain Res Brain Res Rev 2000;33:95-130.

2. Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. Lancet Neurol 2003;2: 605-13.

3. Andreasen N, Blennow K. Beta-amyloid (Abeta) protein in cerebrospinal fluid as a biomarker for Alzheimer's disease. Peptides 2002;23:1205-14.

4. Qizilbash Nea. Evidence-based dementia practice. Oxford: Blackwell Publishing; 2002.

5. Vandermeeren M, Mercken M, Vanmechelen E, Six J, van de Voorde A, Martin JJ, et al. Detection of tau proteins in normal and Alzheimer's disease cerebrospinal fluid with a sensitive sandwich enzyme-linked immunosorbent assay. J Neurochem 1993;61:1828-34.

6. Blennow K, Wallin A, Agren H, Spenger C, Siegfried J, Vanmechelen E. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? Mol Chem Neuropathol 1995;26:231-45.

7. Mori H, Hosoda K, Matsubara E, Nakamoto T, Furiya Y, Endoh R, et al. Tau in cerebrospinal fluids: establishment of the sandwich ELISA with antibody specific to the repeat sequence in tau. Neurosci Lett 1995;186:181-3.

8. Vigo-Pelfrey C, Seubert P, Barbour R, Blomquist C, Lee M, Lee D, et al. Elevation of microtubule-associated protein tau in the cerebrospinal fluid of patients with Alzheimer's disease. Neurology 1995;45:788-93.

9. Vanderstichele H, Blennow K, D'Heuvaert ND, Buyse MA Wallin A, Andreasen N, et al. E. Eds: Fisher, A, Hanin, I, Yoshida, M. Development of a specific diagnostic test for measurement of B-amyloid (1–42) in CSF. Progress in Alzheimer's and Parkinson's Diseases. Plenum Press, New York. 1998:v773-778.

10. Motter R, Vigo-Pelfrey C, Kholodenko D, Barbour R, Johnson-Wood K, Galasko D, et al. Reduction of beta-amyloid peptide42 in the cerebrospinal fluid of patients with Alzheimer's disease. Ann Neurol 1995;38:643-8.

11. Tamaoka A, Sawamura N, Fukushima T, Shoji S, Matsubara E, Shoji M, et al. Amyloid beta protein 42(43) in cerebrospinal fluid of patients with Alzheimer's disease. J Neurol Sci 1997;148:41-5.

12. Jensen M, Schroder J, Blomberg M, Engvall B, Pantel J, Ida N, et al. Cerebrospinal fluid A beta42 is increased early in sporadic Alzheimer's disease and declines with disease progression. Ann Neurol 1999;45:504-11.

13. Mehta PD, Pirttila T, Mehta SP, Sersen EA, Aisen PS, Wisniewski HM. Plasma and cerebrospinal fluid levels of amyloid beta proteins 1-40 and 1-42 in Alzheimer disease. Arch Neurol 2000;57:100-5.

14. Sunderland T, Linker G, Mirza N, Putnam KT, Friedman DL, Kimmel LH,

et al. Decreased beta-amyloid1-42 and increased tau levels in cerebrospinal fluid of patients with Alzheimer disease. JAMA 2003;289:2094-103.

15. Ida N, Hartmann T, Pantel J, Schroder J, Zerfass R, Forstl H, et al. Analysis of heterogeneous A4 peptides in human cerebrospinal fluid and blood by a newly developed sensitive Western blot assay. J Biol Chem 1996;271:22908-14.

16. Schroder J, Pantel J, Ida N, Essig M, Hartmann T, Knopp MV, et al. Cerebral changes and cerebrospinal fluid beta-amyloid in Alzheimer's disease: a study with quantitative magnetic resonance imaging. Mol Psychiatry 1997;2:505-7.

17. Wiltfang J, Esselmann H, Bibl M, Smirnov A, Otto M, Paul S, et al. Highly conserved and disease-specific patterns of carboxyterminally truncated Abeta peptides 1–37/38/39 in addition to 1–40/42 in Alzheimer's disease and in patients with chronic neuroinflammation. J Neurochem 2002;81:481-96.

18. Lewczuk P, Esselmann H, Meyer M, Wollscheid V, Neumann M, Otto M, et al. The amyloid-beta (Abeta) peptide pattern in cerebrospinal fluid in Alzheimer's disease: evidence of a novel carboxyterminally elongated Abeta peptide. Rapid Commun Mass Spectrom 2003;17:1291-6.

19. Vanmechelen E, Vanderstichele H, Davidsson P, Van Kerschaver E, Van Der Perre B, Sjogren M, et al. Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. Neurosci Lett 2000; 285:49-52.

20. Ishiguro K, Ohno H, Arai H, Yamaguchi H, Urakami K, Park JM, et al. Phosphorylated tau in human cerebrospinal fluid is a diagnostic marker for Alzheimer's disease. Neurosci Lett 1999;270:91-4.

21. Kohnken R, Buerger K, Zinkowski, R, Miller, C, Kerkman, D DeBernardis J, et.al. Detection of tau phosphorylated at threonine 231 in cerebrospinal fluid of Alzheimer's disease patients. Neurosci Lett 2000;287:187-90.

22. Hu YY, He SS, Wang X, Duan QH, Grundke-Iqbal I, Iqbal K, et al. Levels of nonphosphorylated and phosphorylated tau in cerebrospinal fluid of Alzheimer's disease patients : an ultrasensitive bienzyme-substrate-recycle enzyme-linked immunosorbent assay. Am J Pathol 2002;160:1269-78.

23. Hampel H, Buerger K, Zinkowski R, Teipel SJ, Goernitz A, Andreasen N, et al. Measurement of phosphorylated tau epitopes in the differential diagnosis of Alzheimer disease: a comparative cerebrospinal fluid study. Arch Gen Psychiatry 2004;61:95-102.

24. Approved recommendation on the theory of reference values. Part 5. Statistical treatment of collected reference values. Determination of reference limits. Clin Chem Lab Med 1987;170:13-32.

25. Otto M, Wiltfang J, Tumani H, Zerr I, Lantsch M, Kornhuber J, et al. Elevated levels of tau-protein in cerebrospinal fluid of patients with Creutzfeldt-Jakob disease. Neurosci Lett 1997;225:210-2.

26. Van Everbroeck B, Green AJ, Pals P, Martin JJ, Cras P. Decreased Levels of Amyloid-beta 1-42 in Cerebrospinal Fluid

of Creutzfeldt-Jakob Disease Patients. J Alzheimers Dis 1999;1:419-24.

27. Itoh N, Arai H, Urakami K, Ishiguro K, Ohno H, Hampel H, et al. Large-scale, multicenter study of cerebrospinal fluid tau protein phosphorylated at serine 199 for the antemortem diagnosis of Alzheimer's disease. Ann Neurol 2001;50:150-6.

28. Kapaki E, Kilidireas K, Paraskevas GP, Michalopoulou M, Patsouris E. Highly increased CSF tau protein and decreased beta-amyloid (1–42) in sporadic CJD: a discrimination from Alzheimer's disease? J Neurol Neurosurg Psychiatry 2001;71:401-3.

29. Otto M, Wiltfang J, Cepek L, Neumann M, Mollenhauer B, Steinacker P, et al. Tau protein and 14-3-3 protein in the differential diagnosis of Creutzfeldt-Jakob disease. Neurology 2002;58:192-7.

30. Van Everbroeck B, Green AJ, Vanmechelen E, Vanderstichele H, Pals P, Sanchez-Valle R, et al. Phosphorylated tau in cerebrospinal fluid as a marker for Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 2002;73:79-81.

31. Riemenschneider M, Wagenpfeil S, Vanderstichele H, Otto M, Wiltfang J, Kretzschmar H, et al. Phospho-tau/total tau ratio in cerebrospinal fluid discriminates Creutzfeldt-Jakob disease from other dementias. Mol Psychiatry 2003;8:343-7.

32. Zetterberg H, Blennow K. Elevated total tau/phospho-tau ratio in autopsy-proven Creutzfeldt-Jakob disease with negative 14-3-3 test results. Neurol Sci 2004;25:301-2.

33. Lopez OL, Becker JT, Kaufer DI, Hamilton RL, Sweet RA, Klunk W, et al. Research evaluation and prospective diagnosis of dementia with Lewy bodies. Arch Neurol 2002;59:43-6.

34. Jellinger KA. Diagnostic accuracy of Alzheimer's disease: a clinicopathological study. Acta Neuropathol (Berl) 1996;91:219-20.

35. Kosunen O, Soininen H, Paljarvi L, Heinonen O, Talasniemi S, Riekkinen PJ, Sr. Diagnostic accuracy of Alzheimer's disease: a neuropathological study. Acta Neuropathol (Berl) 1996;91:185-93.

36. Andreasen N, Vanmechelen E, Van de Voorde A, Davidsson P, Hesse C, Tarvonen S, et al. Cerebrospinal fluid tau protein as a biochemical marker for Alzheimer's disease: a community based follow up study. J Neurol Neurosurg Psychiatry 1998;64: 298-305.

37. Sjogren M, Minthon L, Davidsson P, Granerus AK, Clarberg A, Vanderstichele H, et al. CSF levels of tau, beta-amyloid (1–42) and GAP-43 in frontotemporal dementia, other types of dementia and normal aging. J Neural Transm 2000; 107:563-79.

38. Sjogren M, Davidsson P, Tullberg M, Minthon L, Wallin A, Wikkelso C, et al. Both total and phosphorylated tau are increased in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001;70:624-30.

39. Sjogren M, Davidsson P, Gottfries J, Vanderstichele H, Edman A, Vanmechelen E, et al. The cerebrospinal fluid levels of tau, growth-associated protein-43 and

soluble amyloid precursor protein correlate in Alzheimer's disease, reflecting a common pathophysiological process. Dement Geriatr Cogn Disord 2001;12:257-64.

40. Riemenschneider M, Wagenpfeil S, Diehl J, Lautenschlager N, Theml T, Heldmann B, et al. Tau and Abeta42 protein in CSF of patients with frontotemporal degeneration. Neurology 2002;58:1622-8.

41. Sjogren M, Davidsson P, Wallin A, Granerus AK, Grundstrom E, Askmark H, et al. Decreased CSF-beta-amyloid 42 in Alzheimer's disease and amyotrophic lateral sclerosis may reflect mismetabolism of beta-amyloid induced by disparate mechanisms. Dement Geriatr Cogn Disord 2002;13:112-8.

42. Gomez-Tortosa E, Gonzalo I, Fanjul S, Sainz MJ, Cantarero S, Cemillan C, et al. Cerebrospinal fluid markers in dementia with lewy bodies compared with Alzheimer disease. Arch Neurol 2003;60:1218-22.

43. Kapaki E, Paraskevas GP, Zalonis I, Zournas C. CSF tau protein and beta-amyloid (1–42) in Alzheimer's disease diagnosis: discrimination from normal ageing and other dementias in the Greek population. Eur J Neurol 2003;10:119-28.

44. Wallin A, Sjogren M, Blennow K, Davidsson P. Decreased cerebrospinal fluid acetylcholinesterase in patients with subcortical ischemic vascular dementia. Dement Geriatr Cogn Disord 2003;16:200-7.

45. Andreasen N, Minthon L, Clarberg A, Davidsson P, Gottfries J, Vanmechelen E, et al. Sensitivity, specificity, and stability of CSF-tau in AD in a community-based patient sample. Neurology 1999;53:1488-94.

46. Arai H, Terajima M, Miura M, Higuchi S, Muramatsu T, Machida N, et al. Tau in cerebrospinal fluid: a potential diagnostic marker in Alzheimer's disease. Ann Neurol 1995;38:649-52.

47. Arai H, Satoh-Nakagawa T, Higuchi M, Morikawa Y, Miura M, Kawakami H, et al. No increase in cerebrospinal fluid tau protein levels in patients with vascular dementia. Neurosci Lett 1998;256:174-6.

48. Galasko D, Chang L, Motter R, Clark CM, Kaye J, Knopman D, et al. High cerebrospinal fluid tau and low amyloid beta42 levels in the clinical diagnosis of Alzheimer disease and relation to apolipoprotein E genotype. Arch Neurol 1998;55:937-45.

49. Kanai M, Matsubara E, Isoe K, Urakami K, Nakashima K, Arai H, et al. Longitudinal study of cerebrospinal fluid levels of tau, A beta1-40, and A beta1-42(43) in Alzheimer's disease: a study in Japan. Ann Neurol 1998;44:17-26.

50. Mecocci P, Cherubini A, Bregnocchi M, Chionne F, Cecchetti R, Lowenthal DT, et al. Tau protein in cerebrospinal fluid: a new diagnostic and prognostic marker in Alzheimer disease? Alzheimer Dis Assoc Disord 1998;12:211-4.

51. Shoji M, Matsubara E, Kanai M, Watanabe M, Nakamura T, Tomidokoro Y, et al. Combination assay of CSF tau, A beta 1–40 and A beta 1–42(43) as a biochemical marker of Alzheimer's disease. J Neurol Sci 1998;158:134-40.

52. Nishimura T, Takeda M, Nakamura Y, Yosbida Y, Arai H, Sasaki H, et al. Basic and clinical studies on the measurement of tau protein in cerebrospinal fluid as a

biological marker for Alzheimer's disease and related disorders: multicenter study in Japan. Methods Find Exp Clin Pharmacol 1998;20:227-35.

53. Hulstaert F, Blennow K, Ivanoiu A, Schoonderwaldt HC, Riemenschneider M,

De Deyn PP, et al. Improved discrimination of AD patients using beta-amyloid(1-42) and tau levels in CSF. Neurology 1999;52:1555-62.

54. Kahle PJ, Jakowec M, Teipel SJ, Hampel H, Petzinger GM, Di Monte DA, et al. Combined assessment of tau and neuronal thread protein in Alzheimer's disease CSF. Neurology 2000;54:1498-504.

55. Kanemaru K, Kameda N, Yamanouchi H. Decreased CSF amyloid beta42 and normal tau levels in dementia with Lewy bodies. Neurology 2000;54:1875-6.

56. Sjogren M, Rosengren L, Minthon L, Davidsson P, Blennow K, Wallin A. Cytoskeleton proteins in CSF distinguish frontotemporal dementia from AD. Neurology 2000;54:1960-4.

57. Rosler N, Wichart I, Jellinger KA. Clinical significance of neurobiochemical profiles in the lumbar cerebrospinal fluid of Alzheimer's disease patients. J Neural Transm 2001;108:231-46.

58. Buerger K, Zinkowski R, Teipel SJ, Tapiola T, Arai H, Blennow K, et al. Differential diagnosis of Alzheimer disease with cerebrospinal fluid levels of tau protein phosphorylated at threonine 231. Arch Neurol 2002;59:1267-72.

59. Shoji M, Matsubara E, Murakami T, Manabe Y, Abe K, Kanai M, et al. Cerebrospinal fluid tau in dementia disorders: a large scale multicenter study by a Japanese study group. Neurobiol Aging 2002;23:363-70.

60. Kurz A, Riemenschneider M, Buch K, Willoch F, Bartenstein P, Muller U, et al. Tau protein in cerebrospinal fluid is significantly increased at the earliest clinical stage of Alzheimer disease. Alzheimer Dis Assoc Disord 1998;12:372-7.

61. Burger née Buch K, Padberg F, Nolde T, Teipel SJ, Stubner S, Haslinger A, et al. Cerebrospinal fluid tau protein shows a better discrimination in young old (<70 years) than in old old patients with Alzheimer's disease compared with controls. Neurosci Lett 1999;277:21-4.

62. Hampel H, Teipel SJ, Padberg F, Haslinger A, Riemenschneider M, Schwarz MJ, et al. Discriminant power of combined cerebrospinal fluid tau protein and of the soluble interleukin-6 receptor complex in the diagnosis of Alzheimer's disease. Brain Res 1999;823:104-12.

63. Morikawa Y, Arai H, Matsushita S, Kato M, Higuchi S, Miura M, et al. Cerebrospinal fluid tau protein levels in demented and nondemented alcoholics. Alcohol Clin Exp Res 1999;23: 575-7.

64. Mulder C, Schoonenboom SN, Wahlund LO, Scheltens P, van Kamp GJ, Veerhuis R, et al. CSF markers related to pathogenetic mechanisms in Alzheimer's disease. J Neural Transm 2002;109:1491-8.

65. Maruyama M, Arai H, Sugita M, Tanji H, Higuchi M, Okamura N, et al. Cerebrospinal fluid amyloid beta(1-42) levels in the mild cognitive impairment stage of Alzheimer's disease. Exp Neurol 2001;172:433-6.

66. Maddalena A, Papassotiropoulos A, Muller-Tillmanns B, Jung HH, Hegi T, Nitsch RM, et al. Biochemical diagnosis of Alzheimer disease by measuring the cerebrospinal fluid ratio of phosphorylated tau protein to beta-amyloid peptide42. Arch Neurol 2003;60:1202-6.

67. Andreasen N, Hesse C, Davidsson P, Minthon L, Wallin A, Winblad B, et al. Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease. Arch Neurol 1999;56:673-80.

68. Parnetti L, Lanari A, Amici S, Gallai V, Vanmechelen E, Hulstaert F. CSF phosphorylated tau is a possible marker for discriminating Alzheimer's disease from dementia with Lewy bodies. Phospho-Tau International Study Group. Neurol Sci 2001;22:77-8.

69. Andreasen N, Gottfries J, Vanmechelen E, Vanderstichele H, Davidson P, Blennow K, et al. Evaluation of CSF biomarkers for axonal and neuronal degeneration, gliosis, and beta-amyloid metabolism in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001;71:557-8.

70. Takeda M, Tanaka, T, Arai H, Sasaki, H, Shoji, M, Okamoto, K. Basic and clinical studies on the measurement of b-amyloid (1–42) in cerebrospinal fluid as a diagnostic marker for Alzheimer's disease and related disorders: multi center study in Japan. Psychogeriatrics 2001;1: 56-63.

71. Galasko D, Clark C, Chang L, Miller B, Green RC, Motter R, et al. Assessment of CSF levels of tau protein in mildly demented patients with Alzheimer's disease. Neurology 1997;48:632-5.

72. Riemenschneider M, Buch K, Schmolke M, Kurz A, Guder WG. Cerebrospinal protein tau is elevated in early Alzheimer's disease. Neurosci Lett 1996;212:209-11.

73. Arai H, Ishiguro K, Ohno H, Moriyama M, Itoh N, Okamura N, et al. CSF phosphorylated tau protein and mild cognitive impairment: a prospective study. Exp Neurol 2000;166:201-3.

74. Andreasen N, Vanmechelen E, Vanderstichele H, Davidsson P, Blennow K. Cerebrospinal fluid levels of total-tau, phospho-tau and A beta 42 predicts development of Alzheimer's disease in patients with mild cognitive impairment. Acta Neurol Scand Suppl 2003;179:47-51.

75. Gottfries J, Blennow K, Lehmann MW, Regland B, Gottfries CG. One-carbon metabolism and other biochemical correlates of cognitive impairment as visualized by principal component analysis. J Geriatr Psychiatry Neurol 2001;14:109-14.

76. Arai H, Nakagawa, T, Kosaka, Y, Higuchi, M, Matsui, T, Okamura, N, et al. Elevated cerebrospinal fluid tau protein level as a predictor of dementia in memory-impaired patients. Alzheimer's Res 1997; 3:211-213.

77. Andreasen N, Minthon L, Vanmechelen E, Vanderstichele H, Davidsson P, Winblad B, et al. Cerebrospinal fluid tau and Abeta42 as predictors of development of Alzheimer's disease in patients with mild cognitive impairment. Neurosci Lett 1999;273:5-8.

78. Riemenschneider M, Lautenschlager N, Wagenpfeil S, Diehl J, Drzezga A, Kurz A. Cerebrospinal fluid tau and beta-amyloid 42 proteins identify Alzheimer disease in subjects with mild cognitive impairment. Arch Neurol 2002;59:1729-34.

79. Saez-Valero J, Fodero LR, Sjogren M, Andreasen N, Amici S, Gallai V, et al. Glycosylation of acetylcholinesterase and butyrylcholinesterase changes as a function of the duration of Alzheimer's disease. J Neurosci Res 2003;72:520-6.

80. Green AJ, Harvey RJ, Thompson EJ, Rossor MN. Increased tau in the cerebrospinal fluid of patients with frontotemporal dementia and Alzheimer's disease. Neurosci Lett 1999;259:133-5.

81. Rosso SM, van Herpen E, Pijnenburg YA, Schoonenboom NS, Scheltens P, Heutink P, et al. Total tau and phosphorylated tau 181 levels in the cerebrospinal fluid of patients with frontotemporal dementia due to P301L and G272V tau mutations. Arch Neurol 2003;60:1209-13.

82. Fabre SF, Forsell C, Viitanen M, Sjogren M, Wallin A, Blennow K, et al. Clinic-based cases with frontotemporal dementia show increased cerebrospinal fluid tau and high apolipoprotein E epsilon4 frequency, but no tau gene mutations. Exp Neurol 2001;168:413-8.

83. Kudo T, Mima T, Hashimoto R, Nakao K, Morihara T, Tanimukai H, et al. Tau protein is a potential biological marker for normal pressure hydrocephalus. Psychiatry Clin Neurosci 2000;54:199-202.

84. Tullberg M, Mansson JE, Fredman P, Lekman A, Blennow K, Ekman R, et al. CSF sulfatide distinguishes between normal pressure hydrocephalus and subcortical arteriosclerotic encephalopathy. J Neurol Neurosurg Psychiatry 2000;69:74-81.

85. Kapaki E, Paraskevas GP, Michalopoulou M, Kilidireas K. Increased cerebrospinal fluid tau protein in multiple sclerosis. Eur Neurol 2000;43:228-32.

86. Holmberg B, Johnels B, Blennow K, Rosengren L. Cerebrospinal fluid Abeta42 is reduced in multiple system atrophy but normal in Parkinson's disease and progressive supranuclear palsy. Mov Disord 2003;18:186-90.

87. Urakami K, Wada K, Arai H, Sasaki H, Kanai M, Shoji M, et al. Diagnostic significance of tau protein in cerebrospinal fluid from patients with corticobasal degeneration or progressive supranuclear palsy. J Neurol Sci 2001;183:95-8.

88. Rosler N, Wichart I, Jellinger KA. Total tau protein immunoreactivity in lumbar cerebrospinal fluid of patients with Alzheimer's disease. J Neurol Neurosurg Psychiatry 1996;60:237-8.

89. Buerger K, Zinkowski R, Teipel SJ, Arai H, DeBernardis J, Kerkman D, et al. Differentiation of geriatric major depression from Alzheimer's disease with CSF tau protein phosphorylated at threonine 231. Am J Psychiatry 2003;160:376-9.

90. Schonknecht P, Pantel J, Hartmann T, Werle E, Volkmann M, Essig M, et al. Cerebrospinal fluid tau levels in Alzheim-

er's disease are elevated when compared with vascular dementia but do not correlate with measures of cerebral atrophy. Psychiatry Res 2003;120:231-8.

91. Otto M, Esselmann H, Schulz-Shaeffer W, Neumann M, Schroter A, Ratzka P, et al. Decreased beta-amyloid1-42 in cerebrospinal fluid of patients with Creutzfeldt-Jakob disease. Neurology 2000;54:1099-102.

92. Olsson A, Vanderstichele H, Andreasen N, de Meyer G, Wallin A, Holmberg B et al. Simultaneous measurement of ß – amyloid (1–42), tau and phosphorylated tau (Thr181) in cerebrospinal fluid by the xMAP technology. Clin Chem 2005;51: 336-45.

93. Vanderstichele H, de Meyer G, Andreasen N, Kostanjevecki V, Wallin A, Olson A et al. CSF amino-modified ß – amyloid 42 peptides and prediction of progression of mild cognitive impairment. Clin Chem 2005;51:1650-60.

94. Buerger K, Otto M, Twipel S, Zinkowski R, Blennow K, DeBernardis J et al. Dissociation between CSF total tau and tau protein phosphorylated at threonine 231 in Creutzfeldt-Jakob disease. Neurobiol Aging 2006;27:10-5.

95. Blennow K, Johansson A, Zetterberg H. Diagnostic value of 14-3-3beta immunoblot and T-tau/P-tau ratio in clinically suspected Creutzfeldt-Jakob disease. Int J Mol Med 2005;16:1147-9.

96. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CFS biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol 2006;5:228-34.

97. Vanderstichele H, De Vreese K, Blennov K, Andreasen N, Sindic C, Ivanoui A et al. Analytical performance and clinical utility of INNOTEST PHOSPHU-TAU (181P) for alzheimer's disease and dementia with Lewy bodies. Clin Chem Lab Med 2006;44:1472-80.

98. de Jong D, Jansen RW, Kremer BP, Verbeek MM. Cerebrospinal fluid amyloid beta42/phosphorylated tau ration discriminates between Alzheimer's disease and vascular dementia. J Gerontol A Biol Sci Med Sci. 2006;61:755-8.

21. **Interventions in Dementia Disorders**

Background

Treatment of dementia is defined as any planned action to improve function, symptoms or other aspects of a dementia disorder, such as quality of life and economic consequences.

From a broad perspective, the treatment of cognitive decline in dementia can be described in terms of prevention (Figure 21.1). Primary prevention may be defined as averting a shift from normal cognitive functioning to a state of mild cognitive impairment (MCI). Secondary prevention is aimed at preventing or postponing a shift to cognitive impairment that is sufficient for a diagnosis of dementia. Tertiary prevention includes the treatment of manifest dementia. Primary prevention is included in the chapter on risk factors for dementia. This section on interventions focuses on tertiary prevention only, as well as other considerations in treating manifest dementia.

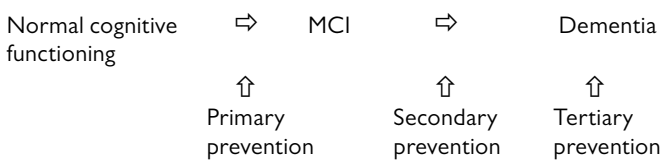

Figure 21.1 *Forms of prevention.*

One important aspect of intervention concerns pharmacological strategies to improve cognitive function. The negative impact of drugs on cognitive function is another important aspect, as are depression and behavioral and psychological symptoms in dementia (BPSD).

The environment also has an impact on the function of a person with dementia. Thus, strategies to adapt interpersonal communication or the physical environment to counteract some of the reduced function are important aspects of treatment.

Both pharmacological treatment and environmental intervention may influence function in dementia, though normally in different – sometimes complementary – ways. The relationship between environment and function is important, and different symptoms may be influenced by different intervention strategies.

A pharmacological study will lead to environmental changes, paying more attention to wellbeing, testing and regular visits. That is the only difference for the placebo group, while the treatment group is affected by the drug treatment as well.

Thus, interventions in dementia disorders include a variety of strategies, both pharmacological and non-pharmacological. An intervention can have a multifaceted impact, including cognitive function, non-cognitive symptoms, ADL functions, resource utilization and quality of life. Among the targets of an intervention may be biological functions of the brain, personal wellbeing and social performance, as well as existential questions and ethical considerations.

Questions of interest

The main questions of interest concerning interventions in dementia were framed as follows:

Questions regarding pharmacological interventions:

- What drugs have been tested for interventions in cognitive and non-cognitive disturbances in AD; VaD and other dementia disorders?
- What drugs have a significant impact on cognitive disturbances (defined as ADL functions, global scales, etc)?

- What drugs have a significant impact on non-cognitive disturbances (such as depression or quality of life)?
- What are the effects of drug treatment at different stages (mild, moderate, severe) of AD?
- Can drugs cause states of confusion (delirium) (with or without dementia)?

Specific questions regarding non-pharmacological interventions:

- What types of interventions in the physical environment have a relevant clinical effect in terms of patient outcome; day care, caregiver support, dementia-specific residential accommodations, nursing homes?
- Is there evidence for the impact of non-pharmacological intervention, such as reality orientation, validation, reminiscence therapy, music, dance, tactile massage, caring activities that promote integrity, mental training, physical activities, communication, debriefing and coping strategies?
- Is there evidence for the impact of professional caregiver support, such as education and instructions?
- Is there evidence for informal caregiver interventions, such as education, support, coping and dementia teams?

Study quality and levels of evidence

All included quantitative studies were analyzed for quality with regard to the reporting of specific aspects. On a general level, the study analysis concerned external validity, internal validity and precision. Included studies were rated on the basis of specific criteria as high, moderate or limited quality. Using a checklist, members of the project group independently rated each study. They did not assess their own published studies.

Given the quantitative studies included, the scientific evidence was assigned one of four evidence grades:

Evidence Grade 1, strong scientific evidence:
Based on two or more RCTs of high quality or one systematic review based on RCTs of high quality, with all studies having the same orientation.

Evidence Grade 2, moderate scientific evidence:
One study of high quality and at least one study of medium quality, or three or more studies of medium quality, or a meta-analysis of studies of medium quality, with all studies having the same orientation.

Evidence Grade 3, limited scientific evidence:
Two studies of medium quality, with all studies having the same orientation.

Insufficient evidence:
None of above.

Methodological aspects of pharmacological studies

Selection and setting

The results of a study should be generalizable, ie the effects in the study population should hold true in any other population with the same diagnosis (high external validity). However, patients in clinical trials are highly selected with respect to both inclusion and exclusion criteria. They commonly come from a university hospital memory clinic. Furthermore, they have dedicated caregivers with expected high compliance and a low rate of non-cognitive symptoms (BPSD) that interfere with participation. They have a "pure" diagnosis, fewer other concomitant medical conditions and less medication. The results of the various trials must also be evaluated in light of the different settings, whether

memory clinics in Western Europe, nursing homes in the United States or institutions in other parts of the world.

Thus, a study population differs from a "clinical" population. However, how that may affect the results is difficult to assess. On one hand, the expected prognosis may be more favorable than for patients with dementia disease in general. On the other hand, patients with more rapid progression and thus a more unfavorable prognosis may be more inclined to go to a specialized memory clinic, so that their expected prognosis would be more favorable than for patients with dementia diseases in general.

Which patients were included in the efficacy analyses: ITT, ITT-LOCF or OC?

In all studies, some patients will drop out at some point and some will not. Dropouts stand out in several respects, including non-response to treatment, adverse events, impaired compliance due to BPSD or caregiver-related factors and severe disease. Analysis based on ITT (intention-to-treat) populations include all randomised patients (regardless of whether they dropped out or not) who received at least one dose of study medication and had at least one assessment after baseline while taking the medication. Many publications also show the results of ITT-LOCF analyses (Last Observation Carried Forward). This method replaces the results of a missing scheduled assessment with those of the immediately preceding assessment, provided that the patient was still on treatment at that time. For instance, if patients drop out before the study end at 6 months, their results from the previous assessment at 3 months are carried forward to the final analysis. Because dementia patients are expected to deteriorate over time, ITT-LOCF analyses underestimate the expected decline. That is a minor problem if patients in the active and placebo group drop out of the study at similar times. However, in the case of frequent early dropouts due to a higher rate of adverse events in patients receiving active treatment, and frequent late dropouts due to lack of efficacy in placebo patients, ITT-LOCF analyses may yield a false, excessively high, favorable impact of active treatment. Conversely, ITT-LOCF analyses do not differ substantially from ITT analyses if the

rates and times of discontinuation due to adverse events are similar in the active treatment and placebo groups. A retrieved dropout analysis (RDO) would be preferable, but the motivation to participate in follow-up studies is lower among patients with diseases that are gradually becoming more severe, so that they do not attend the follow-ups.

In contrast to ITT analyses, analyses of the OC population (observed cases, or TPP, treated per protocol) refer to all randomised patients who were still on treatment at the designated assessment time, such as at the end of the study. Thus, the analyses exclude all patients who dropped out due to adverse effects, lack of efficacy or other reasons. Thus, OC analyses are based on selected patients and do not reflect how all randomised patients responded. In the case of a large dropout rate due to adverse effects in the group receiving active treatment, OC results yield a false, excessively favorable impression of the active compound.

In summary, the efficacy results in each trial must be assessed in terms of the types of patients who participated, the number of – and reasons for – dropouts, and the rate of adverse events.

Long-term effects

In order to analyze the effects of any intervention in dementia (or other incurable, chronic, progressive disorders, such as diabetes and rheumatoid arthritis), the entire course of the disease should ideally be covered, from the early signs to death. There are two reasons for this theoretical position. First, early interventions may influence survival in a way that is of interest for analytical purposes. Second, there may be transitions of outcomes during the course of the disease. Thus, the desirable time frame for the analysis might be 10–15 years or more. Due to practical (and perhaps ethical) considerations, it is difficult to maintain an RCT design for patients who have dementia disorders for extended periods of time. Thus, if describing long-term effects is of interest, alternative designs must be used even if validity in terms of evidence is poorer. In the case of open follow-up studies, or pragmatic design, longer periods of empirical data may be used. Due to selection effects, high attrition and problems in finding controls, such studies are subject to certain

limitations such that whether they may be regarded as controlled becomes questionable. Observational studies are by definition uncontrolled, and how patients are selected for treatment or comparison groups is insufficiently known. Models can describe potential long-term effects, and their sensitivity analyses can examine various effects. But such studies are not ultimately empirical. Meta-analysis and sequence-analysis (which incorporates studies covering different stages of dementia) may be an option, but the selection of studies is crucial. To sum up, no ideal method exists for describing long term-effects, so that a synthetic approach using a variety of designs may be needed.

Concepts of care

Interventions in dementia consist of both pharmacological and non-pharmacological strategies. This report follows that structure in order to identify evidence based on assessments of published scientific studies.

Because biological changes differ among various dementia disorders, the effects of pharmacological interventions might be specific to a particular diagnosis. Some pharmacological interventions, and a majority of non-pharmacological interventions, are valid for a broad range of disorders. Thus, the need for specification of the diagnosis differs among various types of intervention.

Different kinds of social programs/environmental interventions and care concepts have been used in dementia care for several decades. The concepts refer to a variety of interventions, such as day care, caregiver support/counseling and long-term care (LTC)/housing programs. Due to the heterogeneity of such programs, formulating a general statement about them is often difficult. Furthermore, the programs must also be seen in the light of their social context. It may be of interest to study the effects of institutions, such as caregiver time by professional staff, or of emergency hospital care. Following is a brief presentation of different programs. The programs may be the aim of the studies, but they may also form the basis for evaluating various intervention settings.

Quality of life

Quality of life (QOL) is regarded as one of the most important and clinically most relevant outcomes when analyzing interventions in dementia care [1].

The QOL dimension encompasses physical health, functional status, psychological and cognitive health, social wellbeing, etc [2]. The assessment of QOL in dementia has its own special difficulties. Assessments of QOL are normally self-rated, but that is often impossible to achieve in the case of dementia, so that the results – such as the subjective well-being of the patient as compared to the views of proxies – may be unreliable [3]. Alternatively, or as a complement, observations of the patient's behavior can be used [4].

References

1. Winblad B, Hill S, Beermann B, Post SG, Wimo A. Issues in the economic evaluation of treatment for dementia. Position paper from the International Working Group on Harmonization of Dementia Drug Guidelines. Alzheimer Dis Assoc Disord 1997;11(Suppl 3):39-45.

2. Winblad B, Wimo A, Almkvist O. Outcome measures in Alzheimer's disease: do they go far enough? Dement Geriatr Cogn Disord 2000;11 Suppl 1:310.

3. Jönsson L. Economic evaluation of treatments for Alzheimer's disease. Stockholm: Karolinska Institutet; 2003.

4. Albert SM, Del Castillo-Castaneda C, Sano M, Jacobs DM, Marder K, Bell K, et al. Quality of life in patients with Alzheimer's disease as reported by patient proxies. J Am Geriatr Soc 1996; 44:1342-7.

22. **Pharmacological Treatment of Dementia – Established Drugs**

Conclusions

The following may be concluded on the basis of this systematic review of randomised, placebo-controlled clinical trials:

There is moderately strong evidence that treatment with donepezil for 6–12 months and with galantamine for 6 months improves or maintains global function in Alzheimer's disease (AD) with mild to moderate dementia. The effect can be expressed as a mean rate of stabilization or improvement of symptoms in 57–75% of patients with active treatment, as opposed to 42–56% of placebo patients.

There is moderately strong evidence of limited effects on cognitive performance after 6 months of donepezil, rivastigmine or galantamine treatment (12 months as well when it comes to donepezil). The magnitude of the effect is 1 to 1.5 points better on the Mini-mental state examination (MMSE).

There is limited evidence that treatment with memantine for 6 months has some effect in improving or maintaining global and cognitive function in AD with moderate to severe dementia (MMSE 3–14 points).

Patients with AD and concomitant cerebrovascular respond similarly to treatment as patients with pure AD. The efficacy of acetylcholinesterase inhibitors in patients with pure VaD is small.

There is moderately strong evidence that memantine treatment is equivalent to placebo with respect to global function in VaD. The small positive effect that memantine has on the cognitive function of these patients is considered to be of doubtful clinical value.

Adverse events

With the exception of donepezil 5 mg daily, there is moderately strong evidence that nausea and vomiting are more common in patients receiving acetylcholinesterase inhibitors than placebo. Adverse events are generally mild and transient.

There is strong evidence that rates of adverse events are equal in treatment with memantine 20 mg daily and placebo.

Other conclusions

The patient and his/her caregiver/informant must be motivated to make follow-up appointments. Impressions of global and cognitive function (MMSE) should be documented before treatment starts.

The short-term purpose of treatment is an improvement in or maintenance of functions over several months. The long-term treatment is to slow the rate of deterioration. If those goals are not achieved, treatment should be interrupted.

The deterioration rate in patients who were treated with placebo and who completed the trials was slower than previously assumed about the natural course of AD. That may be due to the selection of patients or to the effects of participation in a clinical trial.

Enhancing acetylcholinergic transmission would enhance alertness. This effect may be reflected as an increased ability to focus and thus to perform better on cognitive tests dealing with immediate memory and recall, as well as improved initiation and participation in ADL and social activities. However, the effects compared to placebo are small. Furthermore, rates of progression in AD are highly variable and functions may even be preserved over several months in untreated patients. In other words, the effects may be difficult to determine for the individual patient.

For all trials that compared rivastigmine with placebo, discontinuation due to adverse events was more common in patients who received active

treatment. That can be partly avoided by means of a slower dose titration rate.

Only one study found a beneficial effect of combining memantine and donepezil as opposed to monotherapy. Thus, no evidence may currently be adduced.

Regarding potential effects on behavioral disturbances and psychological symptoms, the results of trials on acetylcholinesterase inhibitors and memantine are conflicting. There is a lack of studies that specifically address this issue.

Background

Currently (July 2004), 4 agents are registered in Sweden with symptomatic treatment of dementia as a primary target. Donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl) are acetylcholinesterase inhibitors indicated for mild to moderate dementia due to AD. Memantine (Ebixa) is indicated for moderate to severe dementia due to Alzheimer's disease (AD).

Acetylcholinesterase inhibitors (AChEIs)

Among the widespread neuronal damage and neurotransmitter losses in AD are cholinergic neurons. Based on the cholinergic deficit hypothesis, one therapeutic strategy has been to enhance cholinergic neurotransmission by using acetylcholinesterase inhibitors to delay the breakdown of acetylcholine released into synaptic clefts. A pilot study published in 1986 showed the benefits of treatment with the acetylcholinesterase inhibitor tetrahydroamminoacridine (THA, tacrine) [1], which later became the first agent registered for treatment of mild to moderate AD in Sweden (1995). However, the benefits of tacrine in clinical practice were small, due to a high frequency of adverse effects, including vomiting and hepatotoxicity, and it was withdrawn a few years later. Several other acetylcholinesterase inhibitors – including oral physostigmine, metrifonate, and eptastigmine – have been investigated in clinical trials but have not been approved by the regulatory authorities. The results of

these studies have been reviewed elsewhere [2,3]. Donepezil (Aricept, registered in 1997) was the first, second-generation acetylcholinesterase inhibitor that is selective to the central nervous system. It was followed by rivastigmine (Exelon, registered in 1998) which is an inhibitor of acetyl- and butyrylcholinesterase, and by galantamine (Reminyl, registered in 2000), which also acts as a modulator at nicotinic cholinergic receptor sites.

Memantine

The excitatory activity of L-glutamate plays a role in the pathogenesis of AD and in the damage caused by ischemic brain lesions. Memantine (Ebixa, registered in 2002) is a low affinity antagonist to N-Methyl-D-aspartate (NMDA) type receptors intended to prevent excitatory amino acid neurotoxicity while not interfering with the physiological action of glutamate that is required for memory and learning.

Aim

The aim of this review is to assess the extent to which these compounds improve the wellbeing of patients with dementia due to AD and with other dementia disorders. At the time of the literature search, there were no published studies on AD patients with mild cognitive impairment.

Methods

Strategy for searching the literature

Medline (1970 through July 1, 2004) was searched on "donepezil", "rivastigmine", "galantamine", and "memantine" for all RCTs published in English. As a second step, Medline was searched without limiting it to these four agents. Additional references and data from unpublished studies were collected from the Cochrane reviews, most recent amendments, September 2003 [4–7]. Data on efficacy measurements and adverse events were gathered from both the original publications and the Cochrane reviews, after which they were checked for agreement.

Included trials: Acetylcholinesterase inhibitors in AD

The majority of the hits in the literature search were discarded because they did not meet the quality criteria. Many were open-label extension studies. With this design, all patients that remain at the end of the double-blind phase are offered treatment with the active drug. During the extension phase, patients are compared to a fictive placebo group based on calculations of the disease progression or on historical controls. Thus, the design does not allow for an efficacy evaluation given that the patients are not randomised and the treatments are not concealed. Furthermore, patients are highly selected. Only double-blind, placebo-controlled RCTs were included in this review. All were rated as either high or medium quality. Almost all were multicenter studies, and all were parallel, with the exception of one that had a crossover design. All studies defined AD according to at least one of the following criteria: NINCDS-ADRDA, ICD-10 and DSM-III, DSM-III-R or DSM-IV. Other inclusion criteria varied, but the most recent studies on mild to moderate dementia patients state that CT or MR should be consistent with a diagnosis of AD, and a modified Hachinski ischemic score <5 was commonly used to further differentiate AD from VaD [8]. Mild to moderate dementia was defined as CDR 1 to 2, with most patients in CDR 1, and/or as MMSE 10 to 26 p or narrower. Most studies stated that they only included patients with a reliable caregiver who could monitor medications, report AEs and attend evaluations of ADL. Information on AEs was collected by questioning the caregiver at each assessment, but the papers rarely described this procedure in detail.

Donepezil

Searching on "donepezil" for RCTs produced 70 hits. Fourteen publications covering 4 159 patients were considered to be original reports on AD patients and met the qualitative inclusion criteria for evaluation. The Cochrane review identified three more RCTs [4]. They were excluded from this review due to inadequate dosage (study 134) or because they are unpublished and not amenable to checking: studies 205 and 306, with 51 patients altogether [4]. Twelve of the 14 studies enrolled mild to moderate dementia cases (mean MMSE 17–21, ranges 10–26 points). One of the

other two trials studied patients with moderate to severe dementia who lived at home or at assisted living facilities (mean MMSE 12–14 points) [8], while the other one included very old patients in US nursing homes with mild to severe dementia (MMSE 5–26 points) [9]. The long-term AD2000 study differed from the others in that there was a large dropout rate and the inclusion criteria specified that "the doctor had to be substantially uncertain that the individual would obtain worthwhile clinical benefit from donepezil" [10]. Three pilot studies included patients who were able to participate in investigations with SPECT [11], PET [12] and MRI [13]. In addition to these placebo-controlled studies, one comparative study between donepezil and rivastigmine [14] and one study comparing donepezil with galantamine [15] are commented on.

Rivastigmine

Medline yielded 29 hits, including 6 original RCTs. In addition, data from 2 large unpublished trials were collected from the Cochrane review [5], for a total of 3 397 patients (Table 22.1). All trials covered mild to moderate AD (mean MMSE 18–20, range 10–26 points).

Galantamine

Six published, original RCTs were among 31 hits on Medline, together with data from one unpublished trial from the Cochrane review [6]. These trials assessed mild to moderate dementia due to AD (n = 3 587, mean MMSE 17–19, ranges 10–24 points) (Table 22.1).

Included trials: Memantine

Out of 28 hits for "memantine", 7 trials were identified that met the required quality criteria (Table 22.2). These studies were heterogeneous with regard to dementia diagnosis – vascular or unspecified dementia in the three early studies – severity (mild to severe), duration (6–28 weeks), setting (Latvian nursing homes, US and Western European outpatients), and memantine dosage (10–30 mg/day). Randomization procedures, concomitant disorders and medications were not described in detail in the earlier publications. Two large recent studies on mild to moderate VaD had equivalent designs [16,17]. The Latvian nursing home trial

lasted for 12 weeks and included AD and MID patients in equal proportions [18]. Only one longer trial included (community dwelling) patients with severe AD [19]. One recent trial examined the effects of memantine/placebo when added to a stable dosage of donepezil in patients with moderate to severe AD [20].

Measurements of efficacy

Efficacy was assessed in most cases by measurements of global function and cognitive tests as primary outcomes. Measures of ADL and behavioral disturbances were mainly used as secondary outcome parameters. Following is a brief presentation of the most commonly used rating scales.

Global function

A Clinician's Interview-Based Impression of Change with caregiver input (CIBIC-plus) provides a global rating of patient function in four areas: general, cognitive, behavioral and ADL [21]. All patients are scored on global severity at baseline, and subsequent assessments are made on a scale of 1 to 7, with 1 indicating pronounced improvement, 3 mild improvement, 4 no change and 7 pronounced deterioration. Information, which is obtained from the caregiver and the patient, is generally rated by an independent clinician who is blinded to all other measurements. Rather than mean CIBIC scores, results are commonly presented as the percentage of responders in treatment and placebo groups, defined either as "improved" (1–3) or "unchanged or improved" (1–4). The older studies used a Clinician's Global Impression of Change (CGI-C) scale without specifying any details. A global measurement of dementia severity, the Clinical Dementia Rating Scale (CDR) is usually reported as a score of 0.5, 1, 2, or 3, indicating questionable, mild, moderate or severe dementia. The scores are derived from ratings in 6 domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care), each scored from 0 (normal) to 3 (severe dementia). The sum of the ratings (0–18) provides the CDR Sum of Boxes (CDR-SB) [22]. The Global Deterioration Scale (GDS) is a crude measurement of disease severity [23]. The Gottfries, Bråne, and Steen scale (GBS) is a comprehensive scale for rating dementia symptoms

based on a semi-structured interview with the caregiver [24]. A 7-point scoring system from 0 (normal function) to 6 (maximum disturbance/presence of symptoms) measures orientation, memory and concentration (12 items), ADL (6 items), emotional function (3 items), and pathological aspects of behavior (6 items). The Mental Function Impairment Scale (MENFIS) is a modification of the GBS [25]. The BGP care dependency subscale reflects cognitive and functional characteristics associated with increased need for care [26]. Other global assessment scales are the Sandoz Clinical Assessment Geriatric Scale (SCAG) [27], the Functional Rating Scale (FRS) [28], and NOSGER [29].

Cognitive function

The Cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-cog) is the most widely used test to evaluate changes in cognitive function in AD over time [30]. Notably, this scale was also used in VaD trials, although its sensitivity to changes in VaD has been insufficiently studied. The most common version of ADAS-cog consists of 11 individual tests: spoken language ability (0–5 points), comprehension of spoken language (0–5 points), recall of test instructions (0–5 points), word finding difficulty (0–5 points), following commands (0–5 points), naming object (0–5 points), construction drawing (0–5 points), ideational praxis (0–5 points), orientation (0–8 points), word recall (0–10 points) and word recognition (0–12 points). The total score ranges from 0 to 70 points in ascending degree of impairment. The results are commonly presented as a comparison of changes from the baseline between active treatment and placebo or as responders in each group. A 2 point change on the ADAS-cog scale roughly reflects a 1 point change on the Mini-mental state examination (MMSE) [31,32], a widely used screening test for dementia in clinical practice [33]. MMSE is easy to administer, the score ranging from 0 (severe impairment) to 30 (normal). MMSE was used to define the study populations, as well as a secondary endpoint in several studies. The Severe Impairment Battery (SIB) is designed to assess changes in cognitive function in patients with severe dementia (0–100 points in descending level of performance) [34]. Early memantine trials used the Syndrom-Kurtztest (SKT) as a cognitive test [27].

ADL

Virtually all ADL scales are based on information provided by the caregiver regarding performance in basic (personal) and instrumental (complex) ADL. The Progressive Deterioration Scale (PDS) is a disease-specific measure of changes in 29 items of ADL [35]. The Disability Assessment for Dementia (DAD) is a 10-domain, 40-item instrument that measures instrumental and basic ADL proceeding from a caregiver interview of what the patient actually did during the weeks before assessment [36]. A wide variety of other ADL scales were used in the reviewed trials: among them were Interview for Deterioration in Daily living activities in Dementia (IDDD) [37], AD Cooperative Study Activities of Daily Living (ADCS-ADL) [38], IADL+ and PSMS+ [39], the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS) [40] and the Caregiver Modified Chrichton Scale (CMCS) [41]. Many of the global scales also include ADL measurements.

Behavioral disturbances and psychological symptoms

The Neuropsychiatric Instrument (NPI) is a 12-item, caregiver-rated instrument to evaluate behavioral and neuropsychiatric symptoms, including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime behavior, and appetite/eating disorder [42]. A lower score indicates improvement. The Behavioral Rating Scale for Geriatric Patients (BGP) is an observer-rated scale for geriatric inpatients that measures ADL and behavioral disturbances [18].

Measurements of acceptability and safety

Acceptability of treatment was measured by rates of withdrawal from trial. Safety was measured by rates of withdrawal due to adverse events (AE), and by the numbers of different AEs in a comparison between active treatment and placebo groups. Information on AEs was collected by questioning the caregiver at each assessment.

Acetylcholinesterase inhibitors in AD

Presentation of results

We focused on studies that lasted 6 months or longer and used the doses that are recommended for clinical practice in the Nordic countries, ie, donepezil 5 to 10 mg/day, rivastigmine 6 to 12 mg/day and galantamine 16 to 24 mg/day. Table 22.3 shows all primary and secondary outcomes, as well as rates of discontinuation (all causes, including AEs), in each study. Unless otherwise indicated, all figures are based on ITT or ITT-LOCF analyses. Results are presented as the measurement differences between baseline and end of the study for each treatment group. Although the results for the three cholinesterase inhibitors appear in the same table, the data cannot be used to compare the various agents, but only to show the differences between active treatment and placebo in each study.

Effects on global function, primary outcomes: CIBIC+ and GBS

Eleven included studies that lasted 6 months had CIBIC+ as a primary efficacy measurement of global function (Table 22.3). For studies with donepezil 5 or 10 mg daily, global function improved (CIBIC+ 1–3) in 21–26% of patients on active treatment and 11–14% of patients on placebo [31,43]. Treatment effects were higher in the Japanese study [41]. One rivastigmine study showed significant differences between active treatment (37% improvement) and placebo (20% improvement) [32]. But rivastigmine treated patients did not significantly improve on CIBIC+ (22–25% for active treatment and 15–25% for placebo) in the other 3 studies. Two galantamine trials reported CIBIC+ 1–3 as an endpoint, and the differences between active and placebo treatment were not significant (17–22% and 12–16%) [44,45]. When responders were de-fined as those who were unchanged or improved (CIBIC+ 1–4), the results significantly favored galantamine in all 3 studies [44–46].

Unchanged/improved global ratings averaged 66% (62–73%) for galantamine 24 mg/day and 52% (49–57%) for placebo. These figures are

comparable to donepezil studies, for which 57–67% (5 mg/day) and 63–75% (24 mg/day) were unchanged or improved for active treatment, as opposed to 49–55% for placebo. The rivastigmine publications did not state this endpoint. In the Nordic study, 31% of donepezil patients and 22% of placebo patients had improved from baseline on the GBS total score after 52 weeks [47].

Effects on global function, secondary outcomes

Treatment with 5 mg and 10 mg donepezil daily had significantly greater effects than placebo in terms of disease severity in terms of CDR-SB in all 24–54-week studies [9,31,41,43,48]. A meta-analysis based on these studies found that patients treated with donepezil 10 mg/day (n = 511) were virtually unchanged after 24 weeks (–0.09 to –0.02), while the scores of placebo patients (n = 517) had declined by 0.36 to 0.70 p [4]. For the Nordic study, twice as many patients in the active group showed post-baseline improvement on the GDS after 52 weeks as in the placebo group [47].

The rate of progression to moderate/severe dementia or worse (GDS ≥5) after 26 weeks did not differ between rivastigmine treatment and placebo in study B304 (Unpublished I) [49] or B352 [50], but it was significantly lower among patients treated with rivastigmine in the B303 [32] and B351 (Unpublished II) [49] studies. The B352 study showed that patients treated with rivastigmine deteriorated significantly less than placebo patients on the GDS (mean scores) [50]. Thus, these 4 studies yielded conflicting results.

Effects on cognitive function, primary outcomes: ADAS-cog

Ten studies showed a change in ADAS-cog (70 point scale) from baseline as a primary endpoint (Table 22.3). The mean differences between active treatment and placebo groups varied from 1.4 to 3.9 points (ITT). After 6 months of treatment, the mean ADAS-cog scores tended to be slightly better than baseline in patients treated with donepezil and

slightly worse in placebo patients [13,31,41,43]. A meta-analysis found the mean differences between active treatment and placebo after 24 weeks to be –2.02 (–2.77 to –1.26) for donepezil 5 mg/day and –2.92 (–3.74 to –2.10) for donepezil 10 mg/day (minus denotes better results, ITT-LOCF) [4]. The results of all four 26-week rivastigmine trials showed a significantly smaller impairment in active treatment than placebo. A meta-analysis showed the mean difference between active treatment and placebo after 26 weeks to be –2.09 p (–2.65 to –1.54) for rivastigmine 6 to 12 mg/day, ITT [5]. A meta-analysis of 3 trials [32,49,50] found that the main items in ADAS-cog that differed between active and placebo treatment were word recall, word recognition, orientation, remembering test instructions and concentration [51]. The differences in ADAS-cog from baseline after 6 months of treatment with galantamine 16 to 24 mg/day and placebo were significant in all 3 trials [44–46], ranging from 2.9 to 3.9 points, ITT. A meta-analysis of these studies showed the mean differences between active treatment and placebo after 5 to 6 months to be –3.1 (–4.1 to –2.1) p for galantamine 16 mg/day and –3.3 (–3.9 to –2.7) points for galantamine 24 mg/day, ITT [6].

A meta-analysis by SBU of 4 RCTs with dropout rates of <30% and ADAS-cog as primary outcome (Figure 22.1) [31,41,44,45] examined the effect size. A moderate statistical and clinical difference between drug treatment and placebo was identified from an effect size of 0.49.

Effects on cognitive function: secondary outcomes

As a secondary outcome, some studies reported the rates of 'responders' in ADAS-cog, in actively treated patients compared to placebo patients. The figures are shown in Table 22.3.

Some of the donepezil and rivastigmine studies measured the change in MMSE from baseline to the end of the study. Two of the three 24-week studies found patients treated with donepezil to have significantly higher MMSE scores than placebo patients. The mean differences for 10 mg donepezil vs placebo were 1.4–1.8 points (Table 22.3). The third (nursing home) study yielded results favoring donepezil at weeks 8 to 20

but not at the end [9]. After 1 year, donepezil-treated patients performed 0.5 points worse and placebo patients performed 2.2 points worse (Δ1.7 points) [47]. In the AD2000 study, the donepezil group's mean MMSE had improved by 0.9 points from baseline after 12 weeks. Scores deteriorated over time, but a significant difference between treatment and placebo of approximately 0.8 points was maintained over 2 years. All 4 rivastigmine studies showed the difference in MMSE between rivastigmine 6–12 mg and placebo after 26 weeks to be significant, mean 0.7–0.8 p (Table 22.3).

Effects on ADL

The 54-week donepezil study used time to clinically evident decline in ADL (ADFACS) as a primary endpoint [48]. There was a significant delay in time to decline in patients who received active treatment: 41% (n = 84/207) reached the endpoint in 1 year, as opposed to 56% (n = 116/206) of placebo patients (Table 22.3). The median time to decline (Kaplan-Meier survival curves) was 5 months longer in the donepezil group. In 4 donepezil studies over 6–12 months, ADL measurements were secondary outpoints. Three of these showed that donepezil patients had a slower rate of ADL decline than placebo patients [41,43,47]. The Winblad study found that 3 single items of the PDS – memory, using the phone and self-care – differed significantly between the treatment and placebo group [47]. The nursing home study did not detect any significant differences in basic ADL preservation (PSMS) between patients treated with donepezil and placebo [9]. In the AD2000 study, the primary endpoint of progress of disability – defined as loss of 2/4 basic ADLs or 6/11 instrumental ADLs – was equal for donepezil and placebo patients after 2 years. Donepezil showed small, statistically significant advantage in mean scores on the BADL scale (secondary endpoint), persisting from week 24 to week 108. With respect to the efficacy of rivastigmine on ADL function, the results were conflicting (Table 22.3). There were significant differences between patients treated with galantamine (16 mg and 24 mg/day) and placebo patients on the ADCS-ADL 6 months after baseline [45]. In terms of the DAD, changes in ADL functions did not reach statistical significance for galantamine 24 mg daily versus placebo in the other 2 studies [44,46]. Thus, the results were conflicting.

Effects on BPSD

Many trials on community-living patients with mild to moderate AD did not aim to examine the potential effects on behavioral disturbances and emotional symptoms. Behavioral problems are expected to be infrequent at baseline in these patients. The nursing home version of NPI was the primary outcome measurement in the US nursing home study [9]. Total NPI scores did not differ significantly between donepezil and placebo treatment after 24 weeks. Donepezil showed significant effects in one variable, agitation/aggression. Similarly, in the Nordic Study, NPI scores did not differ between placebo and active treatment at 1-year follow-up [47]. Nor were there any differences in NPI scores between groups in the AD2000 study [10]. The moderate-severe AD study found significant improvements for donepezil, in contrast to placebo, on the total NPI score (Δ5.6 points out of 144 points) [52]. A meta-analysis of this study, including patients with moderate AD only (MMSE 10–17 points, n = 290), showed positive effects for donepezil on the NPI items of delusions, apathy and aberrant motor behavior [53]. NPI scores in patients treated with 16 mg and 24 mg galantamine were unchanged after 6 months, while placebo patients exhibited a small deterioration, mean difference 2.1 points [45].

Moderate to severe dementia

The donepezil study on moderate to severe AD included patients with MMSE 5 to 17 points [52]. The results favored donepezil vs placebo in all included measurements: global function (unchanged or improved CIBIC+ in 63% vs 42%), cognitive function, ADL and NPI scales, as well as caregiver strain (Table 22.3). Rates of withdrawal, as well as withdrawals due to AE, did not differ between treatment groups. A meta-analysis of patients with moderate to severe AD (GDS 5) in 3 rivastigmine studies [32,49,50] showed significant differences after 6 months between active treatment (n = 819) and placebo (n = 642) on the PDS [54]. When patients from the same studies were stratified according to GDS stage, those with moderate to severe dementia showed greater benefits from rivastigmine compared to placebo than those with mild dementia [55]. A post hoc analysis of 4 galantamine studies

[44–46,56] looked at patients with advanced moderate AD, ie, MMSE 10 to 12 points and/or ADAS-cog >30 points [14]. The mean change in ADAS-cog score from baseline was 6.5 points better after 5 to 6 months in patients treated with galantamine 24 mg/day (n = 705) than placebo patients (n = 714). The rates of unchanged or improved global functioning (CIBIC+ 1–4) were 49% to 55% in the treatment groups and 23% to 32% in the placebo groups, ie, the differences were greater than for patients with mild dementia.

Acceptability and tolerability

Table 22.3 shows rates of discontinuation before the end of the study for any reason. Donepezil treatment for 24 weeks was not associated with an increased risk of all-cause discontinuation in 4 of the 5 larger studies over 6 months (5 mg/day 12–22%, 10 mg/day 16–26%, placebo 14–26%). In the fifth study, dropouts were significantly more frequent for donepezil 10 mg daily (32%) than placebo (20%) [31]. After 52-week treatment in the Nordic Study, dropouts were equal for the donepezil (33%) and placebo groups (33%) [47]. The AD2000 study found discontinuation during the 12-week run-in period to be more frequent in the donepezil group. But after re-randomization and 48 weeks of treatment, the groups did not differ. Attrition was high, partly due to physicians' attitudes to treatment having changed during the course of the trial, and many patients were switched to open-label treatment. The total rates of withdrawal for patients treated for 6 months with 6–12 mg rivastigmine daily were significantly higher in all 4 trials (24–43%) than for placebo (13–25%). The total number of dropouts among patients treated with galantamine 16 or 24 mg/day for 6 months did not differ from placebo in 2 studies (20–22% vs 14–16%) but was significantly higher in the third one (32 vs 19%).

When it came to discontinuation due to adverse events (AE), no difference between donepezil 5 mg/day (2–9%) and placebo (4–10%) emerged in any study (Table 22.3). Patients treated with 10 mg daily had rates of 8–18%, a significant difference compared to placebo, in 2 of 4 studies. However, the 52-week Nordic study showed significantly lower corresponding figures of 7% and 6%. In the rivastigmine studies, 17–29%

of the patients on active treatment with 6–12 mg daily for 26 weeks withdrew before the end due to AE, significantly more often than placebo patients (7–12%). Patients treated with galantamine 16 mg/day for 6 months did not discontinue due to AE more often (7%) than placebo patients (7%). The rate was higher for patients on 24 mg/day (10–23%), a significant difference vs placebo in 1 study.

The two most frequent AEs for all 3 acetylcholinesterase inhibitors, as well as the most common reasons for early withdrawal, were nausea and vomiting. The rates of discontinuation due to AEs were related to the speed at which the doses were raised. In most studies with slow titration, dropout rates were the same between active and placebo patients. Frequencies of nausea did not differ between treatment with donepezil 5 mg/day and placebo in any study, nor between donepezil 10 mg/day and placebo in the Nordic study (11% vs 9%). Mean rates of nausea in the other studies comparing donepezil 10 mg/day and placebo were 17% vs 5%, OR 3.31 (2.34–4.68). The total frequency of nausea in the 4 rivastigmine studies comparing 6–12 mg daily with placebo was 47% vs placebo 12%, OR 5.40 (4.44–6.58). Nausea rates in the galantamine studies varied from 16% to 37% (24 mg/day), as opposed to 3% to 13% in the placebo groups. In no study did rates of vomiting differ between donepezil 5 mg/day and placebo. Mean frequencies of vomiting in the 24-week studies were 12% for donepezil 10 mg/day and 5% for placebo. However, in the 52-week Nordic study, vomiting occurred in less than 5% of patients in both groups. Mean rates of vomiting in all four rivastigmine studies were 30% vs 6%, OR 5.28 (4.19–6.65). Rates of vomiting were significantly higher in all galantamine studies comparing 16 to 24 mg/day (15–21%) with placebo (4–7%). The less frequent AEs of anorexia, diarrhea, weight loss, muscle cramp, fatigue, and insomnia were slightly more frequent in patients treated with donepezil, rivastigmine or galantamine [4–6]. Some studies found rhinitis, dizziness, headache, abdominal pain and tremor to be overrepresented among patients receiving acetylcholinesterase inhibitors, but there was no consistent pattern. The rates of abnormal gait, agitation, confusion, bradycardia, and syncope did not differ in most studies between active and placebo treatment.

Results after short-term treatment, effects of washout and placebo effects

Significant differences between active treatment (donepezil, rivastigmine, galantamine) and placebo on cognitive scales were generally detected after 6 to 12 weeks. There was no evidence of a prolonged beneficial treatment effect for donepezil, rivastigmine or galantamine after washout for 3 to 6 weeks. For example, scores returned toward baseline within 3 weeks of drug washout [57], and no differences between former placebo and donepezil patients were detected after 6 weeks of washout [31]. In the AD2000 study, washout for 4–6 weeks did not lead to irreversible deterioration. All trials showed a clear positive placebo effect at the first post-baseline assessments. Noticeably, placebo patients generally improved their performance on ADAS-cog 3 to 6 weeks after baseline by 1.0 to 1.5 points. The improvement was particularly evident for caregiver-rated scales. For instance, after 6 weeks of treatment in a clinical practice study, 23% of placebo patients and 24% of donepezil patients were deemed to have improved according to the caregiver-rated global impression [57]. Furthermore, mean (caregiver-rated) NPI-scores improved among both placebo and rivastigmine patients at 12 and 20 weeks after baseline [58].

Prediction of response

The AD2000 study reported that early response, defined as MMSE improvement ≥4 points from baseline after 12 weeks, did not predict positive subsequent treatment effects [10]. We did not find any results in the other reviewed studies that either supported or contradicted this finding. None of the studies indicated that advanced age was associated with poorer response. For instance, the donepezil nursing home study that recruited patients with a very high mean age, 85.7 years, found the treatment effects to be similar in patients above 85 (n = 133/208) and younger, ie, the results on the CDR-SB and MMSE significantly favored donepezil [9]. The presence of an apo E e4 allele was previously suggested to be associated with lack of response to tacrine treatment. But that view was refuted by several of the reviewed trials [10,44,57].

One report stated that patients who had more rapid disease progression during the 6 months before the start of treatment obtained greater benefits from rivastigmine, as measured by ADAS-cog, than those with slowly progressive cognitive decline [59]. Several studies showed that patients with moderate to severe dementia obtained greater benefits than those with milder disease (see above). We did not find any studies that contradicted this finding. The presence of vascular risk factors was not associated with impaired response in any of the reviewed trials. Two post hoc analyses of the rivastigmine study B352 [50] concluded that AD patients with concomitant hypertension, as well as AD patients with a modified HIS >0, had the same treatment effects as other AD patients [60,61]. In AD + CVD, 32% of galantamine, and 19% of placebo, patients improved in terms of CIBIC+ after 6 months, while the ΔADAS-cog was significant and similar to the results of pure AD studies, 2.8 points [62] (Table 22.6).

Neuroimaging findings in RCTs

An RCT with SPECT showed regional cerebral blood flow (rCBF) in placebo patients to decline significantly in the anterior cingulate gyri, inferior parietal and middle temporal cortex, and prefrontal cortex after 12 months, while rCBF in patients treated with donepezil 5 mg/day remained unchanged (Table 22.3) [11]. Donepezil study 203 reported significant differences in the regional cerebral metabolic rate of glucose (rCMRglu), as measured by positron emission tomography (PET), favoring donepezil over placebo [12]. Another donepezil study associated active treatment with significantly smaller decreases than placebo in total hippocampal volumes (MRI) after 6 months [13]. In an RCT with PET, patients who responded to rivastigmine treatment, defined as CIBIC 1–4 after 26 weeks, showed greater global CMRglu and greater regional CMRglu in the hippocampus and parahippocampal gyrus than non-responders to rivastigmine [63]. The results of the 2 studies are conflicting with respect to prediction of response. Reduction of frontal rCBF (SPECT) was associated with non-response to donepezil in one study [64], but another study found that responders had significantly lower lateral orbital and dorsolateral frontal perfusion bilaterally [65].

Comparisons among different acetylcholinesterase inhibitors

One RCT compared donepezil with rivastigmine [14], while another compared donepezil with galantamine [15]. Pfizer sponsored Wilkinson's study [14]. Twice as many patients receiving rivastigmine discontinued due to AE (22% vs 11% donepezil). Nausea occurred 4 times as often in the rivastigmine group as in the donepezil group (42% vs 11%). Scores on ADAS-cog and MMSE were similar in the 2 groups after 12 weeks of treatment. The Wilcock study was sponsored by Janssen-Cilag and was blinded to the rater but not the physician [15]. After 52 weeks, MMSE had decreased more from the baseline in the donepezil group than in the galantamine group, but the difference was not significant when the two groups were compared in between. Measurements of ADL function did not differ between the groups. Rates of discontinuation for all causes, including AEs, were the same in both groups.

Memantine in AD and VaD

Table 22.4 presents the main results from the longest studies (12–28 weeks).

Global function

The moderate to severe AD study found that memantine treatment (29%) had significantly better effects than placebo (10%) regarding the percentage of patient who reached the main pre-specified individual response, which was a compound measurement of global, ADL and cognitive functions [19]. However, the difference between the groups in terms of CIBIC+ (mean change from baseline) was of borderline significance. The shorter Latvian nursing home study, which included both VaD and AD patients, showed 73% of memantine patients and 45% of placebo patients to have improved on the CGI-C after 12 weeks [18]. The differences in improvement (59% vs 40%) after 4 weeks of treatment were also significant. In neither of the two recent trials on mild to moderate VaD did global measurements (CIBIC+ or CGI-C) differ between memantine and placebo [16,17].

Cognitive function

In terms of AD, moderate to severe memantine patients maintained their abilities better than placebo patients on the SIB (Δ7 points, range 0–100 points), a cognitive test battery designed for severe dementia. But no significant differences were detected on the MMSE (Δ0.7 points). The two VaD studies showed small but significant differences (Δ1.8 points and Δ2.0 points) favoring memantine with regard to the change in ADAS-cog from baseline, ie, of approximately the same magnitude as in the AChEI trials [16,17]. A pooled analysis of the 2 studies found the difference between memantine and placebo in ADAS-cog to be significant for the 553 patients classified as having small vessel disease but non-significant in the 214 patients with large vessel disease [66]. The difference was due to impairment over time for small-vessel disease patients, while the other VaD patients remained unchanged, compared to baseline. Memantine had the greatest positive effects on cognition in patients with severe dementia, MMSE <15 points.

ADL function and BPSD

ADL deteriorated significantly more in placebo than memantine patients in the moderate to severe AD study [19]. The main outcome (improvement >15% on BGP care dependency) in the Latvian nursing home study fell short of statistical significance, but the results favored memantine when the mean scores on BGP care dependency and the total BGP scores were calculated [18]. Furthermore, 8 of the 16 items on the D-scale for ADL were significantly better in memantine than placebo patients. Worth noting is that even the placebo patients improved during the 3-month study. The two VaD studies did not include ADL measurements [16,17]. There was a non-significant difference between active treatment and placebo of 3.3 points favoring memantine in the NPI scores of moderate-severe AD patients [19].

Acceptability and tolerability

As shown in Table 22.4, no study showed a difference between memantine and placebo patients in terms of the rate of premature discontinuation due to any cause or to AE. For all included trials, the rates of AEs

and SAEs were equal or higher for the placebo group: agitation was reported in 18% of memantine patients and 32% of placebo patients [19].

Combined memantine and donepezil treatment

One recent study investigated the effects of adding memantine to stable doses of donepezil (treatment for at least 6 months, stable doses or at least 3 months) in 404 patients with moderate to severe AD [20]. Memantine had small but significant beneficial effects on global function (55% vs 45% unchanged or improved on the CIBIC+), cognitive function (SIB, Δ3.4 points), ADL function and BPSD (ΔNPI 3.8 points) (Table 22.4). For ADCS-ADL, significant differences showed up after only 4 weeks. In addition, caregivers in the memantine group reported spending significantly less time helping patients with ADL. The average difference with the placebo group was 46 hours a month. Rates of discontinuation due to all causes and to AE were lower in the donepezil/memantine group than in the donepezil/placebo group. The only AEs that occurred in at least 5% of the donepezil/memantine group at least twice as often as the donepezil/placebo group were confusion (8% vs 2%) and headache (6% vs 2%). The rates of discontinuation due to confusion were 2% and 1.5% respectively. The rates of diarrhea and fecal incontinence were higher in placebo patients than memantine patients.

Acetylcholinesterase inhibitors in VaD

Two large randomised 6-month trials assessed the efficacy of donepezil in VaD patients. The trials started in 1997 but were published only recently [67,68]. One large 6-month galantamine trial included patients with both VaD and AD with CVD [62] (Table 22.5). At present, there are no published RCTs on the effects of rivastigmine in VaD.

Results for donepezil

In study VaD308, 67% of included patients had suffered a clinical stroke, and 76% showed evidence of cerebral infarct(s) on CT/MRI [67]. Patients were allocated to treatment with placebo or donepezil 5 mg or 10 mg daily (dose increase after 4 weeks, no reduction was tolerated).

In study VaD307, the protocol and baseline population characteristics were equal to those of VaD308 [68]. More than 75% of included patients had an abrupt onset of cognitive impairment, and 45% were classified as having mild dementia.

In VaD308, 39% of the patients treated with donepezil 5 mg daily were rated as having improved on the CIBIC+ at the end of the study. That was higher than placebo (25%) (Table 22.6). However, treatment with donepezil 10 mg daily had no significant benefits when all CIBIC+ categories were compared. Results from VaD307 were similar: global improvement was recorded in 36%, 28% and 30% of the patients treated with donepezil 5 mg, donepezil 10 mg and placebo respectively [68]. Only a minority of the patients deteriorated during the trial: 23%, 28% and 31% for donepezil 5 mg, donepezil 10 mg and placebo respectively. The benefits on the CDR-SB scale were significant in both studies for the 10 mg/day group only. Regarding cognitive function, donepezil treatment with 5 mg and 10 mg showed benefits compared to placebo starting in week 6 of both trials. The differences compared to placebo between baseline and the end of the study were 1.6–1.7 points for the 5 mg groups and 2.1–2.2 points for the 10 mg groups (Table 22.6). All treatment groups improved on the MMSE compared to baseline: approximately 0.4 points for placebo patients, 1.2 points for 5 mg donepezil daily and 1.6 points for 10 mg donepezil daily. A subgroup analysis including all 893 patients with probable VaD (ie, those with possible VaD were excluded) from studies VaD307 (70% of all patients) and VaD308 (76% of all patients) showed similar global and cognitive outcomes [69]. Donepezil patients had better ADL function (ADFACS total scores) in study VaD307 but not in VaD308. Discontinuation rates for any reason and due to AE did not differ between patients treated with donepezil 5 mg and placebo but were higher in patients treated with 10 mg daily. Of importance is that the rates of syncope, bradycardia, and stroke were low and equally distributed among the treatment groups. Nausea, diarrhea, leg cramps, anorexia, vomiting, rhinitis, headache, and abnormal dreams occurred more frequently in donepezil patients.

Results for galantamine

One published RCT included a heterogeneous patient population [62]. Out of 592 randomised patients, 42% had probable VaD, 48% had AD with CVD and 9% had an intermediate diagnosis according to the NINDS-AIREN or NINCDS-ADRDA criteria. CT findings of multiple, large-vessel infarcts, at least two lacunar infarcts, a single strategically placed infarct or extensive WMC were compulsory for inclusion. Among all patients, significantly more were stable or had improved on the CIBIC+ in the galantamine group (74%) than in the placebo group (59%) (Table 22.6). Subgroup analyses were performed even though the study was underpowered in that respect. Only 31% of galantamine patients VaD and 23% of placebo patients with VaD had improved after 6 months (ns). Similarly, the difference between galantamine and placebo patients on the ADAS-cog was non-significant at Δ1.9 points. Galantamine AD + CVD patients improved by –1.0 points on the ADAS-cog, whereas placebo patients deteriorated by 1.8 points, Δ2.8 points. All VaD patients improved on the ADAS-cog – patients on galantamine by –2.4 points, and placebo patients by –0.4 points, no significant difference between the groups. For AD + CVD and VaD patients together, active treatment had small, favorable effects on the DAD and NPI scales. Of the galantamine patients 24% suffered from nausea and 13% from vomiting (7% and 6% for placebo). Of the galantamine patients 20% discontinued due to AEs, generally before week 6, as opposed to 8% of placebo patients. Doses were escalated from 4 mg/day to 24 mg/day in week 6.

Other neurodegenerative dementia disorders

Cholinesterase inhibitors in dementia with Lewy bodies (DLB)

Only one RCT, the McKeith rivastigmine study, has assessed AChEI in DLB [58] (Table 22.7–22.8). The 20-week trial, which included 120 European patients, compared rivastigmine 6 to 12 mg/day with placebo. Dropout rates were higher in the rivastigmine group (18/59, 30%) than in the placebo group (10/61, 16%). Rivastigmine showed better effects than placebo on four pre-selected NPI items (NPI-4: delusions, hallucinations, apathy and depression) in OC analyses but not in ITT analyses.

There were no significant differences between groups on the MMSE and global ratings, nor on Parkinson symptoms according to the UPDRS motor scale. Rivastigmine had small, beneficial effects on cognitive speed, as well as on tests measuring attention, working memory and episodic secondary memory [70].

Cholinesterase inhibitors in Parkinson's disease (PD) and dementia

One Norwegian pilot RCT that had a crossover design included 14 patients with mild to severe PD, a mean disease duration of 10.8 years and cognitive decline with onset at least one year after onset [71] (Table 22.7–22.8). Patients received donepezil 5 to 10 mg/day or placebo for two periods of 10 weeks each, with no washout period. In ITT-LOCF analyses, 42% of donepezil patients and 17% of placebo-treated patients had improved CIBIC+. The MMSE results also favored donepezil. There was no worsening of parkinsonian symptoms according to the UPDRS. NPI scores were low at baseline and did not change during treatment. One large RCT that compared rivastigmine with placebo in PD with dementia was included in this review even though it was published in December 2004 [72] (Table 22.7–22.8). The inclusion criteria were dementia according to DSM-IV with onset at least two years after a PD diagnosis. The effects of rivastigmine were significantly better on all primary and secondary endpoints, but the rates of cholinergic AEs were higher in the rivastigmine group. One donepezil RCT that had a cross-over design included 21 patients with progressive supranuclear paralysis (PSP). The study concluded that memory improved but ADL and mobility worsened. Thus, donepezil was not recommended for PSP patients [73].

Frontotemporal dementia (FTD)

No study has attempted to assess the efficacy of AChEIs, memantine, or any other agent on cognitive or functional deficits in FTD. One open trial found no effects of paroxetine on behavioral symptoms [74].

Cholinesterase inhibitors in Down syndrome

One 24-week pilot RCT compared donepezil 10 mg daily with placebo in patients with Down syndrome and AD, mean age 54 years [75]. Twentyseven patients out of 30 completed the study. No statistically significant effects were detected on the global, cognitive (SIB), ADL or BPSD scales. Donepezil treatment significantly improved function (Down Syndrome Dementia Scale) for 3–5 months in an open-label trial [76].

Need for research

There is a need for new, more efficient pharmacological agents to treat symptoms and slow down deterioration in AD, VaD and other dementia disorders.

Further studies are needed in order to elucidate the effects of pharmacological treatment in patients with mild cognitive impairment, as well as those with severe dementia.

There is a need for better tools to evaluate efficacy, and to predict response, in the individual patient. That is particularly true for the majority of dementia patients who live alone.

There is a need for studies on combining pharmacological treatment and non-pharmacological interventions.

There is a need for studies that address the potential effects of pharmacological treatment on behavioral disturbances associated with psychological symptoms.

Review: Demens
Comparison: 01 Pharmaceutical effects
Outcome: 01 ADAS

Study or sub-category	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)
01 Donezepil				
Homma [41]	134	–2.43 (5.10)	129	0.11 (5.20)
Rogers [31] (5 mg)	156	–2.10 (5.40)	155	0.40 (5.30)
Subtotal (95% CI)	290		284	
Test for heterogeneity: Chi? = 0.02, df = 1 (P = 0.88), I? = 0%				
Test for overall effect: Z = 5.64 (P < 0.00001)				
02 Galantamine				
Tariot [45]	253	–1.40 (6.20)	255	1.70 (6.23)
Wilcock [44]	220	–0.50 (5.80)	217	2.40 (6.00)
Subtotal (95% CI)	473		472	
Test for heterogeneity: Chi? = 0.00, df = 1 (P = 0.96), I? = 0%				
Test for overall effect: Z = 7.49 (P < 0.00001)				
Total (95% CI)	763		756	
Test for heterogeneity: Chi? = 0.05, df = 3 (P = 1.00), I? = 0%				
Test for overall effect: Z = 9.37 (P < 0.00001)				

Figure 22.1 *Meta-analysis on ADAS-cog as outcome of drug treatment on Alzheimer's disease.*

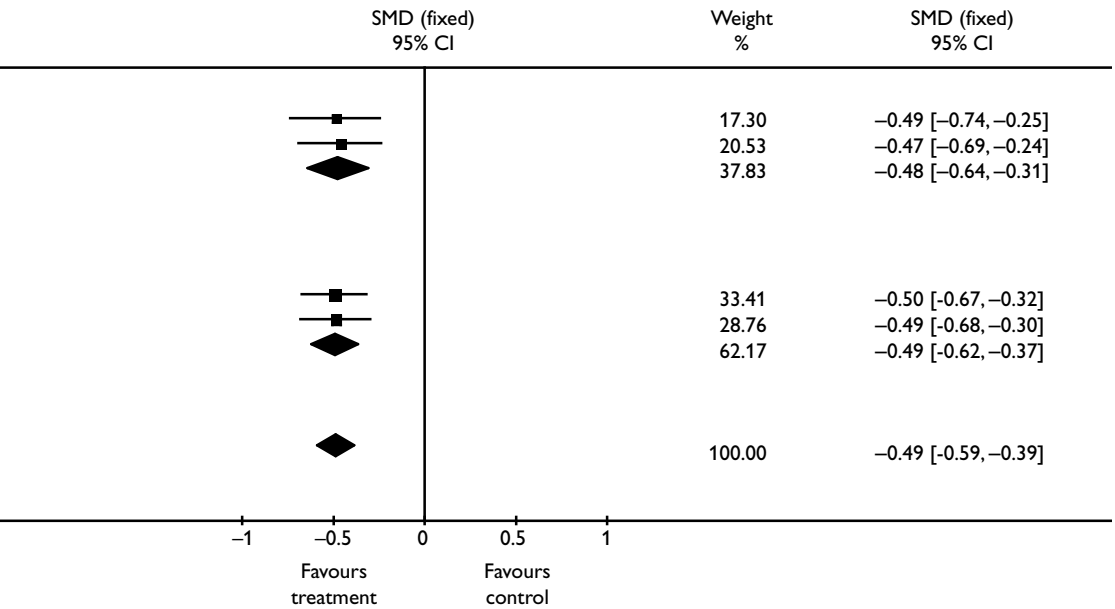
SMD (fixed)
95% CI
Weight
%
SMD (fixed)
95% CI
17.30
–0.49 [–0.74, –0.25]
20.53
–0.47 [–0.69, –0.24]
37.83
–0.48 [–0.64, –0.31]
33.41
–0.50 [-0.67, –0.32]
28.76
–0.49 [-0.68, –0.30]
62.17
–0.49 [-0.62, –0.37]
100.00
–0.49 [-0.59, –0.39]
–1
–0.5
0
0.5
1
Favours treatment
Favours control

Table 22.1 *Cholinesterase inhibitors in Alzheimer's disease: Description of randomised placebo-controlled trials.*

Author Year, reference	Type of study	Setting	Mean MMSE (range)
Donepezil			
Homma et al 2000 [41]	RCT	Japan	17.2 (10–26)
Rockwood et al 2002 [56]	RCT	USA	(10–26)
Rogers et al 1998 [77]	RCT	USA	19.5 (10–26)
Rogers et al 1998 [31]	RCT	USA	19.0 (10–26)
Burns et al 1999 [43]	RCT	Europe	20.2 (10–26)
Tariot et al 2001 [9]	RCT	USA, nursing homes	14.4 (5–26)
Winblad et al 2001 [47] "Nordic study"	RCT	Europe	19 (10–26)
Mohs et al 2001 [48]	RCT	USA	17.1 (12–20)
Feldman et al 2001 [8]	RCT	Canada, Australia	11.8 (5–17)
Courtney et al 2004 [10] "AD2000"	RCT	United Kingdom	19 (10–26)

Randomised patients (n)	Mean age (range)	Length of study	Intervention
268	69.8 (48–90)	24 weeks	Donepezil 5 mg
161	71.5 (55–85)	12 weeks	Donepezil 1, 3, 5 mg
468	73.8 (50–94)	12 weeks	Donepezil 5, 10 mg
473	73.5 (51–94)	24 weeks	Donepezil 5, 10 mg
818	71.7 (50–93)	24 weeks	Donepezil 5, 10 mg
208	85.7 (64–102)	24 weeks	Donepezil 10 mg
286	72.5 (49–88)	52 weeks	Donepezil 10 mg
431	75.4 (49–94)	54 weeks	Donepezil 10 mg
291	73.6 (48–92)	24 weeks	Donepezil 10 mg
565	75.5 (46–93)	2 (–3) years	Donepezil 5–10 mg

The table continues on the next page

Table 22.1 *continued*

Author Year, reference	Type of study	Setting	Mean MMSE (range)
Greenberg et al 2000 [57]	RCT	USA	21.8
Nakano et al 2001 [11]	RCT	Japan	22 (>16 points)
Krishnan et al 2003 [13]	RCT	USA	
Tune et al 2003 [12]	RCT	USA	28
Rivastigmine			
Agid et al 1998 [78]	RCT	Europe	Not stated
Forette et al 1999 [29]	RCT	Europe Canada	19.5 (10–26)
Anand et al 1996 [79]	RCT	USA	(10–26)
Rösler et al 1999 [32]	RCT	Europe, USA, Canada	19.9 (10–26)
"Unpublished I" B304 [49]	RCT	Europe	18.5
"Unpublished II" B351 [49]	RCT	USA	20.0 (10–26)

	Randomised patients (n)	Mean age (range)	Length of study	Intervention
	60	75.0	4 x 6 weeks, c–o	Donepezil 5 mg
	35	70 (57–80)	12 months	Donepezil 5 mg
	67		24 weeks	Donepezil 10 mg
			24 weeks	Donepezil 10 mg
	402	69.4 (50–90)	13 weeks	Rivastigmine 4, 6 mg
	114	71.2	18 weeks	Rivastigmine 6, 12 mg
	50	68 (45–90)	9 weeks	Rivastigmine 6, 12 mg
	725	72.0 (45–95)	26 weeks	Rivastigmine 1–4, 6–12 mg
	678	71.4	26 weeks	Rivastigmine 2–12 mg
	702	74.5 (45–89)	26 weeks	Rivastigmine 3, 6, 9 mg

The table continues on the next page

Table 22.1 *continued*

Author Year, reference	Type of study	Setting	Mean MMSE (range)
Corey-Bloom et al 1998 [50]	RCT	USA	19.6 (10–26)
Potkin et al 2001 [63]	RCT	USA	20.4 (15–26)
Galantamine			
Kewitz et al 1994 [80]	RCT		Mild–moderate dementia
Wilkinson et al 2001 [81]	RCT	United Kingdom	(13–24)
"Unpublished" GAL-95–05 [82]	RCT	International	(12–24)
Wilcock et al 2000 [44]	RCT	Europe, Canada	19.5 (11–24)
Rockwood et al 2001 [83]	RCT	USA, Europe	19.6 (11–24)
Raskind et al 2000 [46]	RCT	USA	19.2 (11–24)
Tariot et al 2000 [45]	RCT	USA	17.8 (10–22)

c–o = Crossover; MMSE = Mini-mental state examination; RCT = Randomised controlled trial

Comments to Table 22.1
The proportion of female patients was 50–67%, except for in Tariot 2001 (82%) [9]. Dose titration: Treatment with donepezil started with 5 mg/day and was raised to 10 mg/day after one week (301, 302, 304) or after four weeks (311, 312, F2000, Nordic study). Rivastigmine was titrated to target dose over 2–3 weeks (B103, B304); over 7 weeks (B303, B352); over 9–10 weeks (B104, B105) or over 12 weeks (B351). Galantamine was rapidly titrated (increase 8 mg weekly to target dose) in GAL-93–01, GAL-95–05, GAL-INT-1, GAL-INT-2, GAL-US-1, while GAL-USA-10 used slow titration (increase 8 mg per 4 weeks).

	Randomised patients (n)	Mean age (range)	Length of study	Intervention
	699	74.5 (45–89)	26 weeks	Rivastigmine 1–4, 6–12 mg
	27	75.9 (64–89)	26 weeks	Rivastigmine 3, 6, 9 mg
	95	(60–87)	13 weeks	Galantamine 50 mg
	285	73	12 weeks	Galantamine 18, 24, 36 mg
	554	72.9	29 weeks	Galantamine 32 mg
	653	72	26 weeks	Galantamine 24, 32 mg
	386	75	12 weeks	Galantamine 24–32 mg
	636	75	26 weeks	Galantamine 24, 32 mg
	978	77	5 months	Galantamine 8, 16, 24 mg

Table 22.2 *Memantine: Description of randomised placebo-controlled trials.*

Author Year, reference	Type of study	Setting	Dementia diagnosis
Ditzler 1991 [27]	RCT	Germany	79% MID
Gortelmeyer 1992 [84]	RCT	Germany	76% VaD
Pantev 1993 [85]	RCT	Germany	Dementia
Winblad 1999 [18]	RCT	Latvia nursing homes	52% VaD 48% AD
Orgogozo 2002 [16]	RCT	France, Belgium, Switzerland	VaD
Wilcock 2002 [17]	RCT	United Kingdom	VaD
Reisberg 2003 [19]	RCT	USA community residents	AD
Tariot 2004 [20]	RCT	USA community residents	AD

Comments to Table 22.2
*** Diagnostic criteria**
Dementia syndrome according to the Lausanne scheme [27], according to DSM-III [84], DSM-III-R [16,17,18,85], DSM-IV [19] or NINCDS-ADRDA [20] MID according to Hachinski IS [27]. AD according to modified Hachinski IS ≤4 [18,19,20], and to CT/MRI [19,20]. Probable VaD according to NINDS-AIREN [16,17]. Proportions of female patients 47–75%.

Severity MMSE points	Randomised patients (n)	Mean age (range)	Length of study	Intervention
Mild-moderate	66	72.2 (65–80)	6 weeks	Memantine 30 mg/day
Mild-moderate 24 p	88	71.5 (59–96)	6 weeks	Memantine 20 mg/day
Mild–severe	60	72.4	6 weeks	Memantine 30 mg/day
Moderate-severe, MMSE <10 p, GDS 5–7	166	70	12 weeks	Memantine 10 mg/day
Mild-moderate 17 p (12–20 p)	321	76	28 weeks	Memantine 20 mg/day
Mild-moderate 18 p (10–22 p)	579	77 (54–97)	28 weeks	Memantine 20 mg/day
Moderate-severe 8 p (3–14 p)	252	76 (50–)	28 weeks	Memantine 20 mg/day
Moderate-severe 10 p (5–14 p)	404	76 (50–)	24 weeks	Adding memantine 20 mg/day to stable dose of donepezil

**** Dose titration**
Ditzler: 10 mg/day–30 mg/day in 2 weeks, Gortelmeyer: 10 mg/day–20 mg in 3 days, Pantev: 20 mg/day–30 mg in 7 days, Winblad: 5 mg/day–10 mg in 7 days, Orgogozo, Wilcock, Tariot: 5 mg/day–20 mg in 3 weeks, Reisberg: 20 mg/day, titration not stated.

AD = Alzheimer's disease; GDS = Global deterioration scale; MMSE = Mini-mental state examination; p = points; RCT = Randomised controlled trial; VaD = Vascular dementia

Table 22.3 *Cholinesterase inhibitors in Alzheimer's disease: Outcomes, adverse events and attrition in six months RCTs.*

Author Year, reference	Intervention, length of study	Results active vs placebo or baseline vs end point I = primary, II = secondary outcomes Significant differences unless otherwise stated	Drop-outs any cause (active treatment vs placebo)
Donepezil			
Homma et al 2000 [41]	5 mg/day, 24 weeks	I: CGIC improved: 48% vs 19% Unchanged/improved: 81% vs 58% ΔADAS-cog 2.54 p II: CDR-SB don > placebo, ADL (CMCS) slower decline MENFIS don > placebo	5 mg: 17/136 (12%) Placebo: 22/132 (17%) ns
Rogers et al 1998 [31]	5,10 mg/day, 24 weeks	I: CIBIC 1–3: 5 mg: 26% vs 11% 10 mg: 25% vs 11% CIBIC 1–4: 5 mg: 67% vs 55% 10 mg: 75% vs 55% ΔADAS-cog 5 mg: 2.5 p, 10 mg: 2.9 p II: CDR-SB don > placebo ADAS-cog ≥0 p: 80–81% vs 58% ΔMMSE 1.2 p 5 mg ΔMMSE 1.4 p 10 mg QoL ns	5 mg: 23/154 (15%) ns 10 mg: 51/157 (32%) placebo 32/162 (20%) OR 1.93 (1.17–3.19)

Drop-outs due to AEs (active treatment vs placebo)	Remarks from reviewer	Assessed quality
5 mg: 2/136 (2%) vs placebo: 6/132 (4%) ns	Significantly more improved and unchanged/improved global function and ADAS-cog donepezil 5 mg/day > placebo. Equal rates of withdrawals	High
5 mg: 9/154 (6%) ns 10 mg: 26/157 (17%) vs placebo: 11/162 (7%) OR 2.59 (1.30–5.13)	Significantly more improved and unchanged/improved global function 5 and 10 mg/day and ADAS-cog donepezil 5–10 mg/day >placebo. Significantly more drop-outs any cause and due to AE 10 mg/day, ns 5 mg/day	Moderate

The table continues on the next page

Table 22.3 *continued*

Author Year, reference	**Intervention, length of study**	**Results active vs placebo or baseline vs end point I = primary, II = secondary outcomes Significant differences unless otherwise stated**	**Drop-outs any cause (active treatment vs placebo)**
Burns et al 1999 [43]	5, 10 mg/day, 24 weeks	I: CIBIC 1–3: 5 mg: 21% vs 14% 10 mg: 25% vs 14% CIBIC 1–4: 5 mg: 57% vs 49% 10 mg: 63% vs 49% ΔADAS-cog 5 mg 1.5 p, 10 mg 2.9 p II: CDR-SB don > placebo ΔMMSE 1.8 p 10 mg Less ADL decline (IDDD) 10 mg, ns 5 mg QoL: ns	5 mg: 60/271 (22%) 10 mg: 72/273 (26%) Placebo: 55/274 (20%) ns
Tariot et al 2001 [9]	Nursing home 10 mg/day, 24 weeks	I: Total NPI-NH ns agitation/ aggression sign improved (45% vs 28%) II: CDR-SB don > placebo MMSE ns Basic ADL (PSMS) ns	10 mg: 19/103 (18%) Placebo: 27/105 (26%) ns
Winblad et al 2001 [47] "Nordic study"	10 mg/day, 52 weeks	I: GBS improvement 31% don, 22% placebo II: GDS improvement don > placebo ΔMMSE 1.7 p ADL (PDS) better preserved, OR 0.53 (0.36–0.78). NPI ns	10 mg: 47/142 (33%) Placebo: 47/144 (33%) ns

Drop-outs due to AEs (active treatment vs placebo)	Remarks from reviewer	Assessed quality
5 mg: 24/271 (9%) ns 10 mg: 50/273 (18%) vs placebo: 27/274 (10%) OR 2.01 (1.24–3.25)	Significantly more improved and unchanged/improved global function 5 and 10 mg and ADAS-cog donepezil 5 and 10 mg/day > placebo. Significantly less ADL decline 10 mg/day. Significantly more dropouts due to AE 10 mg/day	Moderate
10 mg: 11/103 (10%) Placebo: 19/105 (18%) ns	Nursing home patients. Only single item in NPI significant, ADL ns. Lower rates of withdrawals in donepezil group	Moderate
10 mg: 10/142 (7%) Placebo: 9/144 (6%) ns	Small, significant improvement global function. MMSE and ADL better preserved. Low rates of discontinuation due to AEs over 1 year	Moderate

The table continues on the next page

Table 22.3 *continued*

Author Year, reference	**Intervention, length of study**	**Results active vs placebo or baseline vs end point I = primary, II = secondary outcomes Significant differences unless otherwise stated**	**Drop-outs any cause (active treatment vs placebo)**
Mohs 2001 [48]	10 mg/day, 54 weeks	I: 41% vs 56% reached time to clinically evident functional decline in 1 year Median time don > placebo (357 vs 208 days) II: CDR-SB don > placebo MMSE don > placebo	10 mg: 60/214 (28%) Placebo: 56/217 (26%) ns
Feldman 2001 [8]	Moderate-severe AD 10 mg/day, 24 weeks	I: CIBIC 1–4: 63% vs 42% CIBIC + mean 0.54 II: FRS don > placebo sev–MMSE and SIB don > placebo Less ADL decline (DAD, IADL +, PSMS +) NPI don > placebo, mean diff 5.6 p (out of 144 p) Less caregiver strain don vs placebo	10 mg: 23/144 (16%) Placebo: 20/147 (14%) ns
Courtney 2004 [10] "AD2000"	5–10 mg/day, 3 years	I: Entry to institution ns (9% vs 14% 1 year, 42% vs 44% 3 years) Loss of ADL function ns (13% vs 19% 1 year, 55% vs 53% 3 years) II: ΔMMSE 0.8 p 2 years BADLs mean don > placebo MMSE < 10 p ns NPI ns, cg wellbeing ns	After 12 weeks: 5 mg: 36/286 (13%) Placebo: 18/283 (6%) sign After 48 weeks: 5–10 mg: 90/242 (37%) Placebo: 103/244 (42%) ns

Drop-outs due to AEs (active treatment vs placebo)	Remarks from reviewer	Assessed quality
10 mg: 23/214 (11%) Placebo: 16/217 (7%) ns	5 months delay donepezil vs placebo in time to clinically evident functional decline defined as decline in ≥1 basic ADL or ≥20% decline in IADL or ≥1 p increase in CDR. Most cases due to IADL decline. Equal rates of withdrawals	Moderate
10 mg: 12/144 (8%) Placebo: 9/147 (6%) ns	Results favouring donepezil 10 mg in global, cognitive, ADL and BPSD scales. Low rates of discontinuation and AEs in this study on moderate-severe dementia	Moderate
After 12 weeks: 5 mg: 17/282 (6%) Placebo: 3/283 (1%) From week 13: 5–10 mg: 18/242 (7%) Placebo: 8/244 (3%) p = 0.05	Largest trial in terms of person-years. Peculiar inclusion criteria (doctor should be uncertain of that treatment would be beneficial). Underpowered for primary endpoint, aimed to recruite 3000 patients but included 565 only. Many patients switched to open-label treatment. Small positive effects on cognition and ADL still after 2 years, no effect on institutionalisation or significant ADL loss. No permanent cognitive deterioration after 4–6 weeks wash-out	Moderate

The table continues on the next page

Table 22.3 *continued*

Author Year, reference	**Intervention, length of study**	**Results active vs placebo or baseline vs end point I = primary, II = secondary outcomes Significant differences unless otherwise stated**	**Drop-outs any cause (active treatment vs placebo)**
Nakano et al 2001 [11] "SPECT study"	5 mg/day, 12 months	I: rCBF don > placebo II: MMSE decline from baseline: 5 mg 2.2 p, ns placebo 3.5 p, sign	
Tune et al 2003 [12] "PET study"	10 mg/day, 24 weeks	I: CMRglu don > placebo II: ΔADAS-cog 2.1 p (OC, ns)	0/14 (0%) vs 2/14 (14%)
Krishnan et al 2003 [13] "MRI study"	10 mg/day, 24 weeks	I: hippocampal volume don > placebo II: ΔADAS-cog 3.9 p (OC, sign)	6/34 (18%) vs 10/33 (30%)
Rivastigmine			
Rösler et al 1999 [32]	6–12 mg/day, 26 weeks	I: CIBIC 1–3: 37% vs 20% ΔADAS-cog 1.6 p, ns II: Progression to GDS ≥5 riva < placebo ΔMMSE 0.7 p ADL decline (PDS) ns	79/242 (33%) vs 31/239 (13%) OR 3.94 (1.99–4.66)
"Unpublished I" B304 [49]	6–12 mg/day, 26 weeks	I: CIBIC 1–3: 23% vs 19%, ns ΔADAS-cog 1.6 p II: Progression to GDS ≥5 ns ΔMMSE 0.8 p Near sign less ADL decline (PDS)	54/228 (24%) vs 33/222 (15%) OR 1.76 (1.10–2.81)

	Drop-outs due to AEs (active treatment vs placebo)	Remarks from reviewer	Assessed quality
		(Pilot study)	
		(Pilot study)	
	0/34 vs 1/33	(Pilot study)	
	55/242 (22%) vs 16/239 (7%) OR 3.57 (2.26–5.90)	Significantly more improved global function. ADAS-cog and ADL ns. High rates of drop-outs any cause and due to AE in rivastigmine-group	High
	39/228 (17%) vs 20/222 (9%) OR 2.03 (1.18–3.51)	Ns effect global function, ADAS-cog higher scores in rivastigmine. Significantly more drop-outs any cause and due to AE in rivastigmine-group	Moderate

The table continues on the next page

Table 22.3 *continued*

Author Year, reference	**Intervention, length of study**	**Results active vs placebo or baseline vs end point I = primary, II = secondary outcomes Significant differences unless otherwise stated**	**Drop-outs any cause (active treatment vs placebo)**
"Unpublished II" B351 [49]	6–12 mg/day, 26 weeks	I: CIBIC 1–3: 25% vs 25%, ns ΔADAS-cog 1.4 p II: Progression to GDS ≥5 riva < placebo ΔMMSE 0.7 p ADL decline (PDS) ns	152/352 (43%) vs 43/172 (25%) OR 2.17 (1.49–3.17)
Corey-Bloom et al 1998 [50]	6–12 mg/day, 26 weeks	I: CIBIC 1–3: 22% vs 15%, ns ΔADAS-cog 3.8 p, sign II: Progression to GDS ≥5 ns, mean GDS riva better than placebo. ΔMMSE 0.7 p ΔADAS-cog ≥0 p 56% vs 27% ADL decline (PDS) sign less	82/230 (36%) vs 38/235 (17%) OR 2.76 (1.82–4.18)
Potkin et al 2001 [63] "PET study"	3–9 mg, 26 weeks	I: global CMRglu 26% increased riva, 6% placebo II: CIBIC 1–4 15/20 riva, 2/7 placebo	
Galantamine			
Wilcock et al 2000 [44]	24 mg/day, 26 weeks	I: CIBIC 1–3: 17% vs 16%, ns CIBIC 1–4: 62% vs 50% ΔADAS-cog: 2.9 p II: ADAS-cog ≥4 p 29% vs 15% ADL (DAD) ns	44/220 (20%) vs 29/215 (14%) ns

Drop-outs due to AEs (active treatment vs placebo)	Remarks from reviewer	Assessed quality
97/352 (27%) vs 21/172 (12%) OR 2.41 (1.56–3.72)	High rates of drop-outs in both groups and significantly more drop-outs any cause and due to AE in rivastigmine-group. Conflicting results global function, ADAS-cog higher scores in rivastigmine. ADL ns	Moderate
66/230 (29%) vs 17/235 (7%) OR 4.31 (2.68–6.92)	Significantly more drop-outs any cause and due to AE in rivastigmine-group. Conflicting results global function, ADAS-cog higher scores in rivastigmine. Less decline in ADL	Moderate
31/220 (14%) vs 19/215 (9%) ns	Ns effect improved global function, sign effect improved/unchanged. ADAS-cog higher scores in galantamine. ADL ns. Equal rates of withdrawals	Moderate

The table continues on the next page

Table 22.3 *continued*

Author Year, reference	**Intervention, length of study**	**Results active vs placebo or baseline vs end point I = primary, II = secondary outcomes Significant differences unless otherwise stated**	**Drop-outs any cause (active treatment vs placebo)**
Tariot et al 2000 [45]	16, 24 mg/day, 5 months	I: CIBIC 1–3: 20% 16 mg, 22% 24 mg, 12% placebo CIBIC 1–4: 66% 16 mg, 64% 24 mg, 49% placebo ΔADAS-cog: 16 mg and 24 mg: 3.1 p II: ≥4 p ADAS-cog 36–37% 16–24 mg vs 20% placebo ADCS-ADL better preserved 16 and 24 mg. NPI less deterioration 16 and 24 mg (Δ2.0 p)	16 mg: 60/279 (22%) 24 mg: 61/273 (22%) Placebo: 446/286 (16%) ns

All analyses are ITT or ITT-LOCF.

AD = Alzheimer's disease; ADAS = Alzheimer's disease assessment scale–cognitive; ADL = Activities of daily living; AE = Adverse events; BADL = Basic activities of daily living; BPSD = Behavioral and psychological signs and symptoms of dementia; CBF = Cerebral blood flow; CDR = Clinical dementia rating (scale); CGIC = Clinical global impression of change (scale); CIBIC = Clinician's interview-based impression of change; CMCS = Caregiver Modified Chrichton Scale; CMR = Cerebral metabolic rate; DAD = Disability assessment for dementia (scale); GBS = Gottfries-Brane-Steen (scale); GDS = Global Deterioration Scale; IADL = Instrumental activities of daily living; IDDD = Interview for deterioration in daily living activities in dementia; MENFIS = Mental function impairment scale; MMSE = Mini-mental state examination; NPI = Neuropsychiatric inventory; ns = Not stated; OC = Observed cases; OR = Odds ratio; PDS = Progressive deterioration scale; PSMS = Physical self maintenance scale; QoL = Quality of Life; SB = Single-blind

Drop-outs due to AEs (active treatment vs placebo)	Remarks from reviewer	Assessed quality
16 mg: 19/279 (7%) 24 mg: 27/273 (10%) Placebo: 20/286 (7%) ns	Significantly more improved and improved/unchanged global function. ADAS-cog higher scores in galantamine and ADL better preserved. Equal rates of withdrawals	High

Table 22.4 *Memantine: Outcomes, adverse events and attrition.*

Author Year, reference Type of dementia disorder	**Intervention Length of study**	**Results I = primary, II = secondary outcomes Significant differences unless otherwise stated**	**Drop-outs any cause (active treatment vs placebo)**
Winblad et al 1999 [18] MID + AD	10 mg/day, 12 weeks	I: BGP "care dependency" improved >15%: 65% vs 40%, ns BGP "care dependency" score –3.1 +/–12.2 p vs –1.1 +/–11.8 p CGI-C 1–3: 73% vs 45% CGI-C 1–4: 96% vs 90% ns II: BGP total score –7.2 +/–7.1 p vs –4.6 +/–7	7/82 (8%) vs 8/84 (9%) ns
Wilcock et al 2002 [17] VaD	20 mg/day, 28 weeks	I: CGI-C ns ΔADAS-cog 1.8 p II: GBS ns NOSGER ns ΔMMSE 0.3 p (OC) ns	57/295 (19%) vs 58/284 (20%) ns
Orgogozo et al 2002 [16] VaD	20 mg/day, 28 weeks	I: CIBIC+ mean 3.8+/–1.4 p vs 4.1 +/–1.5 p, ns CIBIC+ 1–4: 60% vs 52%, ns ΔADAS-cog: 2.0 p II: GBS mem > placebo NOSGER ns ΔMMSE 1.2 p (OC)	49/165 (30%) vs 38/156 (24%) ns

Drop-outs due to AEs (active treatment vs placebo)	Remarks from reviewer	Assessed quality
ns	Ns primary outcome care dependency, significantly more in memantine-group globally improved. Almost all participants were rated globally unchanged after 12 weeks. Equal rates of withdrawals	Moderate
27/295 (9%) vs 20/284 (7%) ns	Small positive effect ADAS-cog, all other endpoints ns. Equal rates of withdrawals	Moderate
19/165 (12%) vs 20/156 (13%) ns	Small positive effect ADAS-cog and GBS, all other endpoints ns. Equal rates of withdrawals	Moderate

The table continues on the next page

Table 22.4 *continued*

Author Year, reference	**Intervention Length of study**	**Results I = primary, II = secondary outcomes Significant differences unless otherwise stated**	**Drop-outs any cause (active treatment vs placebo)**
Reisberg et al 2003 [19] Moderate/Severe AD	20 mg/day, 28 weeks	I: CIBIC+ and ADCS or SIB repsonders*: 29% vs 10% CIBIC+ mean: 45 +/–1.1 p vs 4.8 +/–1.1, p = 0.06 ADCS-ADLsev –3.1 +/–6.8 p vs –5.2 +/–6.3 p II: FAST 0.2 +/–1.2 +/–0.6 +/–1.4 sign GDS ns SIB –4.0 +/–11.3 p vs –10.1 +/–13.5 p, sign ΔMMSE 0.7 p, ns ΔNPI 3.3 p, ns	29/126 (23%) vs 42/126 (33%) ns
Tariot et al 2004 [20]	20 mg/day or placebo added to donepezil 28 weeks	I: SIB + 0.9 p (0.67) vs –2.5 p (0.67) ADCS-ADL –2.0 (0.5) vs –3.4 (0.5) II: Mean CIBIC+ 4.41 (0.07) vs 4.66 (0.08) CIBIC+ 1–4 55% vs 45% ΔNPI 3.8 p BGP dependency subscale 0.8 (0.4) vs 2.3 (0.4), sign	31/203 (15%) vs 51/201 (25%) ns

ITT-LOCF analyses unless otherwise stated.

ADAS = Alzheimer's disease assessment scale; ADL = Activities of daily living; ADCS = Alzheimer's disease cooperative study; BGP = The behavioral rating scale for geriatric patients; BPSD = Behavioral and psychological signs and symptoms of dementia; CGI = Clinical global impression (scale); CIBIC = Clinician's interview-based impression of change; FAST = Functional assessment staging; GBS = Gottfries-Brane-Steen; MMSE = Mini-mental state examination; NOSGER = Nurses' observation scale for geriatric patients; NPI = Neuropsychiatric inventory; ns = Not stated; p = Points; SIB =The severe impairment battery

Drop-outs due to AEs (active treatment vs placebo)	Remarks from reviewer	Assessed quality
13/126 (10%) vs 22/126 (17%) ns	Memantine significant effect on one of the primary outcomes: * prespecified individual response defined as improved or unchanged CIBIC+ and improved or unchanged ADCS or SIB, but CIVIC+ ns. SIB memantine >placebo, but no clear differences on other secondary outcomes. Equal rates of withdrawals	Moderate
15/203 (7%) vs 25/201 (12%) ns	Small positive effect on global ratings (55% vs 45% improved or better), cognitive function, ADL and BPSD. Equal rates of withdrawals	Moderate

Table 22.5 *Acetylcholinesterase inhibitors in vascular dementia: Description of randomised, placebo-controlled trials.*

Author Year, reference	**Type of study**	**Setting**	**Mean MMSE (range)**
Wilkinson et al 2003 [67]	RCT	USA, Europe, Canada, Australia	22 (10–26)
Black et al 2003 [68]	RCT	USA, Europe, Canada, Australia	22 (10–26)
Erkinjuntti et al 2002 [60,62]	RCT	Europe, Canada, USA	20.5 (10–25)

Females 40–48%.

AD = Alzheimer's disease; CVD = Cerebrovascular disease; RCT = Randomised controlled trial; VaD = Vascular dementia

	Randomised patients (n)	Mean age (range)	Length of study	Intervention
	616 VaD	75 (38–95)	24 weeks	Donepezil 5, 10 mg/day
	603 VaD	74	24 weeks	Donepezil 5, 10 mg/day
	592 VaD and AD + CVD	75	6 months	Galantamine 24 mg/day

Table 22.6 *Actylcholinesterase inhibitors in vascular dementia: Outcomes, adverse events and attrition.*

Author Year, reference	**Intervention, length of study**	**Results I = primary, II = secondary outcomes Significant differences unless otherwise stated**	**Drop-outs any cause (active treatment vs placebo)**
Wilkinson et al 2003 [67]	Donepezil 5, 10 mg/day, 24 weeks	I: CIBIC 1–3: 39% 5 mg, 32% 10 mg, 25% placebo ΔADAS-cog: 1.6 p 5 mg, 2.1 p 10 mg, sign II: CDR-SB improved 10 mg ΔMMSE:1.0 p 5 mg, 1.3 p 10 mg ADL (ADFACS) ns	5 mg: 40/203 (19%) 10 mg: 53/203 (25%) Placebo: 32/189 (17%)
Black et al 2003 [68]	Donepezil 5, 10 mg/day, 24 weeks	I: CIBIC 1–3: 36% 5 mg, 28% 10 mg, 30% placebo CIBIC 1–4: 77% 5 mg 72% 10 mg, 69% placebo, ns ΔADAS-cog: 1.7 p 5 mg, 2.2 p 10 mg II: CDR-SB ns 5 mg, sign 10 mg ΔMMSE: 0.65 p 5 mg, 1.10 p 10 mg Better ADL (ADFACS) 5 and 10 mg	5 mg: 37/196 (19%) 10 mg: 58/195 (28%) Placebo: 30/194 (15%)
Erkinjuntti et al 2002 [86] VaD and AD + CVD	Galantamine 24 mg/day, 6 months	I: CIBIC 1–3: AD + CVD 32% vs 19% VaD 31% vs 23%, ns CIBIC 1–4: All patients: 74% vs 59%, sign ΔADAS-cog: All patients 2.7 p (sign), AD + CVD (n = 239) 2.8 p (sign), VaD (n = 188) 1.9 p, ns II: ADAS-cog ≥0 p all patients: 64% vs 51% ADAS-cog ≥4 p all patients: 35% vs 22% ADL (DAD) less decline ΔNPI 2.2 p	102/396 (26%) vs 33/196 (17%) sign

ITT-LOCF or ITT analyses.

AD = Alzheimer's disease; ADAS = Alzheimer's disease assessment scale; ADFACS = The Alzheimer's disease functional assessment and change scale; ADL = Activities of daily living; CDR = Clinical dementia rating; CIBIC = Clinician's interview-based impression of change;

Drop-outs due to AEs (active treatment vs placebo)	Remarks from reviewer	Assessed quality
5 mg: 21/203 (10%) 10 mg: 35/203 (16%) Placebo: 17/189 (9%)	Small but significant global improvement 5 and 10 mg, cognitive tests donepezil > placebo, ADL ns. Equal rates of withdrawals	Moderate
5 mg: 22/196 (11%) 10 mg: 45/195 (22%) Placebo: 22/194 (11%)	Small significant global improvement 5 mg, ns 10 mg, cognitive tests and ADL donepezil > placebo. More withdrawals in 10 mg	Moderate
78/396 (20%) vs 16/196 (8%) sign	Two different diagnoses in the same study, too small sample for subanalyses. VaD patients did not benefit from galantamine. More withdrawals in galantamine	Medium

CVD = Cerebrovascular disease; DAD = Disability assessment for dementia (scale); MMSE = Mini-mental state examination; NPI = Neuropsychiatric inventory; ns = Not stated; p = points; SB = Single-blind; VaD = Vascular dementia

Table 22.7 *Acetylcholinesterase inhibitors in Lewy body dementia and Parkinsons disease with dementia. Description of randomised placebo-controlled trials.*

Author Year, references	**Diagnosis**	**Type of study**	**Setting**	**Mean MMSE (range)**
McKeith et al 2000 [58]	DLB	RCT	United Kingdom, Spain, Italy	(9–) Mild-moderate
Aarsland et al 2002 [71]	PD + memory impairment	RCT Crossover	Norway, single-center	20.8 (16–26)
Emre et al 2004 [72]	PD dementia	RCT	Several European countries	19.3 (10–24)

DLB = Dementia with Lewy body; PD = Parkinson's disease; RCT = Randomised controlled trial

Randomised patients (n)	Mean age (range)	Length of study	Intervention
120	73.9 (57–87)	20 weeks	Rivastigmine 6–12 mg/day
14		2 x 10 weeks	Donepezil 5–10 mg/day
541	72.7	24 weeks	Rivastigmine 3–12 mg/day

Table 22.8 *Acetylcholinesterase inhibitors in LBD and PDD: Outcomes, adverse events and attrition.*

Author Year, reference	**Diagnosis**	**Results active vs placebo or baseline vs end point I = primary, II = secondary outcomes Significant differences unless otherwise stated**	**Drop-outs any cause (active treatment vs placebo)**
McKeith et al 2000 [58]	DLB	I: ΔNPI-4 1.7 p (ns ITT, sign ITT-LOCF) Cognitive speed score riva > placebo II: NPI-4 >30% improvement: 48% vs 28%, sign NPI-10 ns (ITT), MMSE ns, CGC + ns	18/59 (30%) vs 10/61 (16%)
Aarsland et al 2002 [71]	PD + memory impairment	I: ΔMMSE 1.8 p CIBIC + mean score 3.3 don, 4.1 placebo CIBIC 1–3: 42% vs 17%	2/14 (14%) vs 0
Emre et al 2004 [72]	PD dementia	I: ΔADAS-cog 2.8 p CGIC 1–3: 20% vs 14% CGIC 1–4: 87% vs 77% mean score 3.8 vs 4.3 II: ADCS-ADL, NPI, MMSE riva > placebo	99/362 (27%) vs 32/179 (18%)

AD = Alzheimer's disease; ADAS = Alzheimer's disease assessment scale; ADCS = Alzheimer's disease cooperative study; AE = Adverse events; ADL = Activities of daily living; BPSD = Behavioral and psychological signs and symptoms of dementia; CGIC = Clinical global impression of change (scale); CIBIC = Clinician's interview-based impression of change; ITT = intention-to-treat; LOCF = Last observation carried forward; MMSE = Mini-mental state examination; NPI = Neuropsychiatric inventory; ns = Not stated

	Drop-outs due to AEs (active treatment vs placebo)	Remarks from reviewer	Assessed quality
	7/59 (12%) vs 7/61 (12%)	Non-significant differences in ITT analyses of one of the primary outcomes. High discontinuation rate and AEs (37% nausea, 25% vomiting) in rivastigmine group	Moderate
	2/14 (14%) vs 0	No worsening of parkinsonism in donepezil group	Moderate
	62/162 (17%) vs 14/179 (8%)	Similar small positive effects on global and cognitive function as in AD studies. ADL and BPSD rivastigmine > placebo AEs: 29% vs 11% nausea, 17% vs 2% vomiting, 10% vs 4% tremor in rivastigmine vs placebo patients	Moderate

References

1. Summers WK, Majovski L, Marsh GM, Tachiki K, Kling A. Oral tetrahydroaminoacridine in long-term treatment of senile dementia Alzheimer type. N Engl J Med 1986;315:1241-5.

2. Coelho Filho JM, Birks J. Physostigmine for Alzheimer's disease. Cochrane Database Syst Rev 2003.

3. Lopez-Arrieta JM, Schneider L. Metrifonate for Alzheimer's disease. Cochrane Database Syst Rev 2006.

4. Birks JS, Harvey R. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 2006.

5. Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev 2003.

6. Olin SL. Galantamine for Alzheimer's disease. Cochrane Database Syst Rev 2003.

7. Areosa Sastre A, Sherriff F. Memantine for dementia. Cochrane Database Syst Rev 2003.

8. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. A 24-week, randomised, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001;57:613-20.

9. Tariot PN, Cummings J, Katz IR, MIntzer J, Perdomo CA, Schwam EM, Whalen E. A randomised, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc 2001;49:1590-9.

10. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004;363:2105-15.

11. Nakano S, Asada T, Matsuda H, Uno M, Takasaki M. Donepezil hydrochloride preserves regional cerebral blood flow in patients with Alzheimer's disease. J Nucl Med 2001;42:1441-5.

12. Tune L, Tiseo P, Ieni J, Perdomo C, Pratt RD, Votaw JR, Jewart R, Hoffman JM. Donepezil HCl (E2020) maintains functional brain activity in patients with Alzheimer disease: results of a 24-week, double-blind, placebo-controlled study. Am J Geriatr Psychiatry 2003;11:169-77.

13. Krishnan KR, Charles H, Doraiswamy PM, Mintzer J, Weisler R, Yu X et al. Randomised, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. Am J Psychiatry 2003;160:2003-11.

14. Wilkinson DG, Hock C, Farlow M, van Baelen B, Schwalen S. Galantamine provides broad benefits in patients with 'advanced moderate' Alzheimer's disease (MMSE <or = 12) for up to six months. Int J Clin Pract 2002;56:509-14.

15. Wilcock G, Howe I, Coles H, Lilienfeld S, Truyen L, Zhu Y, Bullock R, Kershaw P, GAL-GBR-2 Study Group. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. Drugs Aging 2003;20:777-89.

16. Orgogozo J-M, Rigaud A-S, Stöffler A, Mobius HJ, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia. A randomised, placebo-controlled trial (MMM 300). Stroke 2002;33:1834-39.

17. Wilcock G, Mobius H, Stoffler A. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM 500). Int Clin Psychopharmacol 2002;17:297-305.

18. Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999;14:135-46.

19. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333-41.

20. Tariot PN, Farlow M, Grossberg GT, Graham SM, McDonald S, Gergel I, Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomised controlled trial. JAMA 2004;291:317-24.

21. Schneider LS, Olin J, Doody RS et al, and the Alzheimer's Disease Cooperative Study. Validity and reliability of the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change. Alzheimer Dis Assoc Disord 1997;11(suppl 2):S22-S32.

22. Berg L, Miller J, Baty J, Rubin EH, Morris JC, Figiel G. Mild senile dementia of the Alzheimer type: 4 evaluations of intervention. Ann Neurol 1992;31:242-9.

23. Reisberg B, Ferris S, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry 1982;139:1136-9.

24. Gottfries CG, Bråne G, Gullberg B et al. A new rating scale for dementia syndromes. Arch Gerontol Geriatr 1982;1:311-30.

25. Homma A, Niina R, Ishii T, Hasegawa K. Development of a new rating scale for dementia in the elderly: Mental Function Impairment Scale (MENFIS). Jpn J Geriatr Psychiatry 1991;2:1217-22.

26. van der Kam P, Mol F, Wimmers M. Beoordelingsschaal voor Oudere Patienten (BOP). Deventer, the Netherlands, van Loghum Slaterus; 1971.

27. Ditzler K. Efficacy and tolerability of memantine in patients with dementia syndrome: a double-blind, placebo controlled trial. Arzneimittelforschung 1991;41: 773-80.

28. Feldman H, Schulzer M, Wang S Twokko H, Beattie BL. The Functional Rating Scale in Alzheimer's disease assessment: a longitudinal study. In: Iqbal K MJ, Winblad B, Wisniewski HM, editor. Research Advances in Alzheimer's Disease and Related Disorders. Chichester, UK: Wiley; 1995. p 235-41.

29. Forette F, Anand R, Gharabawi G. A phase II study in patients with Alzheimer's disease to assess the preliminary efficacy and maximum tolerated dose of rivastigmine (Exelon). Eur J Neurol 1999;6:423-9.

30. Mohs RC, Davis B, Johns CA et al. Oral physostigmine treatment of patients with Alzheimer's disease. Am J Psychiatry 1985;142:28-33.

31. Rogers SL, Farlow M, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 1998;50:136-45.

32. Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, Stahelin HB, Hartman R, Gharabawi M. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999;318:633-8.

33. Folstein NF, Folstein S, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12: 189-98.

34. Panisset M, Roudier M, Saxton J, Boller F. Severe Impairment Battery: a neurological test for severely demented patients. Arch Neurol 1994;51:41-5.

35. DeJong R, Osterlund O, Roy GW. Measurement of quality-of-life changes in patients with Alzheimer's disease. Clin Ther 1989;11:545-54.

36. Gelinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: the disability assessment for dementia. Am J Occup Ther 1999;53:471-81.

37. Teunisse S, Derix M, van Crevel H. Assessing the severity of dementia, patient and caregiver. Arch Neurol 1991;48:274-7.

38. Galasko D, Bennett D, Sano M et al. An inventory to assess the activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alz Dis Assoc Disord 1997;11 (suppl 2):S33-9.

39. Lawton MP, Brody E. Assessment of older people: self-maintaing and instrumental activities of daily living. Gerontol 1969;9:179-86.

40. Schmeidler J, Mohs R, Aryan M. Relationship of disease severity to decline on specific cognitive and functional measures in Alzheimer's disease. Alzheimer Dis Assoc Disord 1998;12:146-51.

41. Homma A, Takeda M, Imai Y, Udaka F, Hasegawa K, Kameyama M, Nishimura T. Clinical efficacy and safety of donepezil on cognitive and global function in patients with Alzheimer's disease. A 24-week, multicenter, double-blind, placebo-controlled study in Japan. E2020 Study Group. Dement Geriatr Cogn Disord 2000;11: 299-313.

42. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornberg J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994; 44:2308-14.

43. Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Möller HJ, Rogers SL, Friedhoff LT. The effects of donepezil in Alzheimer's disease – results from a multinational trial. Dement Geriatr Cogn Disord 1999;10:237-44.

44. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. BMJ 2000;321:1445-9.

45. Tariot PN, Solomon P, MOrris JC, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomised, placebo-controlled trial of galantamine in AD. Neurology 2000;54:2269-76.

46. Raskind MA, Peskind E, Wessel T, Yuan W. Galantamine in AD. A 6-month randomised, placebo-controlled trial with a 6-month extension. Neurology 2000;54:2261-8.

47. Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, Wetterholm AL, Zhang R, Haglund A, Subbiah P. A 1-year, randomised, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001;57:489-95.

48. Mohs RC, Doody R, Morris JC, Ieni JR, Rogers SL, Perdomo CA, Pratt RD. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001;57:481-8.

49. Unpublished I and II. Study trial numbers B304 and 351.

50. Corey-Bloom J, Anand R, Veach J. A randomised trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. Int J Ger Psychopharmacol 1998;1:55-65.

51. Schneider LS, Anand R, Farlow MR. Systematic review of the efficacy of rivastigmine for patients with Alzheimer's disease. Int J Ger Psychopharmacol 1998;1(suppl 1):S26-S34.

52. Feldman H, Gauthier S, Hecker J, Vellas B, Emir B, Mastey V, Subbiah P, Donepezil MSAD Study Investigators Group. Efficacy of donepezil on maintenance of activities of daily living in patients with moderate to severe Alzheimer's disease and the effect on caregiver burden. J Am Geriatr Soc 2003;51:737-44.

53. Gauthier S, Feldman H, Hecker J, Vellas B, Ames D, Subbiah P, Whalen E, Emir B, Donepezil MSAD Study Investigators Group. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. Int Psychogeriatr 2002;14:389-404.

54. Potkin SG, Anand R, Hartman R, Veach J, Grossberg G. Impact of Alzheimer's disease and rivastigmine treatment on activities of daily living over the course of mild to moderately severe disease. Prog Neuropsychopharm Biol Psychiatry 2002;26:713-20.

55. Doraiswamy PM, Krishnan K, Anand R, Sohn H, Danyluk J, Hartman RD, Veach J. Long-term effects of rivastigmine in moderately severe Alzheimer's disease – does early initiation of therapy offer sustained benefits? Prog Neuropsychopharm Biol Psychiatry 2002;26:705-12.

56. Rockwood K, Graham J, Fay S. Goal setting and attainment in Alzheimer's disease patients treated with donepezil. J Neurol Neurosurg Psychiatry 2002; 73:500-7.

57. Greenberg SM, Tennis M, Brown LB, Gomez-Isla T, Hayden DL, Schoenfeld DA, Walsh KL, et al. Donepezil therapy in clinical practice: a randomised crossover study. Arch Neurol 2000;57:94-9.

58. McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, Cicin-Sain A, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet 2000;356:2031-6.

59. Farlow MR, Hake A, Messina J, Hartman R, Veach J, Anand R. Response

of patients with Alzheimer disease to rivastigmine treatment is predicted by the rate of disease progression. Arch Neurol 2001;58:417-22.

60. Erkinjuntti T, Skoog I, Lane R, Andrews C. Rivastigmine in patients with Alzheimer's disease and concurrent hypertension. Int J Clin Pract 2002;56:791-6.

61. Kumar V, Anand R, Messina J, Hartman R, Veach J. An efficacy and safety analysis of Exelon in Alzheimer's disease patients with concurrent vascular risk factors. Eur J Neurol 2000;7:159-69.

62. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet 2002; 359:1283-90.

63. Potkin SG, Anand R, Fleming K, Alva G, Keator D, Carreon D, Messina J, et al. Brain metabolic and clinical effects of rivastigmine in Alzheimer's disease. Int J Neuropsychopharmacol 2001;4:223-30.

64. Hanyu H, Shimizu T, Tanaka Y, Takasaki M, Koizumi K, Abe K. Regional cerebral blood flow patterns and response to donepezil treatment in patients with Alzheimer's disease. Dement Geriatr Cogn Disord 2003;15:177-82.

65. Mega SM, Dinoz I, Lee L, O'Connor SM, Masterman DM, Wilen B, Mishkin F, et al. Orbital and dorsolateral frontal perfusion defect associated with behavioral response to cholinesterase inhibitor therapy in Alzheimer's disease. J Neuropsychiatry Clin Neurosci 2000;12:209-18.

66. Möbius HJ, Stöffler A. New approaches to clinical trials in vascular dementia: Memantine in small vessel disease. Cerebrovasc Dis 2002;13(suppl 2):61-6.

67. Wilkinson D, Doody R, Helme R, Taubman K, Mintzer J, Kertesz A, Pratt RD, the Donepezil 308 Study Group. Donepezil in vascular dementia. A randomised, placebo-controlled trial. Neurology 2003;61:479-86.

68. Black S, Roman G, Geldmacher DS, Salloway S, Hecker J, Burns A, Perdomo C, et al. Efficacy and tolerability of donepezil in vascular dementia. Positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. Stroke 2003;34:2323-32.

69. Pratt RD, Perdomo C. Donepezil-treated patients with probable vascular dementia demonstrate cognitive benefits. Ann N Y Acad Sci 2002;977:513-22.

70. Wesnes KA, McKeith I, Ferrara R, Emre M, Del Ser T, Spano PF, Cicin-Sain A, et al. Effects of rivastigmine on cognitive function in dementia with lewy bodies: a randomised placebo-controlled international study using the cognitive drug research computerised assessment system. Dement Geriatr Cogn Disord 2002;13:183-92.

71. Aarsland D, Laake K, Larsen JP, Janvin C. Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study. J Neurol Neurosurg Psychiatry 2002;72:708-12.

72. Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, et al. Rivastigmine for dementia associated

with Parkinson's disease. N Engl J Med 2004;351:2509-18.

73. Litvan I, Phipps M, Pharr VL, Hallett M, Grafman J, Salazar A. Randomised placebo-controlled trial of donepezil in patients with progressive supranuclear palsy. Neurology 2001;57:467-73.

74. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Frontotemporal dementia: paroxetine as a possible treatment of behavioral symptoms. A randomised, controlled, open 14-month study. Eur Neurol 2003;49:13-9.

75. Prasher VP, Huxley A, Haque MS. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Down syndrome and Alzheimer's disease – pilot study. Int J Geriatr Psychiatry 2002;17:270-8.

76. Lott IT, Osann K, Doran E, Nelson L. Down syndrome and Alzheimer disease: response to donepezil. Arch Neurol 2002;59:1133-6.

77. Rogers SL, Doody R, Mohs RC, Friedhoff LT. Donepezil improves cognition and global function in Alzheimer disease: 12-week, double-blind, placebo-controlled study. Arch Intern Med 1998; 158:1021-31.

78. Agid Y, Dubois B, Anand R, Gharabawi G. Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. Current Therapeutic Res 1998;59:837-44.

79. Anand R, Gharabawi G, Enz A. Efficacy and safety results of the early phase studies with Exelon (ENA-713) in Alzheimer's disease: an overview. J Drug Dev Clin Pract 1996;8:109-16.

80. Kewitz H, Berzewski H, Rainer M, Dal-Bianco P, Friedl E, Deisenhammer J, et al. Galantamine, a selective non-toxic acetylcholinesterase inhibitor is significantly superior over placebo in treatment of SDAT. Neuropsychopharmacology 1994;10(3S):130S.

81. Wilkinson D, Murray J. Galantamine: a randomised, double-blind, dose comparison in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2001;16:852-7.

82. Unpublished. Study trial reference GAL-95-05.

83. Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D. Effects of a flexible galantamine dose in Alzheimer's disease: a randomised controlled trial. J Neurol Neurosurg Psychiatry 2001;71:589-95.

84. Gortelmeyer R, Erbler H. Memantine in the treatment of mild to moderate dementia syndrome. A double-blind placebo-controlled study. Arzneimittelforschung 1992;42:904-13.

85. Pantev M, Ritter R, Gortelmeyer R. Clinical and behavioral evaluation in long-term care patients with mild to moderate dementia under memantine treatment. Zeitschrift fuer Gerontopsychologie und Psychiatrie 1993;6:103-17.

86. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet 2002;359:1283-90.

23. **Hypertension and Dementia**

Conclusions

There is moderately strong evidence that blood pressure lowering treatment prevents stroke-associated cognitive decline and dementia in patients who have had a stroke.

There is insufficient evidence that antihypertensive treatment protects patients from non-stroke associated cognitive decline.

Background

Hypertension is the leading risk factor for stroke, and dementia due to cerebrovascular causes (VaD and AD + CVD) is common. Several population-based longitudinal studies have shown a relationship between hypertension and increased risk of dementia [1] and impaired cognitive function later in life [2]. High blood pressure is also linked to both stroke-related dementia and late-onset AD (LOAD) [1].

Search of literature

Medline (1970–July 1, 2004) was searched for RCTs addressing "hypertension and dementia" or "blood pressure and dementia" (57 hits) and "hypertension and cognitive function" or "blood pressure and cognitive function" (142 hits), most of which did not deal with this issue. Below are the results of all relevant studies that lasted at least 1 year and met the quality criteria.

Results

Early studies focused on possible side-effects on cognition due to blood pressure lowering agents. The Systolic Hypertension in the Elderly Program (SHEP) did not show a difference between the treatment and placebo groups after 1 year [3]. A substudy of the MRC's trial of hypertension in older adults did not find a difference in performance on cognitive tests between patients treated with diuretics or beta blockers and placebo after a mean of 54 months [4].

The Systolic Hypertension in Europe (Syst-Eur) trial randomised patients with very high systolic blood pressure (160–219 mm Hg) to placebo or antihypertensive treatment [5]. The study ended after only 2 years due to favorable effects in the active group with respect to mortality and prevention of vascular endpoints. The initial report showed incident all-cause dementia to be lower in the active treatment group (11) than the placebo group (21, p = 0.05) [5]. When patients were followed for 2 years after the end of double-blind treatment, antihypertensive treatment of 1 000 patients turned out to have prevented 20 cases of dementia (95% CI 7–33) [6].

The Perindopril Protection Against Recurrent Stroke (PROGRESS) Study randomised 6 105 patients with normal or high blood pressure, with or without treatment, with prior stroke or transient ischemic attack to either placebo or treatment with an ACE inhibitor +/– diuretics (indapamide) [7]. The population was followed over a mean of 3.9 years. Neither incident dementia from any cause nor cognitive decline (measured by MMSE) differed between the treatment groups (dementia was found in 6.3% of the active group and 7.1% of the placebo group). But even in patients with normal blood pressure at the outset, active treatment lowered the risk of recurrent stroke. Furthermore, the risk of dementia associated with recurrent stroke decreased by 34% (95% CI 3–55%), and the risk of stroke-associated cognitive decline decreased by 45% (95% CI 21%–61%) in the group that received perindopril +/– indapamide.

The Study on Cognition and Prognosis in the Elderly (SCOPE) compared the angiotensin II receptor blocker candesartan cilexitil with placebo in terms of reducing the risk of vascular events, cognitive decline, and dementia in elderly patients with borderline hypertension [8]. A total of 4 964 patients were randomised, but the protocol was changed after the study had started. As a result, most of the "placebo" patients were actually treated with blood pressure lowering agents. After a mean follow-up time of 3.7 years, neither MMSE scores nor incident cognitive decline and dementia differed between the treatment groups.

A small RCT (n = 69) found that hypertensive patients allocated to losartan treatment performed significantly better on the MMSE and SCAG than those who were treated with hydrochlorothiazide [9].

A pilot study randomised 72 elderly patients treated for hypertension who had evidence of leukoaraiosis on CT to treatment with nicergoline or placebo [10]. After 24 months, the performance of nicergoline patients on several cognitive tests had improved, or deteriorated less, than placebo patients.

Need for research

Large, long-term (several years) treatment studies focusing on patients at high risk are needed to examine the protection offered by antihypertensive treatment from non-stroke associated cognitive decline. Such studies must deal with the problem of premature discontinuation and non-compliance among those in whom cognition deteriorates.

References

1. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson L. 15 year longitudinal study of blood pressure and dementia. Lancet 1996;347:1141-5.

2. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. Hypertension 1998;31:780-6.

3. Gurland BJ, Teresi J, Smith WM, Black D, Hughes G, Edlavitch S. Effects of treatment for isolated systolic hypertension and depression in the elderly. J Am Geriatr Soc 1988;36:1015-22.

4. Prince MJ, Bird AS, Blizard RA, Mann AH. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults. BMJ 1996;312: 801-5.

5. Forette F, Seux ML, Staessen JA, Thijs L, Birkenhager WH, Babarskiene MR, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998;352:1347-51.

6. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe study. Arch Intern Med 2002;162:2046-52.

7. Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J. Effects of blood pressure lowering with perindopril and indapamide treatment on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003;163: 1069-75.

8. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 2003;21:875-86.

9. Tedesco MA, Ratti G, Mennella S, Manzo G, Grieco M, Rainone AC, Iarussi D, Iacono A. Comparison of losartan and hydrochlorothiazide on cognitive function and quality of life in hypertensive patients. Am J Hypertens 1999;12:1130-4.

10. Bes A, Orgogozo JM, Poncet M, Rancurel G, Weber M, Bertholom N, Calvez R, Stehle B., A 24-month, double-blind, placebo-controlled multicenter pilot study of the efficacy and safety of nicergoline 60 mg per day in elderly hypertensive patients with leukoaraiosis. Eur J Neurol 1999;6:313-22.

24. **Treatment of Depression in Dementia**

Conclusions

Depressive symptoms are frequent in dementia. Studies of depression in dementia have primarily focused on mild to moderate dementia. The research on the treatment of depression in patients with severe dementia is inconclusive.

There is limited evidence that SSRIs are tolerated well and are effective in mild to moderate dementia (Evidence Grade 3).

Tricyclic antidepressants have shown conflicting results, and there is only limited evidence for an effect on depressive symptoms in dementia (Evidence Grade 3).

Tricyclic antidepressants produce prominent side-effects, including reduced cognitive functions, in dementia (Evidence Grade 3).

There is limited evidence that serotonin-active antidepressants reduce behavioral symptoms in dementia (Evidence Grade 3).

Background

Depressive symptoms are common in dementia. According to Wragg et al, the reported frequency has varied among different investigations from 0–87%, with a mean of 30–40% [1]. Lyketsos et al studied minor depression, as well as major depression in AD, and found that 51% of the patients showed no signs of depression, 27% had minor depression and 22% had major depressive disorder [2]. Signs of depression are more frequent in VaD than AD [3]. Depression in dementia often includes symptoms of

anxiety, creating an anxiety/depressive state [4]. Given that depressive symptoms are so frequent, it is debated if they should be regarded as part of the dementia syndrome or a superimposed disorder [5].

Search strategy

Medline was searched for RCT by combining either "dementia" or "Alzheimer's disease" with the MeSH term "antidepressive agents". "Dementia" or "Alzheimer's disease" was also searched in combination with the antidepressives citalopram, fluoxetine, fluvoxamine, mirtazapine, reboxetine and trazodone. Review articles and studies concerning treatment of depression in the elderly were searched for subgroups of patients with dementia. Although the cutoff date was July 2004, later studies were also included if regarded as important for conclusions made.

Search results

Twentytwo studies were identified, of which one had been published twice. The majority of the studies concerned effects on depressive symptoms in dementia. A few studies concerned effects on other non-cognitive symptoms or behavioral aspects in dementia.

Most studies were assessed as having limited quality, and a few were considered to have moderately high quality. Treatment of depression in dementia is complex, given that the dementia diagnosis, degree of cognitive decline, depression diagnosis and severity of depressive symptoms must be considered. Thus, even well-designed studies might not be of high quality.

Effects of antidepressants on depression in dementia

The majority of studies concerning antidepressant treatment of the cognitively impaired elderly were on patients with mild or mild to moderate dementia. Only one study was on patients with severe dementia.

Reifler et al conducted the first study of depression in dementia using a relatively low dose of imipramine [6]. However, both groups improved identically, demonstrating a major placebo response and no further effect of imipramine. Petracca et al also found a high placebo response [7]. Tricyclic antidepressants have had conflicting results when it comes to the treatment of depression in dementia. Reifler et al reported no effect from imipramine [6], and Fuchs et al found no effect from maprotiline, a similar drug [8]. Branconnier et al found positive effects of amitriptyline [9,10] and Petracca et al found positive effects from clomipramine in comparison with placebo [7]. Although all these studies used a low dose of tricyclic antidepressants, side-effects with reduced cognitive functions [7,9,11] and delirium [7] were prominent.

Sertraline was superior to placebo [13,14] while citalopram was more effective than placebo in a subgroup with dementia [12]. Moclobemide was also found to be superior to placebo [15]. A comparison of fluoxetine and placebo did not find any differences but reported an unusually large placebo response [16]. One study found no effect from sertraline in depressive nursing home patients [17]. The included patients had severe dementia, and the ratings were difficult to perform in this population.

No difference was reported among the various antidepressants that have been studied in the treatment of depression in dementia. Amitriptyline did not differ from mianserin but induced more cognitive problems [9]. Imipramine had the same effect on depression as paroxetine but reduced cognitive functions more [18]. Low dose amitriptyline did not differ from fluoxetine in terms of antidepressive response [11]. Citalopram and mianserine were compared with the inclusion of a subgroup with dementia, but no difference of effect was seen [19].

Roth et al reported improvement of cognitive functions concomitant with reduced degree of depression [15]. Two other studies found similar effects [11,20]. However, Lyketsos et al found no difference in cognitive functions when depressive symptoms improved in the patients with dementia [21]. Citalopram did not have any influence on cognitive functions in patients with dementia with no diagnose of depression [22]. Steinberg et al studied psychological symptoms at baseline but found no correlation to response to sertraline [23]. Lanctot et al found that aggression, female gender and serotonin function correlated with response to sertraline [24].

Effects of antidepressants on non-depressive symptoms

Treatment with citalopram significantly reduced anxiety, fear, panic, depressive symptoms, restlessness and symptoms of confusion [22]. Olafsson et al found no such improvement from fluvoxamine compared to placebo in patients with dementia but not depression [25]. Finkel et al studied patients with AD who were treated with donepezil [26]. The addition of sertraline reduced behavioral symptoms compared with placebo. Trazodone has been compared with haloperidol for the treatment of behavioral symptoms in dementia. Neither Sultzer et al [27,28] nor Teri et al [29] found any difference. Effects in the latter study were no different from placebo.

Lyketsos et al found depressive symptoms to be closely associated with aggressive behavior [30]. Antidepressants have been tried for the management of behavioral symptoms. Although fluvoxamine significantly improved the effects on psychotic symptoms in dementia compared with placebo, the study was very small [31]. Both groups were treated with perphenazine 12 mg. Sultzer et al found 50–250 mg of trazodone to be as effective as haloperidol 1–5 mg for agitated behavior and produced fewer side-effects [27]. A subsequent article by them reported that mild to moderate depressive symptoms were associated with greater behavioral improvement from trazodone.

Table 24.1 *Treatment of depression in dementia.*

Author Year, reference	Type of study	Setting	Dementia and depression Diagnosis	Severity of dementia	Patients (n) included (attrition)
Branconnier et al 1981, 1982 [9,10] Double publication	RCT	Outpatient	Testing HAM-D (17) >14	"Light cognitive disturbance"	75
Finkel et al 2004 [26]	RCT	Outpatient	NINCDS NPI >5	MMSE = 8–23	244
Fuchs et al 1993 [8]	RCT	Hospital	Alzheimer's disease and major depression disorder according to DSM-III	Light-moderate	120
Karlsson et al 2000 [19]	RCT	In- and outpatients	Dementia and MDD or dysthymia according to DSM-III-R	Light-moderate	53 demented of 336 in the study
Katona et al 1998 [18]	RCT	In- and outpatients	Dementia according to DSM-III-R. Major or minor depression according to research criteria	Light	198
Lanctôt et al 2002 [24]	RCT Crossover	Nursing home	NINCDS Dementia according to DSM-IV	Severe	22

Age-groups Mean, SD/ range	Study period	Inter-vention (end)	Primary outcome	Effects (end)	Remarks from reviewer	Qua-lity of study
68 Range 60–85	7 w	Amitripty-line 150 mg Mianserin 60 mg Placebo	Zung	Amitriptyline = mianserine > placebo	Amitriptyline reduced cogni-tive functions	1
76.3 SD = 7.6	12 w	Sertraline 50–150 mg + donepezil 10 mg Placebo + donepezil 10 mg	NPI CGI-I CGI-S	Sertraline + donepezil > placebo + donepazil	Study of behavioral symptoms in dementia	2
80 Range 48–96	8 w	Maprotiline 75 mg Placebo	Videorating	No difference		1
75 Range 64–95	12 w	Citalopram 20–40 mg Mianserine 30–60 mg	MADRS	No difference	Demented subgroup	2
77 Range 59–98	8 w	Paroxetine 20–40 mg Imipramine 50–100 mg	MADRS	No difference		2
82.4 Range 74–95	2 x 4 w	Sertraline 100 mg Placebo	NPI	Aggression, female gender and serotonine function asso-ciated with response	Study of markers for response only	2

The table continues on the next page

Table 24.1 *continued*

Author Year, reference	Type of study	Setting	Dementia and depression Diagnosis	Severity of dementia	Patients (n) included (attrition)
Levkovitz et al 2001 [31]	RCT	Outpatients	NINCDS BPRS ≥18	Not mentioned	20
Lyketsos et al 2000 [13]	RCT	Outpatients	NINCDS Major depression disorder according to DSM-IV	Light-moderate	22
Lyketsos et al 2003 [21]	RCT	Outpatients	NINCDS Major depression disorder according to DSM-IV	Light-moderate	44
Magai et al 2000 [17]	RCT	Nursing home	NINCDS Minor or major depression according to DSM-IV	Severe	31
Nyth et al 1990 [22]	RCT	In- and outpatients	Dementia according to DSM-III-R	Moderate	98
Nyth et al 1992 [20]	RCT	In- and outpatients	"Mild and moderate dementia" HDRS ≥14	Mild-moderate	29 demented of 149 in the study

Age-groups Mean, SD/ range	Study period	Inter-vention (end)	Primary outcome	Effects (end)	Remarks from reviewer	Qua-lity of study
78.1 Range 65–93	3 w	Perphena-cine 12 mg + fluvoxamine 50 mg Perphena-cine 12 mg + placebo	BPRS	Fluvoxamine-group, fewer psychotic symptoms	Pilot study	1
77 SD = 8.4	12 w	Sertraline 50–150 mg Placebo	Cornell	Sertraline > placebo	Preliminary study	1
79 SD = 5.2 76 SD = 9.5	12 w	Sertraline 50–150 mg Placebo	Cornell	Sertraline > placebo	No improve-ment of cogni-tive functions of treatment	2
89 SD = 6.3	8 w	Sertraline 100 mg Placebo	Cornell	No difference	Severely demented patients, uncertain testing	1
	4 w	Citalopram 10–30 mg Placebo	Gottfries-Bråne-Steen-rating scale	Reduced anxiety/ depression and irritabi-lity. No effect on cognitive functions	Study of citalopram in non-depres-sive dementia	1
76.7 Range 65–91	6 w	Citalopram 20–30 mg Placebo	MADRS	Citalopram > placebo	Improvement of cognitive functions con-comitant with antidepressive effect	1

The table continues on the next page

Table 24.1 *continued*

Author Year, reference	Type of study	Setting	Dementia and depression Diagnosis	Severity of dementia	Patients (n) included (attrition)
Olafsson et al 1992 [25]	RCT		AD or multi infarct dementia according to DSM-III		46
Petracca et al 1996 [7]	RCT	Outpatients	Alzheimer's disease and major depr disorder according to DSM-III-R	Mild	21
Petracca et al 2001 [16]	RCT	Outpatients	NINCDS Major or minor depr disorder according to DSM-IV	Mild	41
Pollock et al 2002 [32]	RCT	Hospital	Dementia according to DSM-IV	Severe-moderate	85
Reifler et al 1989 [6]	RCT	Outpatients	Alzheimer's disease and major depr disorder according to DSM-III	Mild-moderate	28
Steinberg et al 2004 [23]	RCT	Outpatients	NINDCS MDD according to DSM-IV	Light-moderate	44
Sultzer et al 1997 [27]	RCT	Gero-psychiatric inpatients	"Dementia and aggression or agitation"	MMSE = 11.0 SD = 7.0	28

Age-groups Mean, SD/ range	Study period	Inter-vention (end)	Primary outcome	Effects (end)	Remarks from reviewer	Qua-lity of study
81 Range 65–93	6 w	Fluvoxamine 150 mg Placebo	Gottfries-Bråne-Steen-rating scale	Fluvoxamine = placebo	Study of fluvoxamine on behavioral symptoms	1
72 SD = 7.2	6 w	Clomipramine 100 mg Placebo	HAM-D	Clomipramine > placebo	10/18 showed delirium in clomipramine group	1
71 SD = 6.6	6 w	Fluoxetine 40 mg Placebo	HAM-D	No difference	Great placebo response	1
80.1 SD = 8.1	17 d	Perphenazine M = 6.5 mg Citalopram 20 mg Placebo	Neurobehav rating scale	Citalopram > perphenazine. Citalopram > placebo. Perphenazine > placebo	High discontinuation rate	1
72 SD = 8	8 w	Imipramine M = 83 mg/day Placebo	HAM-D	No difference	Great placebo response	1
77.3	12 w	Sertraline 50–150 mg Placebo	Cornell Neuropsychological testing	No baseline symptom correlated with response	More responders in sertraline group	1
72.3 SD = 6.9	9 w	Haloperidol M = 2.5 mg Trazodone M = 218 mg	CMAT	No difference in effect	Haloperidol more side-effects	1

The table continues on the next page

***Table 24.1** continued*

Author Year, reference	Type of study	Setting	Dementia and depression Diagnosis	Severity of dementia	Patients (n) included (attrition)
Sultzer et al 2001 [28]	RCT	Gero-psychiatric inpatients	"Dementia and aggression or agitation"	MMSE = 11.0 SD = 7.0	28
Roth et al 1996 [15]	RCT	Outpatients	Dementia according to DSM-III or "cognitive decline" and major depressive episode according to DSM-III	Mild-moderate	694
Taragano et al 1997 [11]	RCT	Outpatients	NINCDS Major depression disorder according to DSM-III	Mild	37
Teri et al 2000 [29]	RCT	Outpatients	AD according to NINCDS	Moderate-light	149

AD = Alzheimer's disease; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression Scale; CMAI = Cohen-Mansfield Agitation Inventory; DSM = Diagnostic and Statistical Manual; HAM-D = Hamilton Rating Scale for Depression; HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery Åsberg Depression Rating Scale; MDD = Major depressive disorder; MMSE = Mini-mental state examination; NINCDS = National institute of neurological and communicable diseases; NPI = Neuropsychiatric inventory; RCT = Randomised controlled trial; SD = Standard deviation

Age-groups Mean, SD/ range	Study period	Inter-vention (end)	Primary outcome	Effects (end)	Remarks from reviewer	Quality of study
72.3 SD = 6.9	9 w	Trazodone 50–150 mg Haloperidol 1–5 mg	CMAI	Trazodone response related slight depressive symptoms	Same data as Sultzer et al 1997 [27]	1
60–98 M = 78	7 w	Moclobemi-de 400 mg Placebo	HAM-D	Moclobemide > placebo	Improvement of cognitive functions con-comitant with antidepressive effect	1
72 SD = 5	9 w	Amitripty-line 25 mg Fluoxetine 10 mg	HAM-D	No difference	High drop-out level (59% in amitriptyline group) Cognitive improvement	1
74.9 SD = 7.0	16 w	Haloperidol M = 1.8 mg Trazodone M = 200 mg Behavior management techniques Placebo	CGI	No diffe-rence between groups	High drop-out level	1

References

1. Wragg RW, Jeste DV. Overview of depression and psychosis in Alzheimer's disease. Am J Psychiatry 1989;146:577-87.

2. Lyketsos CG, Steele C, Baker L, Galik E, Kopunek S, Steinberg M, et al. Major and minor depression in Alzheimer's disease: prevalence and impact. J Neuropsychiatry Clin Neurosci 1997; 9:556-61.

3. Rao R. Cerebrovascular disease and late life depression: an age old association revisited. Int J Geriatr Psychiatry 2000;15:419-33.

4. Weiss KJ. Management of anxiety and depression syndromes in the elderly. J Clin Psychiatry 1994;55 Suppl:5-12.

5. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Depression and Alzheimer's disease: symptom or comorbidity? Am J Alzheimers Dis Other Demen 2002;17:338-44.

6. Reifler BV, Teri L, Raskind M, Veith R, Barnes R, White E, et al. Double-blind trial of imipramine in Alzheimer's disease with and without depression. Am J Psychiatry 1989;156:45-9.

7. Petracca G, Tesón A, Chemerinski E, Leiguarda R, Starkstein SE. A double-blind placebo-controlled study of clomipramine in depressed patients with Alzheimer's disease. J Neuropsychiatry Clin Neurosci 1996;8:270-5.

8. Fuchs A, Hehnke U, Schell C, Pramsholder B, Danninger B, Schautzer F. Videorating analysis of effect of maprotiline in patients with dementia and depression. Pharmacopsychiat 1993;26:37-41.

9. Branconnier RJ, Cole JO, Ghazvinian S. The Therapeutic profile of mianserin in mild elderly depressives. Psychopharmacol Bull 1981;17:129-31.

10. Branconnier RJ, Cole JO, Ghazvinian S, Rosenthal S. Treating the depressed elderly patient: the comparative behavioral pharmacology of mianserin and amitriptyline. In: Costa E, Racagni G, editors. Typical and Atypical Antidepressants: Clinical Practice. New York: Raven Press; 1982.

11. Taragano FE, Lyketos CG, Mangone CA, Allegri RF, Comesana-Diaz E. A double-blind, randomised, fixed-dose trial of fluoxetine vs. amitriptyline in the treatment of major depression complicating Alzheimer's disease. Psychosomatics 1997;38:246-52.

12. Gottfries CG, Karlsson I, Nyth AL. Treatment of depression in elderly with and without dementia disorder. Int Clin Psychopharmacol 1992;6:55-64.

13. Lyketsos CG, Sheppard JM, Steele CD, Kopunek S, Steinberg M, Baker AS, et al. Randomised, placebo-controlled, double-blind clinical trial of sertraline in the treatment of depression complicating Alzheimer's disease: initial results from the Depression in Alzheimer's Disease study. Am J Psychiatry 2000;157:1686-9.

14. Charney DS, Reynolds CF, 3rd, Lewis L, Lebowitz BD, Sunderland T,

Alexopoulos GS, et al. Depression and Bipolar Support Alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in late life. Arch Gen Psychiatry 2003;60:664-72.

15. Roth M, Mountjoy CQ, Amerin R, Group TICS. Moclobemide in elderly patients with cognitive decline and depression: an international double-blind placebo-controlled trial. Br J Psychiatry 1996;168:149-7.

16. Petracca GM, Chemerinski E, Starkstein SE. A double-blind, placebo-controlled study of fluoxetine in depressed patients with Alzheimer's disease. Int Psychogeriatr 2001;13:233-40.

17. Magai C, Kennedy G, Cohen CI, Gomberg D. A controlled clinical trial of sertraline in the treatment of depression in nursing home patients with late-stage Alzheimer's disease. Am J Geriatr Psychiatry 2000;8:66-74.

18. Katona CLE, Hunter BN, Bray J. A double-blind comparison of the efficacy and safety of paroxetine and imipramine in the treatment of depression with dementia. Int J Geriatr Psychiatry 1998;13:100-8.

19. Karlsson I, Godderis J, Augusto De Mendonca Lima C, Nygaard H, Simanyi M, Taal M, et al. A randomised, double-blind comparison of the efficacy and safety of citalopram compared to mianserin in elderly, depressed patients with or without mild to moderate dementia. Int J Geriatr Psychiatry 2000;15:295-305.

20. Nyth AL, Gottfries CG, et al. A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. Acta Psychiatrica Scandinavica 1992;86:138-45.

21. Lyketsos CG, DelCampo L, Steinberg M, Miles Q, Steele CD, Munro C, et al. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. Arch Gen Psychiatry 2003;60:737-46.

22. Nyth AL, Gottfries CG. The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. a Nordic Multicentre study. Br J Psychiatry 1990;157:894-901.

23. Steinberg M, Munro CA, Samus Q, V Rabins P, Brandt J, Lyketsos CG. Patient predictors of response to treatment of depression in Alzheimer's disease: the DIADS study. Int J Geriatr Psychiatry 2004;19:144-50.

24. Lanctôt KL, Herrmann N, van Reekum R, Eryavec G, Naranjo CA. Gender, aggression and serotonergic function are associated with response to sertraline for behavioral disturbances in Alzheimer's disease. Int J Geriatr Psychiatry 2002;17: 531-41.

25. Olafsson K, Jørgensen S, Jensen HV, Bille A, Arup P, Andersen J. Fluvoxamine in the treatment of demented elderly patients: a double-blind, placebo-controlled study. Acta Psychiatr Scand 1992;85: 453-6.

26. Finkel SI, Mintzer JE, Dysken M, Krishnan KR, Burt T, McRae T. A randomised, placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated

with donepezil. Int J Geriatr Psychiatry 2004;19:9-18.

27. Sultzer DL, Gray KF, Gunay I, Berisford MA, Mahler ME. A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. Am J Geriatr Psychiatry 1997;5:60-9.

28. Sultzer DL, Gray KF, Gunay I, Wheatley MV, Mahler ME. Does behavioral improvement with haloperidol or trazodone treatment depend on psychosis or mood symptoms in patients with dementia? J Am Geriatr Soc 2001;49: 1294-300.

29. Teri L, Logsdon RG, Peskind E, Raskind M, Weiner MF, Tractenberg RE, et al. Treatment of agitation in AD: a randomised, placebo-controlled clinical trial. Neurology 2000;55:1271-8.

30. Lyketsos CG, Steele C, Galik E, Rosenblatt A, Steinberg M, Warren A, et al. Physical aggression in dementia patients and its relationship to depression. Am J Psychiatry 1999;156:66-71.

31. Levkovitz Y, Bloch Y, Kaplan D, Diskin A, Abramovitchi I. Fluvoxamine for psychosis in Alzheimer's disease. J Nerv Ment Dis 2001;189:126-9.

32. Pollock BG, Mulsant BH, Rosen J, Sweet RA, Mazumdar S, Bharucha A. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. Am J Psychiatry 2002;159:460-5.

25. **Treatment of Psychotic and Behavioral Symptoms in Dementia**

Conclusions

There is strong evidence of an increased risk of death following atypical antipsychotic drug treatment (Evidence Grade 1).

There was a significant but small effect on behavioral symptoms in dementia from moderate and high doses of traditional antipsychotics (Evidence Grade 3). However, haloperidol up to 1.1 mg did not differ from placebo, while reduction of symptoms was found in doses 1.5 mg and higher.

Moderate and high doses of haloperidol induce clinically relevant extra pyramidal side-effects (Evidence Grade 3).

Low doses of other traditional antipsychotics have not been shown to differ from placebo. Risperidone in doses around 1 mg reduces behavioral symptoms to a small but significant degree, with generally acceptable side-effects. Olanzapine, 5–10 mg reduces psychotic or behavioral symptoms (Evidence Grade 3).

Few RCTs have been published on BPSD with antiepileptic drugs. No evidence of effects can be concluded based on 1 study of medium quality and 4 of low quality.

Although no evidence can be adduced, only carbamazepin had small but significant effects on behavioral symptoms. Valproate and divalproex had no clinical value, while RCTs have not analyzed other antiepileptics for their effect on behavioral and psychological symptoms in dementia.

Background

Cognitive reduction is the most prominent symptom in dementia disorders, but several non-cognitive symptoms are also common. Such symptoms are often problematic for others and may cause considerable stress for caregivers. Although non-cognitive symptoms in dementia have many different aspects, they are collectively described as Behavioral and Psychological Signs and Symptoms of dementia (BPSD) [1]. BPSD includes all significant non-cognitive symptoms of dementia, including aggressiveness, psychotic symptoms, reduced mood, sleep/wakefulness disturbances, wandering or other signs of overactivity. The concept of BPSD is symptomatic and does not include any possible association with a superimposed disease state, such as affective disorder, depression, delirium or psychosis.

The concept of BPSD focuses mainly on biological factors as the cause of disturbing symptoms. Many symptoms develop in a disturbed relation between the patient and others. Reduced cognitive functions often give rise to misunderstanding or misinterpretation by others. Thus, examining the quality of the relation between the patient and others is essential to evaluating and treating BPSD. The concept of BPSD can overestimate the dementia disorder as a cause of behavioral symptoms. Evaluating the separate influence of biological and environmental factors on BPSD is difficult, but strategies for treating BPSD should consider both nursing care and drugs. The section of this report concerning nursing care evaluates the environmental aspects of BPSD. This section is confined to the pharmacological treatment of non-cognitive symptoms in dementia: the effects of antipsychotic treatment for psychotic symptoms and BPSD, the treatment of BPSD with antiepileptics, the treatment of depression in dementia and the treatment of BPSD with antidepressants.

Effects of antipsychotic treatment of psychotic symptoms and BPSD

Psychotic symptoms are common in dementia, with a mean of 34% in a meta-analysis (range 10–73%), but antipsychotic drugs have been mainly used in dementia for the treatment of behavioral symptoms included in the concept of BPSD [2,3].

Search

Medline was searched for the MeSH terms "antipsychotic agents" and dementia or Alzheimer's disease through July 2004. Studies later in 2004 were included only if they provided new information. However, the search strategy failed to identify several studies, mostly old ones. For that reason, "dementia" and "Alzheimer's disease" were combined with the generic name of any single antipsychotic agent that might have been used in patients with dementia. Only RCTs were included. Studies of the elderly who had not been diagnosed as demented were not included.

A total of 34 publications of RCTs with antipsychotic treatment in dementia were identified. Different results from one study appeared in four publications, and two other studies appeared in two publications. Three systematic meta-analyses were found, as well as two Cochrane reviews, one concerning thioridazine and one concerning haloperidol. Seven studies followed the effect of withdrawal from antipsychotic treatment in patients with dementia.

Results

The majority of the studies did not differentiate dementia diagnoses. Some studies included more than one dementia diagnosis, such as AD, VaD or mixed dementia. Eleven studies included AD patients only. Due to the heterogeneity of the studies, the various diagnoses cannot be analyzed separately. The degree of cognitive reduction among the included patients varied from mild to severe dementia. Behavioral symptoms were present in all studies. Sixteen of the studies were rated as moderate qual-

ity and one as acceptable quality. Although several studies were well-designed, a high discontinuation rate reduced their quality. However, a high discontinuation rate is to be expected in this patient group.

Several studies concerned haloperidol. A mean dose of at least 2 mg was superior to placebo, while 0.5–1.8 mg was not [4–10]. Coccaro et al reported a small effect from a mean of 1.5 mg haloperidol [11]. Devanand et al found that the serum concentration of haloperidol predicted effect better than the dose administered [12].

All studies showed more extra pyramidal symptoms (EPS) in haloperidol groups than in placebo groups, and one study reported that 2–3 mg could cause severe extra pyramidal symptoms [7]. Chan et al found EPS in mean as low as 0.9 mg haloperidol [13]. Thus extra pyramidal side-effects are found at doses lower than those reported to reduce agitation, as well as at levels where clinical effects are evident.

Barnes et al did not find more improvement with thioridazine (63 mg) or loxapine (10.5 mg) than in the placebo group [14]. Petrie et al found equal effects of loxatine (21.9 mg) and haloperidol (4.6 mg), significantly better than the placebo group [4]. Carlyle et al found equal effects of haloperidol 7 mg and loxapine 36 mg, but with more side-effects in the haloperidol group [15]. Gutzmann et al found equal effects of tiapride 200 mg and 100 mg melperone [16], while Allain et al found equal effects of 200 mg tiapride and 4 mg haloperidol, both active groups improving more than placebo [5]. Extra pyramidal side-effects were more prominent with haloperidol than with tiapride.

A comparison of risperidone with placebo found significant effects [6,17,18]. Flexible doses were used, and the mean was 1.1 and 0.95 mg respectively [6,18]. DeDeyn et al used fixed doses and found effects of 1 and 2 mg risperidone, while 0.5 mg only showed significant effect on the aggression item at 12 weeks [6]. The same study did not find a significant effect for haloperidol, as opposed to risperidone, on the primary effect variable. A subgroup analysis of patients with psychotic symptoms in a study by Katz [17], Schneider et al found significant effects of 1 and 2 mg risperidone on psychotic symptoms [2]. A study by Meguro et al

on wandering behavior in patients with dementia found 1 mg risperidone to be more effective than placebo [19].

Comparing 5, 10 and 15 mg of olanzapine with placebo in nursing home patients, Street et al found 5 and 10 mg to be superior to placebo, particularly 5 mg [20]. The study was analyzed further. One study found effects on anxiety symptoms [21], a second study showed reduced psychotic symptoms [22], and a third study found effects in a subgroup of patients that met the criteria for Lewy body dementia [23]. Fontaine et al compared olanzapine and risperidone in a two-week study [24]. Both substances were individually adjusted. Similar effects were found with a mean dose of olanzapine 6.65 mg and risperidone 1.47 mg. Meehan et al found 2.5 mg or 5 mg of intramuscular olanzapine superior to 1 mg lorazepam or placebo [25], and the same group published similar data in a study with identical design [26]. A comparison of risperidone and olanzapine by Mulsant et al found no difference in effect or side-effects among comparable doses [27].

Three meta-analyses of antipsychotic treatment in dementia were identified [28–30]. Schneider et al found that treatment with traditional antipsychotics was superior to placebo but that the effect size was small (0.18) – of 100 treated patients, only 18 improved [29]. Lanctot et al found that low-potency, medium-potency, and high-potency antipsychotics had similar therapeutic effects, concluding that antipsychotic treatment had a significant but small positive effect compared to placebo for behavioral symptoms in dementia [28].

Kirchner et al performed a Cochrane review of thioridazine for dementia [31]. They also included old studies. They concluded that thioridazine reduced anxiety but had no significant effect on clinical global change. Side-effects were not systematically analyzed.

Lonergan et al performed a Cochrane review of haloperidol for agitation in dementia [32]. They concluded that there was no significant improvement in agitation among haloperidol patients compared with controls. Aggression was reduced with haloperidol, but other aspects of agitation were not affected.

No meta-analysis has been performed on treatment with atypical antipsychotics in dementia.

Study on withdrawal of antipsychotic treatment in dementia

Ray et al and Thapa et al compared the withdrawal of antipsychotics with control groups in combination with an educational program [33,34]. Both studies concluded that withdrawal had no, or a positive, effect on behavioral symptoms, but their quality was low. Bridget-Parlet et al performed a blind withdrawal and reported no significant effect on behavioral symptoms, except for two patients who had to drop out [35]. A double-blind crossover study of antipsychotic withdrawal in nursing home patients with dementia by Cohn-Mansfield et al observed no significant difference [36]. van Reekum et al reported that a double-blind withdrawal of antipsychotics increased apathetic behavior in the placebo group, while behavioral symptoms became more frequent in the active treatment group [37]. Ballard et al studied withdrawal of antipsychotics over a period of 3 months and found no difference compared with blind continued treatment [38]. The best effect was found in patients with only a few behavioral symptoms. Ruths et al reported that 11 out of the 15 patients in a withdrawal study improved, while 4 exhibited additional symptoms [39].

Treatment of BPSD with antidepressants

Antidepressives were compared with antipsychotics in patients with dementia and behavioral symptoms. Citalopram 20 mg was equivalent to perphenazine 6.5 mg [40]. Trazodone, mean dose 218 mg, had the same effect as haloperidol, mean dose 2.5 mg [41,42], while trazodone 200 mg and haloperidol 1.8 mg [10] were equivalent.

Rate of decline of cognitive symptoms during antipsychotic treatment

McShane et al studied the effect of antipsychotic treatment on the rate of cognitive decline in patients with dementia in nursing homes [43]. They found evidence of a more rapid cognitive decline in patients treated with antipsychotics. However, the group was small and the study design questionable.

Effects of antipsychotics on cerebral vascular events in patients with dementia

Wooltorton et al reported an increase in the rate of cerebral vascular events from 1.2% to 3.3% in patients with dementia who had received risperidone [44]. A similar threefold increase in cerebral vascular events, as well as twice as much mortality, was found for olanzapine in this patient group [45]. Similar data have been reported for aripirazol [46].

Herrmann et al studied the risk of cerebral vascular accidents with atypical antipsychotics in patients older than 66 [47]. No differences between risperidone, olanzapine and older antipsychotics were found. Kozma et al studied the risk of stroke in patients older than 60 who were treated with antipsychotics (n = 1 818), benzodiazepines (n = 2 419) and acetyl cholinesterase inhibitors (n = 8 733) [48]. No difference was found between risperidone and olanzapine, haloperidol or benzodiazepines. A lower risk was found in patients treated with acetyl cholinesterase inhibitors. Gill et al studied the risk of ischemic stroke in 32 710 patients with dementia who had been given antipsychotics [49]. They found no difference between older (traditional) and newer (atypical) antipsychotics. A recently published meta-analysis by Schneider et al found that atypical antipsychotic drugs may be associated with a small increased risk of death compared with placebo [50].

Treatment of BPSD symptoms with antiepileptic drugs

Search

Medline was searched for RCTs with the terms "dementia" and "antiepileptics". Seven studies were identified, of which 2 were open pilot studies [51,52]. Tekin et al studied the effects of lamotrigine on cognitive functions [52]. The terms "phenantoin", "carmabazepine", "valproate", "lamotrigine" and "topiramate" were all searched with "dementia," and additional open studies were identified [53,54].

Results

The study by Tariot et al included 51 patients with dementia and agitation [55]. Over 6 weeks, the mean total BPSD scores decreased by 7.7 points for the carbamazepine group and 0.9 points for the placebo group. The CGI ratings showed a global improvement in 77% of the patients taking carbamazepine and 21% of those taking placebo. The two groups were followed in a withdrawal study, and those who had previously shown behavioral improvement with carbamazepine therapy reverted to their baseline state after washout, whereas there was no change in the patients previously treated with placebo [56]. But a pilot study by Olin et al reported only modest positive effects on a group that had shown no response to antipsychotic treatment [57].

Porsteinsson et al performed a 6-week, randomised study of 56 nursing home patients with agitation and dementia who received either placebo or individualized doses of divalproex [58]. The effects were modest, and side-effects were considerably more common with divalproex. Sival et al found no effect of valproate compared to placebo on aggressive behavior in dementia [54]. A 12-week open follow-up study reported some effect, but 7 of the 39 analyzed patients died [53]. All 4 studies were of limited quality. Lonergan et al published a Cochrane review on the effects of valproate for the treatment of agitation in dementia [59]. They identified

the abovementioned studies, except for the non-placebo controlled study [53]. Their conclusion was that the reviewed trials should be regarded as preliminary. Individual reports suggest that low dose sodium valproate is ineffective in treating agitation among patients with dementia and that high dose divalproex sodium is associated with an unacceptable rate of adverse effects.

Table 25.1 *Treatment of behavioral symptoms with antipsychotic drugs.*

Author Year, reference	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition)	Age-groups Range (SD)
Allain et al 2000 [5]	RCT	Out-patients	Dementia according to DSM-III-R	Moderate-severe	316	79.6 SD 7.6
Auchus et al 1997 [8]	RCT	Out-patients	AD according to NINCDS	Moderate	15	75.7 SD 7.5
Barnes et al 1982 [14]	RCT	Nursing home	Dementia according to DSM-III	Not mentioned	60	>65
Battaglia et al 2003 [26]	RCT	Hospital	AD according to NINCDS	Not mentioned	206	≥55
Brodaty et al 2003 [18]	RCT	Nursing home	AD or vascular dementia according to DSM-IV	Light-severe	337	83.0 SD 0.58
Carlyle et al 1993 [15]	RCT	Hospital	Dementia according to DSM-III-R	Not recorded	40	79 65–91

Study period	Intervention (end)	Primary outcome	Effects (end)	Remarks from reviewer	Quality of study
3 w	Haloperidol 4 mg Tiapride 200 mg Placebo	MOSES	Haloperidol = tiapride > placebo	EPS: Haloperidol > tiapride	1
6 w	Fluoxetine 20 mg Haloperidol 3 mg Placebo	CMAI	No difference between groups	Too small groups. Haloperiol and fluoxetin more side-effects	1
8 w	Thioridazine 62.5 mg Loxapine 10.5 mg Placebo	BPRS	Small improvement in all three groups, no significant difference between groups	Prominent side-effects of active treatment	1
Acute treatment only	Olanzapine 2.5 mg/dose Lorazepam 1 mg/dose Placebo	Doses needed for effect	Olanzapine = lorazepam > placebo	Acutely agitated patients	1
12 w	Risperidone M = 0.95 mg Placebo	CMAI	Risperidone > placebo	Few side-effects	2
4 w	Haloperidol M = 7 mg Loxapine M = 36 mg	CMAI	No difference in effect	More side-effects with haloperiol	1

The table continues on the next page

Table 25.1 *continued*

Author Year, reference	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition)	Age-groups Range (SD)
Chan et al 2001 [13]	RCT	Hospital	AD or vascular dementia according to DSM-IV	Moderate-severe	58	80.5 SD 8.2
Clark et al 2001 [22] (data from Street et al [20])	RCT	Nursing home	AD according to NINCDS. Subgroups without hallucinations or delusions	Severe-moderate	206	82.7 SD 6.6
Coccaro et al 1990 [11]	RCT	Nursing home	Dementia according to DSM-III	Not mentioned	59	75.3 58–99
Cummings et al 2002 [23]	RCT	Nursing home	AD according to NINCDS. Criteria for Lewy body dementia	Light-severe	29	83.9 SD 5.4
De Deyn et al 1999 [6]	RCT	Nursing home	AD or vascular dementia according to DSM-IV	Light-severe	344	81 63–97
De Deyn et al 2004 [60]	RCT	Nursing home	AD according to NINCDS and psychotic symptoms	Light-severe	625	76.6 SD 10.6

Study period	Intervention (end)	Primary outcome	Effects (end)	Remarks from reviewer	Quality of study
12 w	Risperidone M = 0.85 Haloperidol M = 0.9	CMAI	No difference	More side-effects with haloperiol	2
6 w	Olanzapine 5 mg Olanzapine 10 mg Olanzapine 15 mg Placebo	NPI	Olanzapine > placebo	Further analyses of Street et al [20]	
8 w	Haloperidol M = 1.5 mg Oxazepam M = 30 mg Diphenhydramine M = 49 mg	BPRS	Small effects with all three drugs	Side-effects not mentioned	1
6 w	Olanzapine 5, 10 and 15 mg Placebo	NPI-NH	5 and 10 mg > placebo	Subgroup of Street et al [20] with Lewy body dementia	2
12 w	Risperidone M = 1.1 mg Haloperidol M = 1.2 mg Placebo	Behave-AD	Risperidone > placebo Haloperidol = placebo	EPS: Haloperidol > risperidone = placebo	2
10 w	Olanzapine 1, 2.5, 5, and 7.5 mg Placebo	NPI/NH CGI	Olanzapine 2.5, 5, 7.5 mg > olanzapine 1 mg = placebo	Study of effect on psychotic symptoms	2

The table continues on the next page

Table 25.1 *continued*

Author Year, reference	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition)	Age-groups Range (SD)
Devanand et al 1989 [9]	Cross-over with blind rating	Out-patients	AD according to NINCDS	Light-severe	9	Presenile and senile
Devanand et al 1992 [12]	Drug concen-tration Corre-lation	Out-patients	AD according to NINCDS	Not mentioned	19	67.6 SD 9.7
Devanand et al 1998 [7]	RCT + Cross-over	Out-patients	AD according to NINCDS	Severe-moderate	71	72.1 SD 9.6
Gutzmann et al 1997 [16]	RCT	Hospital	Dementia according to DSM-III-R	Light-severe	175	74.8 SD 11.5
Fontaine et al 2003 [24]	RCT	Nursing home	Dementia according to DSM-IV	Severe-moderate	39	83.2 SD 7.6
Frank et al 2004 [61]	RCT	Nursing home	Dementia and behavioral symptoms	Light-severe	279	82.8 SEM 0.7

Study period	Intervention (end)	Primary outcome	Effects (end)	Remarks from reviewer	Quality of study
4 + 8 + 4 w	Haloperidol 4 mg Placebo	BPRS	Haloperidol > placebo	Prominent side-effects	1
6–8 w	Haloperidol 0.5–5 mg	BPRS	Blood level corr better than dose with effect	EPS corr with blood level	1
6 + 6 w	Haloperidol 2–3 mg Haloperidol 0.5–0.75 mg Placebo	BPRS	Haloperidol 2–3 mg > haloperidol 0.5–0.75 mg = placebo	EPS: 2–3 mg > 0.5–0.75 mg = placebo	2
4 w	Tiapride 400 mg Melperone 100 mg	CGI	No difference	No placebo-group	1
2 w	Olanzapine 2.5–10 mg (M = 6.7) Risperidone 0.5–2 mg (M = 1.5)	CGI NPI	No difference	No placebo-group	2
12 w	Risperidone 0.5–2.0 mg Placebo	Modified nursing care assessment scale	Risperidone > placebo	Nursing care burden	2

The table continues on the next page

Table 25.1 *continued*

Author Year, reference	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition)	Age-groups Range (SD)
Katz et al 1999 [17]	RCT	Nursing home	AD or vascular dementia according to DSM-IV	Light-severe	625	82.7 SD 7.7
Katz et al 2004 [62]	RCT	Nursing home	AD or vascular dementia according to DSM-IV	Light-Severe	537	82.7 SD 7.7
Kennedy et al 2001 [63] (Data from Street et al [20])	RCT	Nursing home	AD according to NINCDS	Moderate-severe	206	82.7 61–97
Meguro et al 2004 [19]	RCT	Nursing home	AD according to NINCDS. Wandering or aggressiveness		34	78
Meehan et al 2002 [25]	RCT	Nursing home	AD or vascular dementia according to DSM-IV for AD	Light-severe	272	77.6 SD 9.7
Mintzer et al 2001 [21] (Data from Street et al 2000 [20])	RCT	Nursing home	AD according to NINCDS	Moderate-severe	206	82.7 61–97

Study period	Intervention (end)	Primary outcome	Effects (end)	Remarks from reviewer	Quality of study
12 w	Risperidone fix dose 0.5, 1.0, 2.0 mg, placebo	Behave-AD	Risperidone > placebo	EPS increased with dose	2
12 w	Risperidone fix dose 0.5, 1.0, 2.0 mg, placebo	Rating of falls	Risperidone 1 mg better than placebo. Placebo better than risperidone 2 mg	Subanalysis of Katz et al [17]	2
6 w	Olanzapine 5, 10, 15 mg Placebo	5 items from adverse event list	No significant difference	Not validated efficacy variable	1
1 month	Risperidone 1 mg Placebo	Behave-AD	Risperidone > placebo	Study of wandering behavior	2
Acute treatment	Olanzapine 2.5, 5.0 mg intramuscular, lorazepam 1.0 mg intra muscular and placebo	CMAI	After 24 h: Olanzapine 2.5 and 5 mg = lorazepam > placebo	Short-term effect	1
6 w	Olanzapine 5, 10, 15 mg Placebo	NPI/NH anxiety	Olanzapine 5 mg > placebo Olanzapine 5, 10 mg = placebo	Post-hoc analyses	2

The table continues on the next page

Table 25.1 *continued*

Author Year, reference	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition)	Age-groups Range (SD)
Mulsant et al 2004 [27]	RCT	Long term care	AD, VaD or mixed dementia according to DSM-IV	Light-severe	85	84 range 63–96
Nygaard et al 1994 [64]	RCT	Nursing home	Clinical dementia rating scale	Light-severe	73	83 70– >90
Pelton et al 2003 [65]	RCT	Out-patients	AD according to NINCDS	Severe-moderate	71	72.1 SD 9.6
Petrie et al 1982 [4]	RCT	Hospital	Dementia according to DSM-III	Severe-moderate	61	72.7 SD 7.0
Pollock et al 2002 [40]	RCT	Hospital	Dementia according to DSM-IV	Severe-moderate	85	80.1 SD 8.1
Schneider et al 2003 [2]	RCT	Nursing home	AD or vascular dementia according to DSM-IV and psychotic symptoms	Light-severe		

Study period	Intervention (end)	Primary outcome	Effects (end)	Remarks from reviewer	Quality of study
6 w	Risperidone 0.75–1.5 mg Olanzapine 5–10 mg	UKU NPI	No difference in side-effects or behavioral symptoms	Anticholinergic effects seen with olanzapine	1
4 w	Zuclopentixol 2.0, 4, 6 and 4–20 mg	CGI illness	All groups improved		1
6 w	Haloperidol 2–3 mg Haloperidol 0.5–0.75 mg Placebo	BPRS	Serum level of haloperidol correlated with effect	Same material as Devanand et al [7]	2
8 w	Haloperidol M = 4.6 mg Loxepine M = 21.9 mg Placebo	BPRS	Haloperidol = loxapine > placebo	45% EPS in both active groups	1
17 d	Perphenazine M = 6.5 mg Citalopram 20 mg Placebo	Neurobehav rating scale	Citalopram > perphenazine Citalopram > placebo Perphenazine > placebo	High discontinuation rate	1
12 w	Risperidone fix dose 0.5, 1.0, 2.0 mg Placebo	Behave-AD	Risperidone 1 and 2 mg > placebo	Subgroup of Katz et al [17]	2

The table continues on the next page

Table 25.1 *continued*

Author Year, reference	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition)	Age-groups Range (SD)
Street et al 2000 [20]	RCT	Nursing home	AD according to NINCDS	Severe-moderate	206	82.7 SD 6.6
Sultzer et al 2001 [41]	RCT	Hospital	Dementia diagnoses by clinical research investigator	Severe-light	28	72.3 SD 6.9
Sultzer et al 2001 [42]	RCT	Hospital	Dementia diagnoses by clinical research investigator	Severe-light	28	72.3 SD 6.9
Teri et al 2000 [10]	RCT	Out-patients	AD according to NINCDS	Moderate-light	149	74.9 SD 7.0

AD = Alzheimer's disease; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression Scale; CMAI = Cohen-Mansfield Agitation Inventory; CMAT = Cognitive multidisciplinary assessment team; DSM = Diagnostic and Statistical Manual; EPS = Extra pyramidal symptoms; MOSES = Multidimentional Observation Scale for Elderly Subjects; NINCDS = National institute of neurological and communicable diseases; NPI = Neuro-psychiatric inventory; NPI-NH = Neuropsychiatric inventory, Nursing Home version; RCT = Randomised controlled trial; SD = Standard deviation; UKU = Udvalg for kliniska undersogelser (Danish for selection of clinical investigations); VaD = Vascular dementia

Study period	Intervention (end)	Primary outcome	Effects (end)	Remarks from reviewer	Quality of study
6 w	Olanzapine 5 mg Olanzapine 10 mg Olanzapine 15 mg Placebo	NPI	Olanzapine 5 and 10 mg > placebo		2
9 w	Haloperidol M = 2.5 mg Trazodone M = 218 mg	CMAT	No difference in effect	Halopridol more side-effects	1
9 w	Haloperidol M = 2.5 mg Trazodone M = 218 mg	CMAT	Mild depressive symptom associated with more improvement with trazodone	Further analyses of the material in Sultzer et al [41]	1
16 w	Haloperidol M = 1.8 mg Trazodone M = 200 mg Behavior management techniques Placebo	CGI	No difference between groups		2

Table 25.2 *Effects of withdrawal of antipsychotic drugs in dementia.*

Author Year, reference	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included	Age-groups Range (SD)
Ballard et al 2004 [38]	RCT	Nursing home	AD according to NINCDS	Severe	100	83.4 SD 8.2
Bridges-Parlet et al 1997 [35]	RCT	Nursing home	"Demented aggressive nursing home patients"	Severe	36	82.8 SD 6.1
Cohen-Mansfield et al 1999 [36]	RCT	Nursing home	Residents in nursing home receiving antipsychotic treatment or lorazepam	Mean MMSE 8.7	58	86
Ray et al 1993 [33]	Intervention	Nursing home	Nursing home residents	Not given	278	82 SD 0.8

Study period	Intervention	Primary outcome	Effects (end)	Remarks from reviewer	Quality of study
3 months	Withdrawal of antipsychotic treatment. Placebo	NPI	No difference between groups. Best effects of withdrawal in those with low NPI		1
4 w	Withdrawal of antipsychotic treatment. Placebo	Global measure of untolerable symptoms	No difference		1
7 w	Withdrawal of antipsychotic treatment or lorazepam	BPRS	No difference	Very high rate of non-completers	1
4 months	Implementation of behavioral techniques to reduce use of antipsychotic treatment	Use of antipsychotics	Reduced use of antipsychotic agents without increase of behavioral symptoms	No definition of dementia in material	0

The table continues on the next page

Table 25.2 *continued*

Author Year, reference	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included	Age-groups Range (SD)
Ruths et al 2004 [39]	RCT	Nursing home	Dementia according to ICD-10-R	Severe	30	83.5
Thapa et al 1994 [34]	Inter-vention	Nursing home	Nursing home recidents receiving antipsychotic treatment	Mean MMSE 13.2	271	78.9
van Reekum et al 2002 [37]	RCT	Nursing home	Nursing home reci-dents with dementia receiving antipsychotic treatment	MMSE 7.6 SD 8.2	31	83.7 SD 5.8

AD = Alzheimer's disease; BPRS = Brief Psychiatric Rating Scale; ICD = International classification of diseases; MMSE = Mini-mental state examination; NHBPS = Nursing home behavior problem scale; NINCDS = National institute of neurological and communicable diseases; NPI = Neuropsychiatric inventory; RCT = Randomised controlled trial; SD = Standard deviation

Study period	Intervention	Primary outcome	Effects (end)	Remarks from reviewer	Quality of study
4 w	Blind withdrawal of antipsychotic treatment	NPI-Q	11/15 in study group stable or improved, 4 worse		1
6 months	Withdrawal on antipsychotic treatment	NHBPS, BPRS	No difference in behavioral symptoms, depressive symptoms reduced after withdrawal	No definition of patient diagnoses, no randomization	0
6 months	Withdrawal of antipsychotic treatment	Behave-AD	Group on antipsychotic treatment had more behavioral symptoms	High rate of noncompleters	1

Table 25.3 *Randomised controlled studies of antiepileptic drugs in dementia.*

Author Year, reference	Type of study	Setting	Dementia/diagnosis	Severity of dementia	Patients (n) included	Age-groups Mean
Olin et al 2001 [57]	RCT	University clinic, outpatient	NINCDS	Light-severe	21	74.7 SD 6.2
Porsteinsson et al 2001 [58]	RCT	Long term care	AD, VD, mixed dementia, BPRS ≥3	MMSE = 6.9 SD 6.7	56	85.0 SD 7.1
Sival et al 2002 [54]	RCT Double-blind, crossover	Short term geropsychiatric ward	Dementia according to DSM-IV and aggressive behavior	MMSE = 11.4 SD 5.0	28	80.4 SD 6.8
Tariot et al 1998 [55]	RCT	Nursing home	AD according to DSM-III and NINCDS	MMSE = 6.0 SD 6.4	51	86.0 SD 5.2
Tariot et al 1999 [56]	RCT	Nursing home	AD according to DSM-III and NINCDS		45	

AD = Alzheimer's disease; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression Scale; DSM = Diagnostic and Statistical Manual; MMSE = Mini-mental state examination; NINCDS = National institute of neurological and communicable diseases; RCT = Randomised controlled trial; SD = Standard deviation; SDAS = Social dysfunction and aggression scale; VaD = Vascular dementia

	Study period	Intervention	Primary outcome	Effects (end)	Remarks from reviewer	Quality of study
	6 w	Carbamazepine 300 mg/day	BPRS	Modest clinical benefit in the carbamazepine group	Pilot study	1
	6 w	Divalproex, mean dose 826 mg SD 216 Placebo	BPRS	Treatment resulted in lower score	High degree of side-effects	1
	2 x 3 w	Valproate Placebo	SDAS-9 CGI	No difference in aggressiveness between groups. Improvements in restlessness, melancholic state and anxiety		1
	6 w	Carbamazepine 300 mg/day Placebo	BPRS CGI	Carbamazepine > placebo		2
	3 w	Withdrawal of carbamazepine treatment	BPRS CGI	Recurrence of previous symptoms	Extension of Tariot et al [55]	1

References

1. Finkel SI, Costa e Silva J, Cohen G, Miller S, Sartorius N. Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. Int Psychogeriatr 1996;8 Suppl 3:497-500.

2. Schneider LS, Katz IR, Park S, Napolitano J, Martinez RA, Azen SP. Psychosis of Alzheimer disease: validity of the construct and response to risperidone. Am J Geriatr Psychiatry 2003;11:414-25.

3. Schneider LS, Dagerman KS. Psychosis of Alzheimer's disease: clinical characteristics and history. J Psychiatr Res 2004;38:105-11.

4. Petrie WM, Ban TA, Berney S, Fujimori M, Guy W, Ragheb M, et al. Loxapine in psychogeriatrics: a placebo- and standard-controlled clinical investigation. J Clin Psychopharmacol 1982;2:122-6.

5. Allain H, Dautzenberg PH, Maurer K, Schuck S, Bonhomme D, Gerard D. Double blind study of tiapride versus haloperidol and placebo in agitation and aggressiveness in elderly patients with cognitive impairment. Psychopharmacology (Berl) 2000;148:361-6.

6. De Deyn PP, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PL, Eriksson S, et al. A randomised trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 1999; 53:946-55.

7. Devanand DP, Marder K, Michaels KS, Sackeim HA, Bell K, Sullivan MA, et al. A randomised, placebo-controlled dose-comparison trial of haloperidol for psychosis and disruptive behaviors in Alzheimer's disease. Am J Psychiatry 1998;155: 1512-20.

8. Auchus AP, Bissey-Black C. Pilot study of haloperidol, fluoxetine, and placebo for agitation in Alzheimer's disease. J Neuropsychiatry Clin Neurosci 1997;9:591-3.

9. Devanand DP, Sackeim HA, Brown RP, Mayeux R. A pilot study of haloperidol treatment of psychosis and behavioral disturbance in Alzheimer's disease. Arch Neurol 1989;46:854-7.

10. Teri L, Logsdon RG, Peskind E, Raskind M, Weiner MF, Tractenberg RE, et al. Treatment of agitation in AD: a randomised, placebo-controlled clinical trial. Neurology 2000;55:1271-8.

11. Coccaro EF, Kramer E, Zemishlany Z, Thorne A, Rice CM, 3rd, Giordani B, et al. Pharmacologic treatment of noncognitive behavioral disturbances in elderly demented patients. Am J Psychiatry 1990;147:1640-5.

12. Devanand DP, Cooper T, Sackeim HA, Taurke E, Mayeux R. Low dose oral haloperidol and blood levels in Alzheimer's disease: a preliminary study. Psychopharmacol Bull 1992;28:169-73.

13. Chan WC, Lam LC, Choy CN, Leung VP, Li SW, Chiu HF. A double-blind randomised comparison of risperidone and haloperidol in the treatment of behavioral and psychological symptoms in Chinese dementia patients. Int J Geriatr Psychiatry 2001;16:1156-62.

14. Barnes R, Veith R, Okimoto J, Raskind M, Gumbrecht G. Efficacy of antipsychotic medications in behaviorally disturbed dementia patients. Am J Psychiatry 1982;139:1170-4.

15. Carlyle W, Ancill RJ, Sheldon L. Aggression in the demented patient: a double-blind study of loxapine versus haloperidol. Int Clin Psychopharmacol 1993;8:103-8.

16. Gutzmann H, Kuhl KP, Kanowski S, Khan-Boluki J. Measuring the efficacy of psychopharmacological treatment of psychomotoric restlessness in dementia: clinical evaluation of tiapride. Pharmacopsychiatry 1997;30:6-11.

17. Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomised, double-blind trial. Risperidone Study Group. J Clin Psychiatry 1999;60:107-15.

18. Brodaty H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, et al. A randomised placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003;64:134-43.

19. Meguro K, Meguro M, Tanaka Y, Akanuma K, Yamaguchi K, Itoh M. Risperidone is effective for wandering and disturbed sleep/wake patterns in Alzheimer's disease. J Geriatr Psychiatry Neurol 2004;17:61-7.

20. Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomised, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry 2000;57:968-76.

21. Mintzer J, Faison W, Street JS, Sutton VK, Breier A. Olanzapine in the treatment of anxiety symptoms due to Alzheimer's disease: a post hoc analysis. Int J Geriatr Psychiatry 2001;16 Suppl 1:S71-7.

22. Clark WS, Street JS, Feldman PD, Breier A. The effects of olanzapine in reducing the emergence of psychosis among nursing home patients with Alzheimer's disease. J Clin Psychiatry 2001;62:34-40.

23. Cummings JL, Street J, Masterman D, Clark WS. Efficacy of olanzapine in the treatment of psychosis in dementia with lewy bodies. Dement Geriatr Cogn Disord 2002;13:67-73.

24. Fontaine CS, Hynan LS, Koch K, Martin-Cook K, Svetlik D, Weiner MF. A double-blind comparison of olanzapine versus risperidone in the acute treatment of dementia-related behavioral disturbances in extended care facilities. J Clin Psychiatry 2003;64:726-30.

25. Meehan KM, Wang H, David SR, Nisivoccia JR, Jones B, Beasley CM, Jr, et al. Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomised study in acutely agitated patients with dementia. Neuropsychopharmacology 2002;26:494-504.

26. Battaglia J, Lindborg SR, Alaka K, Meehan K, Wright P. Calming versus

sedative effects of intramuscular olanzapine in agitated patients. Am J Emerg Med 2003;21:192-8.

27. Mulsant BH, Gharabawi GM, Bossie CA, Mao L, Martinez RA, Tune LE, et al. Correlates of anticholinergic activity in patients with dementia and psychosis treated with risperidone or olanzapine. J Clin Psychiatry 2004;65:1708-14.

28. Lanctot KL, Best TS, Mittmann N, Liu BA, Oh PI, Einarson TR, et al. Efficacy and safety of neuroleptics in behavioral disorders associated with dementia. J Clin Psychiatry 1998;59:550-61; quiz 562-3.

29. Schneider LS, Pollock VE, Lyness SA. A metaanalysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 1990;38:553-63.

30. Schneider LS. Meta-analysis of controlled pharmacologic trials. Int Psychogeriatr 1996;8 Suppl 3:375-9; discussion 381-2.

31. Kirchner V, Kelly CA, Harvey RJ. Thioridazine for dementia. Cochrane Database Syst Rev 2001:CD000464.

32. Lonergan E, Luxenberg J, Colford J. Haloperidol for agitation in dementia. Cochrane Database Syst Rev 2002: CD002852.

33. Ray WA, Taylor JA, Meador KG, Lichtenstein MJ, Griffin MR, Fought R, et al. Reducing antipsychotic drug use in nursing homes. A controlled trial of provider education. Arch Intern Med 1993;153:713-21.

34. Thapa PB, Meador KG, Gideon P, Fought RL, Ray WA. Effects of antipsychotic withdrawal in elderly nursing home residents. J Am Geriatr Soc 1994;42:280-6.

35. Bridges-Parlet S, Knopman D, Steffes S. Withdrawal of neuroleptic medications from institutionalized dementia patients: results of a double-blind, baseline-treatment-controlled pilot study. J Geriatr Psychiatry Neurol 1997;10:119-26.

36. Cohen-Mansfield J, Lipson S, Werner P, Billig N, Taylor L, Woosley R. Withdrawal of haloperidol, thioridazine, and lorazepam in the nursing home: a controlled, double-blind study. Arch Intern Med 1999;159:1733-40.

37. van Reekum R, Clarke D, Conn D, Herrmann N, Eryavec G, Cohen T, et al. A randomised, placebo-controlled trial of the discontinuation of long-term antipsychotics in dementia. Int Psychogeriatr 2002;14:197-210.

38. Ballard CG, Thomas A, Fossey J, Lee L, Jacoby R, Lana MM, et al. A 3-month, randomised, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor of clinical outcome. J Clin Psychiatry 2004; 65:114-9.

39. Ruths S, Straand J, Nygaard HA, Bjorvatn B, Pallesen S. Effect of antipsychotic withdrawal on behavior and sleep/wake activity in nursing home residents with dementia: a randomised, placebo-controlled, double-blinded study. The Bergen District Nursing Home Study. J Am Geriatr Soc 2004;52:1737-43.

40. Pollock BG, Mulsant BH, Rosen J, Sweet RA, Mazumdar S, Bharucha A, et al. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. Am J Psychiatry 2002;159:460-5.

41. Sultzer DL, Gray KF, Gunay I, Berisford MA, Mahler ME. A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. Am J Geriatr Psychiatry 1997;5:60-9.

42. Sultzer DL, Gray KF, Gunay I, Wheatley MV, Mahler ME. Does behavioral improvement with haloperidol or trazodone treatment depend on psychosis or mood symptoms in patients with dementia? J Am Geriatr Soc 2001;49: 1294-300.

43. McShane R, Keene J, Gedling K, Fairburn C, Jacoby R, Hope T. Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up. BMJ 1997; 314:266-70.

44. Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. CMAJ 2002;167:1269-70.

45. Lilly E. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2004/zyprexa_hpc-cps_e.html.

46. Bristol-Meyers Squibb Company. 2005. Data on file.

47. Herrmann N, Mamdani M, Lanctot KL. Atypical antipsychotics and risk of cerebrovascular accidents. Am J Psychiatry 2004;161:1113-5.

48. Kozma C, Engelhart, LM, Long, S, Greenspan, A, Hahmoud, R, Baser, O. Absence of increased of relative stroke risk in elderly dementia patients treated with risperidone versus other antipsychotics. Abstract from Third Annual ICGP Meeting, San Juan 2003. 2003.

49. Gill SS, Rochon PA, Herrmann N, Lee PE, Sykora K, Gunraj N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. BMJ 2005;330:445.

50. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomised, placebo-controlled trials. Am J Geriatr Psychiatry 2006;14:191-210.

51. Porsteinsson AP, Tariot PN, Erb R, Gaile S. An open trial of valproate for agitation in geriatric neuropsychiatric disorders. Am J Geriatr Psychiatry 1997;5:344-51.

52. Tekin S, Aykut-Bingol C, Tanridag T, Aktan S. Antiglutamatergic therapy in Alzheimer's disease – effects of lamotrigine. Short communication. J Neural Transm 1998;105:295-303.

53. Sival RC, Duivenvoorden HJ, Jansen PA, Haffmans PM, Duursma SA, Eikelenboom P. Sodium valproate in aggressive behavior in dementia: a twelve-week open label follow-up study. Int J Geriatr Psychiatry 2004;19:305-12.

54. Sival RC, Haffmans PM, Jansen PA, Duursma SA, Eikelenboom P. Sodium valproate in the treatment of aggressive behavior in patients with dementia – a randomised placebo controlled clinical trial. Int J Geriatr Psychiatry 2002;17: 579-85.

55. Tariot PN, Erb R, Podgorski CA, Cox C, Patel S, Jakimovich L, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. Am J Psychiatry 1998;155: 54-61.

56. Tariot PN, Jakimovich LJ, Erb R, Cox C, Lanning B, Irvine C, et al. Withdrawal from controlled carbamazepine therapy followed by further carbamazepine treatment in patients with dementia. J Clin Psychiatry 1999;60: 684-9.

57. Olin JT, Fox LS, Pawluczyk S, Taggart NA, Schneider LS. A pilot randomised trial of carbamazepine for behavioral symptoms in treatment-resistant outpatients with Alzheimer disease. Am J Geriatr Psychiatry 2001;9:400-5.

58. Porsteinsson AP, Tariot PN, Erb R, Cox C, Smith E, Jakimovich L, et al. Placebo-controlled study of divalproex sodium for agitation in dementia. Am J Geriatr Psychiatry 2001;9:58-66.

59. Lonergan ET, Cameron M, Luxenberg J. Valproic acid for agitation in dementia. Cochrane Database Syst Rev 2004: CD003945.

60. De Deyn PP, Carrasco MM, Deberdt W, Jeandel C, Hay DP, Feldman PD, et al. Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2004;19:115-26.

61. Frank L, Kleinman L, Ciesla G, Rupnow MF, Brodaty H. The effect of risperidone on nursing burden associated with caring for patients with dementia. J Am Geriatr Soc 2004;52:1449-55.

62. Katz IR, Rupnow M, Kozma C, Schneider L. Risperidone and falls in ambulatory nursing home residents with dementia and psychosis or agitation: secondary analysis of a double-blind, placebo-controlled trial. Am J Geriatr Psychiatry 2004;12:499-508.

63. Kennedy JS, Bymaster FP, Schuh L, Calligaro DO, Nomikos G, Felder CC, et al. A current review of olanzapine´s safety in the geriatric patient: from pre-clinical pharmacology to clinincal data. Int J Geriatr Psychiatry 2001;16:33-61.

64. Nygaard HA, Bakke K, Brudvik E, Elgen K, Lien GK. Dosing of neuroleptics in elderly demented patients with aggressive and agitated behavior: a double-blind study with zuclopenthixol. Curr Med Res Opin 1994;13:222-32.

65. Pelton GH, Devanand DP, Bell K, Marder K, Marston K, Liu X, et al. Usefulness of plasma haloperidol levels for monitoring clinical efficacy and side effects in Alzheimer patients with psychosis and behavioral dyscontrol. Am J Geriatr Psychiatry 2003;11:186-93.

26. **Drug-induced Cognitive Impairment**

Conclusions

The literature presents a vast array of studies addressing the cognitive side-effects of drugs, some of them dealing with cognitive impairment and others with delirium. Several are case reports or observational studies, but there are also many RCTs.

For some drugs – such as anticholinergics, benzodiazepines, corticosteroids and opioids – there is strong evidence of cognitive side-effects (Evidence Grade 1). A dose-dependent effect was observed for some of them, including anticholinergics and opioids. For others, such as anticonvulsants and antipsychotics, the evidence is moderate or limited. When it comes to the remainder of the drugs investigated – such as NSAID and beta-blockers – the results have less support or are contradictory. Table 26.1 summarizes drug groups for which there is scientific evidence of adverse effects on cognitive function.

However, not all drugs have been the subject of well-executed RCTs, and poor evidence does not automatically mean that a drug cannot have significant adverse effects on cognition. An important general limitation is that most drug groups have not been properly studied in elderly subjects. With respect to drug sensitivity, elderly patients can be very different from healthy adults by virtue of pharmacokinetic and pharmacodynamic changes, as well as polypharmacy and multiple diseases.

Background

Many different types of drugs can cause cognitive impairment, ranging from mild symptoms such as memory disturbances to obvious delirium or dementia. Generally speaking, the elderly are more sensitive to these side-effects by virtue of multiple drug use, age-related changes in pharmacokinetics and the central nervous system (CNS) function, and disease. Patients with dementia, particularly AD (Alzheimer's disease) in which a loss of cholinergic activity is found, are at particular risk due to neurodegeneration and the consequent impairment of neurotransmission.

Types of drug-induced cognitive impairment

Delirium is the most dramatic form of drug-induced cognitive impairment. Onset is rapid, and the cognitive disturbances, which typically have a fluctuating course, are associated with disorientation and an altered state of consciousness. Some patients experience hallucinations, delusions, hyperactivity or hypoactivity.

Drug toxicity can manifest as dementia. Drugs are generally one of several factors contributing to cognitive impairment, but they may also be the sole cause.

In other cases, drugs may cause more subtle cognitive disturbances that can be measured by neuropsychological tests but might otherwise go undetected.

Pathophysiology

Delirium is caused by a global decrease in the oxidative metabolism of the brain and an imbalance in several neurotransmitter systems.

The brain's cholinergic pathways play an important role in cognitive processes. The significance of cholinergic dysfunction for the cognitive deficits observed in AD is well established. Anticholinergic drugs are also known to cause delirium and other types of cognitive disturbances,

particularly in AD patients. According to one hypothesis, cholinergic blockade is the final common pathway of drug-induced cognitive impairment. But many other neurotransmitters – including GABA, dopamine, and noradrenaline – are likely contributors.

Epidemiology

Studies in elderly hospital patients reported that drugs are the cause of delirium in 10–30% of the cases [1]. Drug-induced cognitive impairment was found in 35 of 308 outpatients with suspected dementia. Cognition improved in each case when the suspected drugs were withdrawn [2]. Of 157 cognitively impaired patients in a residential care facility, 6–12% were found to have a reversible component. In 7 of the cases that showed the greatest improvement, adverse drug reaction (ADR) was deemed to be the likely cause [3]. According to estimates, more than 10% of patients attending memory clinics have iatrogenic disease [4].

Aims

The aim of the present inquiry was to review the literature for evidence of cognitive impairment and/or delirium induced by drugs.

Method

The primary search was in MEDLINE search covering 1975 to June 2004. The following search strategies were used, either alone or in combination:

- Aged OR Alzheimer disease
- Cognition/*drug effects OR Confusion/*drug effects OR Delirium/*drug effects
- Cognition disorders OR Delirium, dementia, amnestic, cognitive disorders OR Confusion
- Pharmaceutical preparations/*adverse effects OR Drug therapy/*adverse effects

- Confusion/*chemically induced OR Cognition disorders/*chemically induced OR Delirium/*chemically induced OR Dementia/*chemically induced OR Amnestic disorders/*chemically induced.

When appropriate, relevant references in the identified studies were also included.

Because this chapter deals with side-effects of drugs, which have not been extensively investigated in RCTs, we have included a wider range of studies. Studies were reviewed if they were at least prospective – even those with low quality are included in the tables. Case reports and the like are sometimes cited for the sake of completeness, but we do not accord them any evidentiary value.

Cognitive side-effects of specific drug classes

Anticholinergic drugs

Several different types of drugs used by the elderly have anticholinergic properties. The drugs include not only the classic belladonna derivatives such as scopolamine, but a range of medications for example drugs against incontinence, tricyclic antidepressants and low-potency neuroleptics.

Several RCTs have investigated the effect of scopolamine on cognitive function in humans, most comparing elderly and young normal subjects. A double-blind, placebo-controlled study by Zemishlany et al gave scopolamine 0.2 mg and placebo to 12 elderly and 14 young subjects [5] (Table 26.2). A comprehensive test battery measuring verbal memory, practice and language that was administered 45 minutes after the injection showed significant impairment of new learning and practice in the elderly but not in the young. Language function was not impaired [5]. A study by Flicker et al compared three doses of scopolamine to glycopyrrolate, a peripheral-acting anticholinergic drug that penetrates the blood-brain barrier poorly [6]. The elderly performed worse than the young in all memory tests, although two tests also found impairment in young subjects at the highest dose. In contrast, attentional tasks were

affected similarly in the elderly and young. A double-blind study by Sunderland et al compared the effect of three doses of scopolamine and placebo in 10 AD patients and 10 matched elderly controls [7]. Two test batteries were administered, one 90 minutes after injection and the other repeatedly during the treatment period. For most cognitive tasks, the AD patients were impaired at lower doses than the controls and appeared to be more impaired at higher doses. The differences were most obvious in tests of new learning and semantic knowledge. Behavioral symptoms such as mild euphoria, motor incoordination and hostility were found in the AD patients but not in the controls. The differences in cognitive and behavioral measures between the two groups generally became more pronounced after scopolamine had been administered.

Several studies have related cognitive function or signs of cognitive impairment to serum anticholinergic levels. The levels are analyzed in blood serum by incubating it with a radioactively labeled muscarinic receptor antagonist – [3H]quinuclidinyl benzilate (QNB) and a suspension of rat striatal membranes rich in muscarinic receptors. The degree of competition with the radio-labeled QNB reflects the anticholinergic levels. Using this assay, many drugs have been found to possess anticholinergic activity. A number of them – including cimetidine, theophylline, prednisolone and digoxin – have previously gone unrecognized in this respect [8].

A study of 29 patients (aged 29–75, mean 55) undergoing cardiac surgery, found that 8 of the 25 who gave blood samples became delirious during the first postoperative week. High serum anticholinergic levels were found in 7 of those 8 patients, as opposed to only 4 of the patients who had not become delirious [8]. A low dose (0.005 mg/kg) of scopolamine administered to 18 patients in a randomised, double-blind, placebo-controlled study of 36 elderly presurgical patients yielded low levels of serum anticholinergic activity and cognitive impairment, which was measurable in two of the tests. These mild changes were not detected by two other tests, including the MMSE [9]. Rovner et al related serum anticholinergic levels in 22 nursing home patients with dementia to cognition and capacity for self-care, finding that patients with high levels had a significantly lower self-care score on the Psychogeriatric Dependency Rating

Scales [10]. Because this study was cross-sectional, a causal relationship cannot be established. However, the authors pointed out that other factors – including dementia severity, medical conditions, and number of anticholinergic drugs – were similar in the two groups.

Anxiolytics and hypnotics/sedatives

A prospective study by Larson et al covering 308 outpatients with suspected dementia found that 35 were having adverse drug reactions that caused cognitive impairment (Table 26.3). Use of sedatives/hypnotics, of which long-acting benzodiazepines were the most common, was the strongest predictor of adverse reactions [2]. A prospective cohort study of 2 765 subjects from the Duke EPESE showed that current users of benzodiazepines performed worse on memory tests (Short Portable Mental Status Questionnaire and Orientation-Memory-Concentration Test) and that those with recommended and higher dose, as well as long-term users, made more errors [11]. Memory impairment was found with both short-acting and long-acting agents. A study from the Boston Collaborative Drug Surveillance Program (BCDSP) examined 2 111 users of nitrazepam among 11 000 hospitalized medical patients in 5 countries. Signs of CNS depression (drowsiness, fatigue, confusion and ataxia) were reported in 49 patients (2.3%). However, the frequency was much higher in the elderly (11% in the 80 and over age group). That was attributed to the high doses. Among those aged 80 or over who took 10 mg or more, 55% experienced unwanted CNS depression [12]. Another study from the BCDSP that examined 2 542 patients using flurazepam showed similar results, with higher prevalence of CNS depression in the elderly, particularly at higher doses [13]. However, both studies were unblinded and lacked control groups. In addition, the extent to which CNS depression involved cognitive impairment is unknown.

Several double-blind, placebo-controlled trials have investigated the effects of benzodiazepines on cognitive functioning and/or psychomotor skills. But only some of them included elderly subjects and cognitive measures. Pomara et al gave 12 normal elderly volunteers single doses of 2.5 or 5 mg diazepam or placebo in three separate sessions. Memory was tested using the Buschke selective reminding task (immediate and delayed), a visual memory task (immediate and delayed) and a digit

span/supraspan task. Five of the measures were significantly impaired at all doses of diazepam [14,15]. Hinrichs and Ghoneim studied the effect of diazepam versus placebo in three age-groups of 12 healthy subjects (aged 19–28, 40–45 and 61–73) each [16]. Each subject was given diazepam (0.2 mg/kg) or placebo in two sessions. A large number of tests – including addition, card rotation and number learning, as well as immediate and delayed free recall – assessed cognitive performance. Diazepam had a detrimental impact on virtually all tasks. Many of them showed a similar effect of aging, while diazepam and its effect appeared to be additive rather than synergistic in older subjects.

Patterson reported five cases of triazolam syndrome, ie, reversible delirium, automatic movement and anterograde amnesia following ingestion of the short-acting benzodiazepine triazolam [17].

Barker et al reported a meta-analysis of 13 studies using neuropsychological tests to evaluate the cognitive effects of long-term use of benzodiazepines [18]. The mean number of benzodiazepine users was 33.5, and the mean number of controls was 27.9. The mean duration of use was 9.9 years. Long-term benzodiazepine users were consistently found to be more impaired in all cognitive categories.

The newer hypnotics, which are structurally different from the benzodiazepines but have the same mode of action via the GABA receptor, are increasingly prescribed for the elderly. One study found zolpidem (10 mg) to have no impact on cognitive function in elderly volunteers as measured by Sternberg Memory Scanning Task [19]. A randomised crossover study tested Zopiclone against placebo in 12 healthy elderly volunteers. A single dose of 7.5 mg had no effect on memory performance [20]. A recent double-blind, randomised, four-way, crossover study competed zolpidem (5 mg), zopiclone (3.75 mg), lormetazepam (1 mg) and placebo in 48 healthy elderly volunteers. The Learning Memory Tasks were unaffected by both zopiclone and zolpidem. The effects were not different from placebo in the Sternberg Memory Scanning Test either, with the exception of one item on which both zopiclone and lormetazepam increased the mean reaction time [21]. However, there are also some case reports of zolpidem-associated delirium [22–24].

In conclusion, there is firm evidence from RCTs that diazepam can cause cognitive impairment in the elderly. The evidence is weaker for two of the other long-acting benzodiazepines, nitrazepam and flurazepam as it is based on observational data, although in a very large number of patients. Case reports suggest that triazolam may cause delirium. RCTs to date indicate that the newer hypnotics of zopiclone and zolpidem have no or little effect on cognition, although case reports suggest that zolpidem may cause delirium.

Antipsychotics

Antipsychotics may cause cognitive impairment through several different mechanisms. The low-potency drugs, such as thioridazine, have significant anticholinergic properties (see above). Antipsychotics may also cause sedation through histamine H1-receptor antagonism that in turn could lead to impaired cognition.

Few systematic studies have been conducted on the cognitive side-effects of antipsychotics in the elderly. Most of the available data are from clinical trials, most of which have examined different antipsychotics in treating the behavioral symptoms of dementia. Traditional agents have been the focus of some, mostly small, studies. An early open crossover study by Steele et al compared the efficacy and side-effects of haloperidol and thioridazine in 16 AD patients with serious behavioral symptoms [25]. None of the drugs produced any significant effects on cognition. However, the study population was small. Moreover, only 6 patients completed the crossover. A single-blind, placebo-controlled pilot study gave 9 AD patients with psychosis or behavioral disturbance haloperidol for 8 weeks, preceded and followed by placebo for 4 weeks. Haloperidol (1–5 mg/day) showed a statistical trend ($p<0.10$) towards cognitive impairment with only partial recovery during the placebo phase [26]. However, the study was also small. No effect on cognitive status (MMSE) emerged in a later 6-week, double-blind, crossover trial by Devanand and Marder comparing two doses of haloperidol and placebo among 71 AD patients [27]. A more recent study compared the acute effects of haloperidol (2 mg) and amisulpiride (50 and 200 mg) on cognition in 16 healthy, elderly volunteers. Cognitive functions were measured using

a test battery (CDR computerized assessment system). Amisulpiride did not produce any significant impairment of cognition. Haloperidol produced a significant decrease for two tasks compared to amisulpiride, but no change compared to placebo [28].

The newer antipsychotics have been the subject of several double-blind RCTs. Risperidone (0.5, 1, or 2 mg daily for 12 weeks) was compared with placebo in 625 patients with different types of dementia, as well as significant psychotic and behavioral symptoms [29]. Risperidone was found to cause no significant decrease in cognitive performance as measured by the MMSE. A 13-week, double-blind study compared risperidone to haloperidol and placebo in 344 patients with dementia and behavioral symptoms. No significant decline in cognition was found due to risperidone (mean dose 1.1 mg daily), whereas haloperidol (1.2 mg daily) caused a significant decline in the MMSE score compared to placebo [30]. A recent study compared the effects of single doses of risperidone (0.25 and 0.5 mg) on psychomotor performance and cognitive functions to placebo and lorazepam in 12 healthy elderly subjects. Risperidone had no effect on speed of reaction, vigilance, sustained attention, working or long-term memory and caused only minor impairment on information processing [21].

A 6-week, double-blind study compared olanzapine to placebo in 206 AD patients in nursing care [31]. The MMSE scores in the three olanzapine groups (5, 10, and 15 mg daily) did not differ significantly from baseline or placebo. A prospective, open-label, 8-week trial of olanzapine in 27 elderly schizophrenic patients found no significant change in the MMSE [32]. Olanzapine has also been tested in healthy, elderly volunteers. With the specific aim of investigating cognitive and psychomotor effects, a double-blind, crossover study of 14 subjects compared olanzapine 3 mg with haloperidol 3 mg and placebo. Each treatment lasted for 4 days, with a 16-day interval in between. Cognitive functions were measured using the CDR computerized assessment system. Both olanzapine and haloperidol were found to affect cognition. However, while olanzapine produced acute effects that generally returned to pre-dosing levels after 24 hours, the effects of haloperidol tended to increase up to day 4 and even to carry over [33].

Besides these RCTs, there are some case reports of delirium with both risperidone [34–36] and olanzapine [37].

The atypical antipsychotic clozapine has central anticholinergic properties. The fact that physostigmine reversed clozapine-induced delirium suggests that these anticholinergic effects were involved [38]. A study based on pharmacy records diagnosed 10% of clozapine patients with delirium. The risk was higher in those who had received other drugs with central anticholinergic effects [39]. The combination with benzodiazepines also seems to augment the risk of delirium [40].

Based on previous findings of a more rapid decline in cognitive function among AD patients showing psychotic symptoms, sleep disturbance and aggression, a 2-year prospective study by McShane et al investigated whether antipsychotic treatment might accelerate cognitive decline in 71 community-dwelling elderly with dementia [41]. Cognitive function was measured every 4 months using an expanded version of the MMSE. The 16 patients who took antipsychotics (mainly thioridazine, promazine, haloperidol, and chlorpromazine) showed a mean decline in the MMSE score twice that of the others. In addition, the start of antipsychotic treatment coincided with a more rapid decline. However, as discussed by the authors, these results did not prove a causal relationship between antipsychotic use and cognitive decline. Perhaps those receiving antipsychotics had a more severe disease and a steeper cognitive decline in general.

In conclusion, few of the studies presenting data about cognitive side-effects of antipsychotics were specifically designed to address this question. In addition, most studies used only the MMSE as a measure of cognitive functioning. Studies on traditional antipsychotics were generally small and examined only a few of these drugs, mostly haloperidol. The results did not reveal any major effects on cognition. However, later studies that compared new antipsychotics to haloperidol observed a significant cognitive impairment from this drug. Generally speaking, the newer antipsychotics, including risperidone and olanzapine, have proven to have little impact on cognitive function.

Lithium

Delirium is a well known consequence of lithium intoxication. Cognitive deficits tend to persist for long after the lithium concentrations have declined [42,43].

Honig et al reviewed the literature on cognitive side-effects of lithium therapy in bipolar disorder, identifying 4 out of 17 studies with adequate methodological quality. Analysis of the 4 studies showed that lithium had a negative effect on memory and speed of information processing [44].

Antidepressants

Cognitive impairment in depression is a complex matter given that both medication and the disease itself may be the cause. Antidepressants can be broken down into two major groups with different pharmacological and side-effect profiles: the older tricyclic agents (TCAs) and the newer selective serotonin reuptake inhibitors (SSRIs). Each group has been studied, mostly by double-blind RCTs, in both healthy elderly and those with depression.

Several studies using varying types of neuropsychological tests have shown amitriptyline, which has the most potent anticholinergic effects of all TCAs, to cause cognitive impairment. A placebo-controlled crossover study by Branconnier et al found that amitriptyline 50 mg markedly disrupted verbal recall from secondary memory but did not affect recognition [45] (Table 26.5). The profile of anterograde memory impairment was similar to that of the antimuscarinic agent scopolamine. Another study found that the same single dose of amitriptyline produced more pronounced impairment on several cognitive tasks than trazodone [46]. Ogura et al concluded that a relatively low dose of amitriptyline (25 mg) significantly decreased critical flicker fusion (CFF) for up to 24 hours [47]. Some TCAs may have less impact on cognitive functioning. Ghose and Sedman found that lofepramine, as opposed to amitriptyline, had no negative effect on psychomotor performance or CFF [48]. However, the study was small.

Studies in elderly patients with depression examined several types of TCAs. Amitriptyline was found to impair memory retrieval [49]. A comparison with the SSRI fluoxetine in 66 elderly depressed patients showed that memory improved, although more slowly in the case of amitriptyline [50]. TCAs other than amitriptyline have been shown to have less or no significant effects on cognition. Imipramine (300 mg daily for 25 days) had no effect in most tests of intellectual function [51]. Imipramine actually improved short-term memory in another placebo-controlled study [52]. Treatment with maprotiline improved cognition in a study of 75 elderly with depression, although the degree of improvement was less than for mianserin and nomifensine [53]. Nortriptyline has also been reported to have little effect on cognition. No significant effect was observed in an extensive battery of tests after 7 weeks of treatment [54]. However, another study reported a dose-dependent effect on immediate free recall [55].

Several studies have investigated the cognitive effects of SSRIs. Hindmarch et al compared 9 days of sertraline and mianserin treatment in elderly volunteers and found no effects of sertraline (up to 200 mg) on psychomotor and cognitive performance [56]. However, 10 subjects discontinued the mianserin treatment due to pronounced intolerance, such as hypotension. Sertraline was also shown to improve vigilance compared with amitriptyline and placebo. A study by Kerr et al found memory performance to improve faster in fluoxetine than amitriptyline patients [50].

Mianserin has been shown to induce transient impairment of immediate memory [57]. Bailer et al reported three cases of mirtazapin-induced delirium [58]. However, these patients had subclinical brain disease that may have favored the occurrence of delirium.

In conclusion, the TCA amitriptyline has been clearly linked to cognitive impairment in both healthy elderly and those with depression. Some other TCAs – including imipramine, lofepramine and maprotiline – may have less impact on cognitive performance. However, the detrimental effects of antidepressant therapy may be underestimated due to improvement in the disease itself. The available studies on SSRI show no signi-

ficant negative effect on cognitive performance. Some data suggest that mianserin, and possibly mirtazapin, can cause cognitive impairment or delirium.

Antiparkinsonian agents

Anticholinergic drugs for Parkinson's disease (PD) can clearly cause cognitive impairment. A double-blind crossover trial in elderly normal subjects found that trihexyphenidyl caused memory impairment on several tests, ie, the subjects rated their memory function as significantly more impaired [59]. A study by Van Spaendonck et al found that PD patients taking anticholinergic antiparkinsonian drugs performed worse than matched controls on tests of cognitive shifting [60] (Table 26.6). Another study showed that patients on combined therapy or anticholinergics alone performed worse in a series of psychometric tests than those on L-Dopa monotherapy [61].

The effects of L-Dopa vary among the different studies. The DATATOP study compared cognitive status before and after 6 months of L-Dopa therapy in 387 subjects, but no significant difference was found on any of the tests [62]. However, another study found acute L-Dopa treatment to delay cognitive processing compared to matched controls, as measured by simple reaction time [63]. There is also reliable evidence that L-Dopa may cause hallucinations [64] and delirium [65].

Other dopaminergic drugs have also been investigated. A study on advanced PD found that bromocriptine caused mental changes in 17 of 66 patients, 3 of whom manifested organic confusional syndrome and 3 of whom manifested schizophreniform psychosis [66]. A study by Goetz et al found concomitant use of agonists to be more common among patients with hallucinations [64].

A small study of PD patients on long-term L-Dopa treatment showed that the MAO-B-inhibitor selegiline improved memory, motor speed, and naming performance in patients without progressive dementia, while some functions – such as set shifting and vigilance – deteriorated [67]. Selegiline has also been reported to cause delirium.

Antihistamines

Antihistamines can impair cognitive function in several ways. First, they can cause sedation by blocking histamine H1 receptors in the CNS. Second, some of the drugs have anticholinergic effects. Generally speaking, the degree of CNS impact is related to ability to penetrate the blood-brain barrier. The first-generation agents – including diphenhydramine, hydroxyzine, chlorpheniramine, promethazine and clemastine – penetrate more readily and are therefore more prone to cause sedation. In addition, many first-generation drugs not only block histamine receptors, but have significant anticholinergic properties.

A comprehensive study reviewed 55 placebo-controlled and verum-controlled trials on sedative effects and other CNS side-effects of antihistamines between 1965 and 1977 [68]. All trials had a double-blind crossover design. Twenty-one different antihistamines were included, of which 14 were second-generation. The cognitive tests included short-term and continuous memory tasks, and several tests of CNS arousal included mental arithmetic and logical reasoning. The authors concluded that although most antihistamines possessed some sedative effect, the first-generation agents clearly had more side-effects, consistently impairing performance at all doses tested. Very few antihistamine studies have been conducted in the elderly. However, a reasonable assumption is that elderly are particularly sensitive to the CNS effects of antihistamines, especially first-generation drugs with potent sedative and anticholinergic effects.

Anticonvulsants

Essentially all anticonvulsants can cause dose-dependent cognitive impairment [69]. However, the drugs appear to have some differences. A 5-year prospective multicenter study of 622 patients showed that carbamazepine had fewer cognitive side-effects than phenytoin, phenobarbital or primidone [70] (Table 26.7). However, another study with a double-blind RCT design did not find any major difference between carbamazepine and phenytoin [71]. Dodrill and Troupin reported a difference favoring carbamazepine over phenytoin, but discrepancies in serum levels were later identified as the true explanation [72]. Thus, there is

no evidence of any major difference between these two anticonvulsants in terms of cognitive side-effects.

A more consistent result from several RCTs is that phenobarbital causes more pronounced cognitive impairment than other anticonvulsants, while there are only slight, if any, differences among carbamazepine, phenytoin and valproate [73,74]. The newer anticonvulsant vigabatrin has been found to have no, or only modest, effects on cognitive function [75,76].

Opioids

Lawlor reviewed the cognitive effects of opioids [77]. Several studies have been carried out in healthy elderly, as well as those with non-malignant and cancer pain. Table 26.8 lists some of the RCTs in healthy elderly [78–82]. The results vary, but it would appear that there are more cognitive side-effects with parenteral administration and higher doses. The results are contradictory for non-malignant pain. One RCT showed no difference between morphine and placebo [83].

Prospective studies must be relied on when it comes to cancer pain. Again the results vary. For example, one study by Banning et al showed a prolongation of continuous reaction time in patients taking peroral morphine compared to those who did not [84]. On the other hand, a larger study by Sjögren et al showed that long-term opioid use had no effect per se on cognitive performance [85].

One problem with investigating the cognitive effects of opioids is that the outcome depends on a number of factors – such as type of opioid, dose and regimen, and route of administration – that may vary. Moreover, the cognitive effects may be more pronounced at the start of therapy and as the dose increases [77].

As is the case with many other drug groups, another problem is that these studies included very few elderly. Risks of cognitive disturbances and delirium may be greater in the elderly due to age changes in terms of pharmacokinetics – particularly a decrease in renal function – pharmacodynamics, polypharmacy, and multiple diseases. Opioid use has

been found to be an independent risk factor for delirium in the elderly [86]. Opioids may also cause, or contribute to, postoperative delirium. A prospective controlled trial of 83 higher-risk elderly men found that postoperative confusion occurred in 18% of those receiving intramuscular morphine injections compared to 2.3% on patient-controlled analgesia [87].

NSAIDs

Contradictory effects of NSAIDs on cognitive function have been described in the literature. Several studies have reported that long-term therapy may protect against AD or slow the cognitive decline associated with AD and ageing. These findings are described in Chapter 8 on Risk Factors and are not discussed further here. Other studies have reported that short-term NSAID use may cause cognitive impairment. However, the evidence is rather scarce. A cognitive assessment before and after three weeks of naproxene treatment in a prospective study showed a decline among 4 of 12 osteoarthritic elderly patients. However, the change was not statistically significant. In addition, the sample size was small and the trial was uncontrolled [88] (Table 26.9). Two prospective cohort studies of similar design have been published. From the Duke EPESE, Hanlon et al reported that elderly patients taking moderate or high NSAID doses performed significantly worse on memory tests [89]. Another EPESE study by Saag et al found high-dose NSAID use to be strongly associated with a decline in word recall [90]. However, these studies are observational, and their concomitant assessment of NSAID use and cognitive measures makes it difficult to draw any conclusions about the causal relationship. Some studies have reported a lack of deleterious effect of NSAIDs on cognitive function. May et al found no association between NSAID or aspirin use on MMSE scores and items in 1 310 ambulatory elderly [91]. A double-blind crossover study of 20 healthy elderly patients receiving indomethacin or placebo for 7 days suggested that tests of sensorimotor coordination and short-term memory may have improved, whereas tests of attention and psychotmotor speed remained unaffected [92]. In summary, few studies have provided evidence that NSAIDS have major negative effects on cognitive function. However, that does not rule out the risk of CNS effects in individual patients.

Corticosteroids

Corticosteroids have several different effects on brain function, including modulation of various transmitter systems, as well as implications for myelin synthesis, neuronal glucose uptake, dendritic branching and synapse formation. The hippocampus is an important receptor site for corticosteroids, where they are known to play an important role in long-term potentiation. While corticosteroids are integral to memory processes, such as interpreting and storing new information, prolonged exposure to, or elevated levels of, glucocorticoids may lead to hippocampal degeneration, which could cause cognitive impairment [93].

The BCDSP examined more than 700 consecutively hospitalized patients on corticosteroids and found significant psychiatric disturbances in 1.6% of those receiving <40 mg, 4.6% in those receiving 40–80 mg and 18.4% in those receiving >80 mg prednisolone daily [94] (Table 26.10).

Several placebo-controlled, experimental studies on healthy subjects demonstrated that corticosteroids (prednisone, dexamethasone and hydrocortisone) have adverse effects on memory processes, such as immediate and delayed free recall, working memory, and declarative memory [95–101].

Several studies also reported various cognitive disturbances following corticosteroid therapy for medical diseases, including rheumatoid arthritis, asthma, and ulcerative colitis. In a series of 14 cases, Hall et al found that patients treated with corticosteroids – daily doses of prednisone 40 mg or its equivalent – were more likely to develop psychotic symptoms [102]. Another study by Keenan et al found that 25 patients using prednisone for at least 1 year performed worse than controls on tests of hippocampal-dependent memory tasks [103]. Varney et al identified 6 patients who developed dementia-like cognitive changes following corticosteroid treatment. All of them recovered after discontinuation or reduction of the medications [104].

Anti-ulcer agents

Cantu and Korek reviewed the incidence of risk factors for CNS reactions to histamine H2 blockers in 1991 and concluded that all H2 blockers can induce CNS toxicities. The estimated incidence was low (0.2%) in outpatients, but 1.6% to 80% in inpatients. The association was more frequent for cimetidine, although there was no firm evidence for differences among the drugs. Advanced age was the only, albeit limited, risk factor [105]. Catalano et al reported six cases of famotidine-associated delirium in hospitalized patients who returned to normal upon removal of the drug [106].

An RCT in 12 healthy volunteers reported that increasing doses of cimetidine up to 1 600 mg had no significant impact on cognitive performance [107] (Table 26.11). However, the H2 antagonists are dependent on renal function, and there is evidence that renal impairment may increase the risk of CNS reactions. Schentag found moderate to severe mental status changes in 6 of 36 patients on cimetidine, all of whom had both renal and hepatic dysfunction, as well as high serum levels of cimetidine. The changes became more severe as levels rose [108]. A prospective, observational open study of 41 patients on ranitidine showed that CNS adverse reactions such as confusion and disorientation were more frequent in patients with renal function impairment and higher plasma levels [109].

H2 blockers possess anticholinergic effects, and the fact that physostigmine has been shown to resolve delirium in users of H2 blockers suggests that it may be an important mechanism for the adverse CNS effects of these drugs [110].

Some case reports suggest that proton pump inhibitors [111,112] and misoprostol [113] can also cause delirium [112].

Cardiovascular drugs

Advanced age has been shown to be an independent risk factor for digitalis toxicity [114]. Several case reports of digitalis-induced delirium appear in the literature, mostly in elderly patients [115]. Delirium may be the first symptom of digitalis intoxication [116].

A study in the Netherlands reported on 179 patients with digitalis toxicity, of whom 12 presented transient psychosis and 4 delirium [117]. Important to note is that CNS disturbances may occur in the elderly even at normal digoxin concentrations [118,119].

Disopyramide and quinidine both have significant anticholinergic effects and have been reported to cause delirium [1,115].

A review of 55 studies on the cognitive side-effects of beta-blockers found inconsistent results. Sixteen percent of the studies showed improved function, seventeen percent worsened function and the rest no significant effect [120]. One placebo-controlled RCT of propranolol showed only limited effects on cognitive function [121] (Table 26.12). A double-blind crossover study on the cognitive effects of six different antihypertensives (six-week treatment periods with atenolol, metoprolol, hydrochlorothiazide, methyldopa, enalapril and verapamil) showed that – irrespective of the type of medication – treatment reduced simple motor speed, as well as slowing completion of two tests measuring perceptuomotor speed and mental flexibility. On the other hand, all antihypertensive agents favorably affected performance on several tests that required working memory [122]. However, there are also case reports of insidious mental impairment [123] and delirium [124].

Whether lipophilic beta-blockers may be more prone to cause CNS effects has been a subject of discussion. A double-blind crossover study by Westerlund in 14 patients with a previous history of nightmares or hallucinations when taking lipophilic beta-blockers, compared the hydrophilic beta-blocker atenolol with the lipophilic agents metoprolol and propranolol. The number of episodes was significantly lower for patients receiving atenolol, thereby supporting the hypothesis [125]. However, the study by Dimsdale et al found no difference, too [120].

Nygaard reviewed studies on adverse drug events (ADE) related to topical administration of beta-blockers for glaucoma and found several reports of not only congestive heart failure, arrhythmias and respiratory symptoms, but depression, hallucinations and confusion, too [126].

Antibiotics, antiviral drugs and chemotherapy

Numerous case reports indicate that quinolone antibiotics can cause delirium [127–130]. Moreover, the macrolide antibiotics clarithromycin [131] and azithromycin [132] have been reported to cause delirium in geriatric patients. Because the macrolides are potent inhibitors of the cytochrome P450 isoenzyme CYP 3A4, they may also indirectly cause cognitive disturbances by increasing the levels of other drugs with potential CNS effects [133]. There are also a few case reports of psychotic symptoms following administration of sulfonamides [134].

Case reports have associated the antiviral drugs acyclovir, ganciclovir and famciclovir with delirium [135–137].

There is growing evidence that chemotherapy can cause long-term cognitive changes in breast cancer patients [138,139]. Survivors treated with systemic chemotherapy scored significantly lower on the battery of neuropsychological tests than those who had received local therapy only. They were also more likely to self-report greater problems with working memory [139].

Table 26.1 *Drug groups for which there is scientific evidence for adverse effects on cognitive function.*

Drug group	Drugs studied	Scientific evidence
Anticholinergic drugs	Scopolamine	Strong
Benzodiazepines	Diazepam	Strong
Antihistamines	First-generation, eg diphenhydramine, hydroxyzine, promethazine	Strong
Corticosteroids	Hydrocortisone, cortisone, cortisol, prednisolone, dexamethasone	Strong
Opioids	Morphine, hydromorphone, oxycodone	Strong
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital	Moderately strong
Tricyclic antidepressants	Amitriptyline	Moderately strong
Antiparkinsonian drugs	L-dopa, anticholinergic drugs	Limited
Antipsychotic drugs	Haloperidol	Limited

Table 26.2 *Anticholinergic drugs.*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups	Follow-up time
Zemishlany et al 1991 [5]	RCT, DB, PC	Com	N	–	12 elderly, 14 young	57–73 22–35	2 h
Flicker et al 1992 [6]	RCT, DB	Com	N	–	10 elderly, 10 young	60–85 18–30	4 h
Sunderland et al 1987 [7]	RCT, DB, PC	Nh, Com	AD/N	Mild-moderate	10 AD, 10 N	Mean 58.8 61.3	30 min
Tune et al 1981 [8]	Pro	Ho	Cardiac surgery	–	29	29–75	1 week
Miller et al 1988 [9]	RCT, DB, PC	Ho	Pre-surgical patients	–	36	59–81	1 h
Rovner et al 1988 [10]	CS	Nh	D	Ns	22	Mean 80.8	–

AD = Alzheimer's disease; Com = Community dwelling; CS = Cross sectional; D = Dementia; DB = Double blinded; Ho = Hospital; MMSE = Mini-mental state examination; N = Normal subjects; Nh = Nursing home; ns = Not stated; PC = Placebo-controlled; Pro = Prospective study; RCT = Randomised controlled trial

Intervention	Primary outcome measures	Results	Remarks	Quality of study
Scopolamine 0.2 mg/placebo	Verbal memory, praxis and language	Impairment of new learning and praxis in the elderly		High
Scopolamine/ glycopyrrolate	Memory and attentional tests	Elderly impaired in all tests, young in two with highest dose		High
Scopolamine/ placebo	Cognitive and behavioral tests	AD more impaired. Particularly new learning and semantic knowledge. Behavioral symptoms in AD		High
–	Diagnosis of delirium	7/8 with delirium had high serum anticholinergic levels. 4/17 in controls		Low
Scopolamine 0.005 mg/kg/ placebo	Cognitive tests: MMSE	Low serum anticholinergic levels and cognitive impairment in two tests, in scopolamine treated		Moderate
–	Cognition and self-care capacity (PDRS)	High levels of serum anticholinergic activity associated with lower self-care score	CS	Low

Table 26.3 *Anxiolytics, hypnotics-sedatives.*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups	Follow-up time
Larson et al 1987 [2]	Pro	Com	D (suspected)	Ns	308	60+	≥1 y
Hanlon et al 1998 [11]	Pro	Com	–	–	2 765	<74 (1 873) 75–84 (775) 85+ (117)	3 y
Greenblatt et al 1978 [12]	Pro, MCT	Com	–	–	2 111	Mean 57	–
Greenblatt et al 1977 [13]	Pro	Com	–	–	2 542	Mean 54.5	–
Pomara et al 1984 [14,15]	RCT, DB, PC, C–O	Com	N	–	12	60–77	1 h, 3 h
Hinrichs et al 1987 [16]	RCT, DB, PC, C–O	Com	N	–	12 + 12 + 12	19–28 40–45 61–73	3.5 h
Fairweather et al 1992 [19]	RCT, DB, PC	Com	N	–	24	63–80	7 d
Hemmeter et al 2000 [20]	RCT, DB, PC	Com	N		12	60–70	10 h

Intervention	Primary outcome measures	Results	Remarks	Quality of study
–	Probable ADR as cause of cognitive impairment	35 with probable ADR causing cognitive impairment. Sedatives-hypnotics use strongest predictor		Low
–	Memory tests (SPMSQ, OMC)	Current use of Bz performed worse on memory tests. More errors if higher dose or long term use		Low
Nitrazepam	Signs of CNS depression	Signs of CNS depression in 11% of elderly 80+ using nitrazepam		Low
Flurazepam	Signs of CNS depression	Signs of CNS depression in 7.1% of elderly 80+ using flurazepam		Low
Diazepam 2.5, 5, 10 mg/ placebo	Buschke selective reminding, visual memory, digit span/supraspan	Five tasks significantly impaired with all doses		High
Diazepam 0.2 mg/kg/ placebo	Addition, number learning, immediate and delayed free recall etc	Negative effect of diazepam in almost all tasks		High
Zolpidem 5, 10 mg/ placebo	Sternberg memory scanning	No impact on cognitive function		High
Zopiclone 7.5 mg/temazepam 20 mg/placebo		No effect on memory performance		High

The table continues on the next page

Table 26.3 *continued*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups	Follow-up time
Allain et al 2003 [21]	RCT, DB, PC, C–O	Com	N		48	65+	10 h

ADR = Adverse drug reaction; Bz = Com = Community dwelling; C–O = Crossover; D = Dementia; DB = Double-blind; MCT = Multi-centre trial; N = Normal subjects; ns = Not stated; PC = Placebo-controlled; Pro = Prospective study; RCT = Randomised controlled trial

	Intervention	Primary outcome measures	Results	Remarks	Quality of study
	Zopiclone 3.75 mg/ zolpidem 5 mg/ lormetazepam 1 mg/placebo	Sternberg memory scanning, learning memory	No effect on all tests but one item in Sternbergs test (zopiclone)		High

Table 26.4 *Antipsychotics.*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups	Follow-up time
Devanand et al 1989 [26]	SB,PC, C–O	Com	AD, psychosis or behavioral symptoms	Ns	9	Mean 71.6	8 w
Devanand et al 1998 [27]	RCT, DB, PC	Com	Probable AD, psychotic or disruptive behavior	CDR 1–2 (43) CDR 3 (28)	71		6 w
Legangneux et al 2000 [28]	RCT, DB, PC, C–O	Com	N	–	16	65–80	24 h
Katz et al 1999 [29]	RCT, DB, PC	Nh	AD, psychosis or behavioral symptoms	Severe FAST ≥7A	625	82.7	12 w
De Deyn et al 1999 [30]	RCT, DB, PC	Nh	AD, behavioral symptoms	Severe FAST ≥6 (92%)	344	56–97	13 w
Street et al 2000 [31]	RCT, DB, PC	Nh	AD, psychotic and/or behavioral symptoms	Ns	206	61–97	6 w
Sajatovic et al 1998 [32]	O, C–O		Schizophrenia	Ns	27	65–80	8 w

Intervention	Primary outcome measures	Results	Remarks	Quality of study
Haloperidol 1–5 mg/placebo	Cognition measured by MMSE	Trend towards cognitive decline, only partial recovery	Small study	Low
Haloperidol 0.5–0.75 mg; 2–3 mg/placebo	Cognition measured by MMSE	No effect observed		High
Haloperidol 2 mg/amisulpiride 50, 200 mg/placebo	Cognition measured by CDR computerized assessment	Significant impairment by haloperidol compared to amisulpiride (but not placebo)	Small sample. One drop-out, replaced	Moderate
Risperidon 0.5, 1, 2 mg/placebo	Cognition measured by MMSE	No significant effect		High
Risperidon 0.25–4 mg/haloperidol 0.25–4 mg/placebo	Cognition measured by MMSE	No significant effect of risperidone but with haloperidol compared to placebo		High
Olanzapine 5, 10, 15 mg/placebo	Cognition measured by MMSE	No significant effect		High
Olanzapine 2.5–20 mg	Cognition measured by MMSE	No significant effect		Low

The table continues on the next page

***Table 26.4** continued*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups	Follow-up time
McShane et al 1997 [41]	Pro	Com	D	Mean MMSE 15.5 at entry	71	Mean 72.6	2 years
Allain et al 2003 [21]	RCT, DB, PC, C–O	Com	N	–	12		8 h

AD = Alzheimer's disease; ADR = Adverse drug reaction; Bz = Border Zone; Com = Community dwelling; C–O = Crossover; D = Dementia; DB = Double-blind; FAST = Functional assessment staging; MCT = Multi-centre trial; MMSE = Mini-mental state examination; N = Normal subjects; Nh = Nursing home; ns = Not stated; O = Open study; PC = Placebo-controlled; Pro = Prospective study; RCT = Randomised controlled trial

	Intervention	Primary outcome measures	Results	Remarks	Quality of study
	–	Cognition measured by expanded MMSE	Double mean decline in anti-psychotic users	Cogntive decline and antipsychotic use measured concomitantly	Low
	Risperidone 0.25, 0.5 mg/lorazepam 1 mg /placebo	Battery including psycho-motor and cognitive tests	No effect on working or long-term memory. Minor impairment of information processing	Small sample	Moderate

Table 26.5 *Antidepressants.*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Branconnier et al 1982 [45]	RCT, DB, PC, C–O	Com	N	–	15	60–75
Moskowitz et al 1986 [46]	DB, PC, C–O	Com	N	–	15	Mean 63
Ghose et al 1987 [48]	RCT, DB, PC, C–O	Com	N	–	6	66–72
Ogura et al 1983 [47]	DB, C–O	Students, Nh	N	–	7 young, 7 elderly	21–25 65–74
Marcopulos et al 1990 [49]	CS, CC	Com	Depression	Ns	27 treated, 27 matched controls	

Follow-up time	Intervention	Primary outcome measures	Results	Remarks	Quality of study
4 h	Amitriptyline 50 mg/placebo	Battery of tests for episodic, sensory, primary and secondary memory	Marked disruption of verbal recall (no effect on recognition) from secondary memory		High
4 h	Amitriptyline 50 mg/trazodone 100 mg/placebo, in 3 sessions	Test battery for visual search, attention, tracking, information processing and vigilance	Amitriptyline impaired vigilance, divided attention and critical tracking tasks	No info about randomization	Moderate
24 h	Lofepramine 70, 105, 140 mg/amitriptyline 50 mg/placebo	Choice reaction time (CRT), CFF, letter cancellation, short term memory tests	Lofepramine (140) improved CRT and letter cancellation. No difference from placebo in other tests. Negative effects of amitriptyline in several tests		Moderate
24 h	Dotheipine 25 mg; amitriptyline 25 mg		Decreased CFF by amitriptyline for up to 24 h	No placebo	Moderate
–	Amitriptyline 10–150 mg; doxepin 50–200 mg; miscellaneous	WAIS battery	Mild, but significant, deficit in 6 measures of memory performance		Low

The table continues on the next page

Table 26.5 *continued*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Kerr et al 1993 [50]	RCT, DB, parallel-group	Ns	Depression	MADRS 15–20	66	
Legg et al 1976 [51]	RCT, DB, PC	Ho	Depression	Ns	49	16–70
Glass et al 1981 [52]	RCT, DB, PC, C–O	Com	Major (n = 25) or minor depressive disorder. Matched N	Ns	32 + 32	30–63
Georgotas et al 1989 [54]	RCT, DB, PC	Com	Unipolar major depression	Hamilton ≥16	78	55–82
Siegfried et al 1986 [53]	RCT, DB	Nh, Ho	Major depression	Hamilton ≥18	75	67–83

Follow-up time	Intervention	Primary outcome measures	Results	Remarks	Quality of study
42 d	Amitriptyline 75 mg; fluoxetine 20 mg/ placebo	MADRS, HAM-D, CFF, CRT, word recognition, memory scanning	CFF threshold improved in fluoxetine but not amitriptyline group. Better memory improvement with fluoxetine	12 withdrawn due to ADE. Little info about subjects	Low
3 w	Imipramine 300 mg; chlorpromazine 600 mg/ placebo, 5 weeks	Six WAIS-subtests, Wechsler memory scale, Benton visual retention etc	Impairment of short term visual memory (Benton). Also failure to improve in tests of new learning	32% dropout due to poor effect. Randomization not described	Low
3 w	Imipramine 75 mg/placebo, 3 weeks	Tapping speed, lift-off reaction time, item recognition procedure	Improvement in short-term memory. Else no effects		High
7 w	Nortriptyline; phenelzine/ placebo	Cognitive battery including WAIS, Guild memory scale etc	No effect on any measure	Doses not given	Moderate
4 w	Maprotiline 100 mg; mianserin 40 mg; nomifensine 100 mg, 4 weeks	HAM-D, CFF, digit span CRT, Test d2, paired associated learning	All drugs gave cognitive improvement, but most slowly with maprotiline	No placebo	Moderate

The table continues on the next page

***Table 26.5** continued*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Hindmarch et al 1990 [56]	RCT, DB, PC, C–O	Com	N	–	10 women, 21 men	25–45 60–75

ADE = Adverse drug event; CC = Case-control; CFF = Critical flicker fusion; Com = Community dwelling; C–O = Crossover; CS = Cross-sectional; DB = Double-blind; Ho = Hospital; MCT = Multi-center trial; MMSE = Mini-mental state examination; N = Normal subjects; Nh = Nursing home; ns = Not stated; O = Open study; PC = Placebo-controlled; RCT = Randomised controlled trial; WAIS = Wechsler adult intelligence scale

	Follow-up time	Intervention	Primary outcome measures	Results	Remarks	Quality of study
	9 d	Sertraline 25–100 mg; mianserin 10–30 mg	CFF, CRT, immediate memory tests, sensorimotor tracking	No effect of sertraline on any objective measure of performance	10 drop-outs in 2nd study mianserin group	Moderate

Table 26.6 *Antiparkinsonian drugs.*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Van Spaendonck et al 1993 [60]	CS	Com	PD	Ns	11 on anticholinergic therapy 30 de novo	Mean 61.5 and 58.1
Meco et al 1984 [61]	CS	Com	PD and healthy controls	Hoehn and Yahr stage 2–3	33 PD 14 controls	Mean 66.2 and 62.9
Growdon et al 1998 [62]	Pro	Com	PD	Hoehn and Yahr mean 2.2	387	Mean 63.7
Müller et al 2001 [63]	DB, PC	Ho	PD, treated or untreated	Hoehn and Yahr 2.10–2.29	16 + 14 + 10	29–69 47–72 37–74
Goetz et al 2001 [64]	Pro	Com	PD	Hoehn and Yahr stage 2–3	89	Mean 67.7
Serby et al 1980 [66]	RCT?	Ns	Advanced PD	Advanced	81	Ns

	Follow-up time	Intervention	Primary outcome measures	Results	Remarks	Quality of study
	–	–	WAIS-R and card sorting test	Patients on anticholinergic therapy performed worse on card sorting test		Low
	–	–	Bender visual motor gestalt, Wechsler-Bellevue, Toulouse-Pieron	Patients on anticholinergics, alone or in combination performed the worst. Best results with L-Dopa alone		Low
	6 months	L-Dopa (mean 286 mg daily)	Digit span, digit symbol, selective reminding, verbal fluency etc	No impairment on any test		Low
	90 min	L-Dopa 250 mg/ placebo	Simple reaction time (SRT)	Significant increase in SRT	Randomization not described	Moderate
	48 months	–	Rush Hallucination Inventory	Association of persistent hallucinations with L-Dopa + agonist treatment		Low
	–	Bromocriptine mean 33 mg; lergotrile mean 39 mg	Ns	In both bromocriptine and lergotril patients, 26% developed mental changes	Very poor method description	Low

The table continues on the next page

Table 26.6 *continued*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Portin et al 1983 [67]	Pro	Ns	PD	Ns	7 with L-Dopa 18 de novo	58–74 50–76
McEvoy et al 1987 [59]	RCT, DB, C–O	Com	N	–	30	60–72

CFF = Critical flicker fusion; Com = Community dwelling; C–O = Crossover; CS = Cross-sectional; DB = Double-blind; Ho = Hospital; N = Normal subjects; ns = Not stated; PC = Placebo-controlled; PD = Parkinson's disease; Pro = Prospective study; RCT = Randomised controlled trial; WAIS = Wechsler adult intelligence scale

	Follow-up time	Intervention	Primary outcome measures	Results	Remarks	Quality of study
	8–10 y	Selegiline 5–10 mg daily, 4 weeks	Various memory tests, tests for cognitive function, vigilance and motor speed	Improvement in memory and motor speed in patients without progressive dementia, but deterioration in vigilance and set shifting	Poor method description (eg randomization)	Low
	4 d	Amantadine 100 mg; trihexyphenidyl 4 mg, twice daily for 4 days	Digit span, free recall, recognition-signal detection, retrieval-familiar categories	Memory deficits and subjective memory loss and confusion with trihexyphenidyl		Moderate

Table 26.7 *Anticonvulsants.*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Smith et al 1987 [70]	RCT, DB	Multicenter Com	Simple, complex or generalised seizures. Controls	Ns	622 patients, 75 controls	18–82, 17–72
Meador et al 1991 [71]	RCT, DB, PC, C–O	Com	N	–	21	21–48
Meador et al 1990 [73]	RCT, DB, C–O	Com	Partial complex epilepsy	Ns	15	19–62
Meador et al 1995 [74]	RCT, DB, C–O	Com	N	–	59	19–46

Follow-up time	Intervention	Primary outcome measures	Results	Remarks	Quality of study
36 m	Phenobarbital, carbamazepine, phenyoin and primidone	Tests of intellectual ability (WAIS), behavior (CFF etc) and mood/emotion (POMS)	Less effects of carbamazepine on tests of attention/concentration and motor performance		High
1 m	Carbamazepine 200 mg; phenytoin 100 mg, 1 month/ placebo	Extensive battery of cognitive tests and POMS	Impairment of Stroop, CRT, grooved pegboard, Hopkins and POMS. Only small differences between the drugs	9 of 30 dropped out due to ADE	Moderate
3 m	Carbamazepine 6–12 µg/ml; phenobarbital 10–20 µg/ml; phenytoin 15–40 µg/ml	Digit span, selective reminding, digit symbol, CRT, POMS etc	Phenobarbital gave significantly more impairment of digit symbol	6 patients discontinued	Moderate
7,5 m	Phenobarbital 120–360 mg; phenytoin 200–600 mg; valproate 500–1 500 mg, 1 month	Large test battery for cognitive and motor speed, memory, other cognitive tasks, mood and symptoms	All three drugs gave some untoward effect compared to baseline. Phenobarbital gave worst performance. No difference between phenytoin and valproate	16 patients discontinued	Moderate

The table continues on the next page

Table 26.7 *continued*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Grünewald et al 1994 [76]	RCT, DB, PC, C–O	Com	Refractory partial seizures	Ns	45	15–61

AED = Astheno emotional disorder; Com = Community dwelling; C–O = Crossover; CRT = Choice reaction time; DB = Double-blind; N = Normal subjects; ns = Not stated; PC = Placebo-controlled; RCT = Randomised controlled trial

	Follow-up time	Intervention	Primary outcome measures	Results	Remarks	Quality of study
	68 w	Vigabatrin 1.5 g twice daily, 20 weeks/ placebo	Measures for memory, concentration, mood behavior	Small but significant reduction in motor speed and design learning		High

Table 26.8 *Opioids.*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Hanks et al 1995 [78]	RCT, DB, PC, C–O	Com	N		12	30–47
O'Neill et al 2000 [79]	RCT, DB, PC, C–O	Com	N		10	25–40
Zacny et al 1994 [80]	RCT, DB, PC, C–O	Com	N		12	21–33
Walker et al 1999 [81]	RCT, DB, PC, C–O	Com	N		16	21–32
Saarialho-Kere et al 1989 [82]	RCT, DB, PC, C–O	Com	N		9	20–26
Moulin et al 1996 [83]	RCT, DB, PC, C–O	Com	Chronic non-malig-nant pain	5/10 on VAS	46	22–67

Follow-up time	Intervention	Primary outcome measures	Results	Remarks	Quality of study
6 h	Morphine 10, 15 mg, po/ lorazepam 1 mg, po/ placebo	CRT, memory scanning, picture recognition etc	Morphine (10, 15 mg) impaired word recall and picture recognition. CRT improved with 15 mg		High
36 h	Morphine 10 mg, po/ dextropropoxiphene 100 mg, po/ lorazepam 1 mg, po/ placebo	CRT, memory scanning, picture recognition etc	No substantial effect of any opioid on cognition, compared with lorazepam		High
5 h	Morphine 0–10 mg/ 70 kg	Digit symbol substitution (DSST), reaction times	Morphine impaired DSST, mostly dose dependently		High
7 h	Morphine, meperidine, hydromorphone, graded iv doses	DSST, logical reasoning	All three gave dose-dependent impairment of DSST, least with morphine		High
4.5 h	Oxycodone 0.13 mg/kg, im/diphenhydramine 100 mg, po/placebo	DSST, reaction time, divided attention	Reaction time and attention transiently impaired by oxycodone		High
22 w	Morphine 60 mg twice a day/benztropine 1 mg twice a day	High sensitivity cognitive screen	No difference between morphine and placebo	15 drop-outs	Moderate

The table continues on the next page

Table 26.8 *continued*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Banning et al 1992 [84]	Pro	Ns	Cancer pain	Ns	16 on opioids 16 controls	
Sjögren et al 2000 [85]	Pro	Ns	Cancer pain	60–90/ 100 on VAS	130	40–76
Schor et al 1992 [86]	Pro	Ho			234	65+
Egbert et al 1990 [87]	RCT	Ho	After major elective surgery		83	Mean 67

CFF = Critical flicker fusion; Com = Community dwelling; C–O = Crossover; CRT = Choice reaction time; CS = Cross-sectional; DB = Double-blind; Ho = Hospital; N = Normal subjects; ns = Not stated; PC = Placebo-controlled; PCA = patient-controlled analgesia; Pro = Prospective study; RCT = Randomised controlled trial; VAS = Visual analogue scale

Follow-up time	Intervention	Primary outcome measures	Results	Remarks	Quality of study
Ns	Morphine 30–400 mg	Continuous reaction time	Prolongation in morphine group		Low
7 h	Morphine 20–420 mg	Continuous reaction time, finger tapping, paced auditory serial addition task	Long term opioid use per se did not influence test performance		Low
14 d	–	Instrument for detection of delirium	Delirium developed in 91 patients, narcotic use was one risk factor		Low
3 d	Morphine intra muscular or in patient-controlled analgesia (PCA)	Postoperative confusion	Significant postoperative confusion in 18% of intra muscular and 2.3% of PCA treated		Moderate

Table 26.9 *Non-steroidal anti-inflammatory drug (NSAID).*

Author Year, reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Hanlon et al 1997 [89]	Pro, Co	Com	N (cognitively intact at baseline)	–	2 765	Ns
Saag et al 1995 [90]	Pro, Co	Com	N (cognitively intact at baseline)	–	2 087	67–97
Wysenbeek et al 1988 [88]	Pro	Com	Osteoarthritis	Ns	12	Mean 70.1
May et al 1992 [91]	Pro, Co	Com	Miscellaneous	–	1 310	
Bruce-Jones et al 1994 [92]	RCT, DB, PC, C–O	Com	N	–	20	55–65 65+

Com = Community dwelling; C–O = Crossover; Co = Cohort study; CRT = Choice reaction time; CS = Cross-sectional; DB = Double-blind; MMSE = Mini-mental state examination; N = Normal subjects; ns = Not stated; NSAID = Non-steroidal anti-inflammatory drug; PC = Placebo-controlled; PCA = patient-controlled analgesia; Pro = Prospective study; RCT = Randomised controlled trial; VAS = Visual analogue scale; WAIS = Wechsler adult intelligence scale

Follow-up time	Inter-vention	Primary outcome measures	Results	Remarks	Quality of study
3 y	–	Short portable mental status questionnaire	Moderate or high NSAID doses significantly worse in memory tests	NSAID use and cognitive measures assessed concomitantly	Low
4 y	–	Immediate word recall	High dose NSAID associated with decline in word recall	NSAID use and cognitive measures assessed concomitantly	Low
3 w	Naproxen 750 mg/d	WAIS, Bender Gestalt test	Four subjects deteriorated in one test and one of them in two	Small sample, non-controlled	Low
–	–	MMSE	No effect of NSAID or aspirin use on MMSE score or in the five dimensions of cognition		Low
7 d	Indomethacin 75 mg/d/placebo	Test battery of arousal, attention, integration, coordination, memory and mood	No effect on attention and psychomotor speed. Signs of improvement of sensorimotor coordination and short-term memory		Moderate

Table 26.10 *Corticosteroides.*

Author Year Reference	Type of study	Setting	Disease diagnosis	Severity	No of individuals	Age-groups
Newcomer et al 1994 [96]	RCT, DB, PC	Com	N	–	19	Mean 38.3
Kirschbaum et al 1996 [99]	RCT, PC	Com	N	–	40	Mean 24.7
Newcomer et al 1999 [97]	RCT, DB, PC	Com	N	–	51	18–30
Schmidt et al 1999 [98]	RCT, DB, PC	Com	N	–	24	18–38
Young et al 1999 [101]	RCT, DB, PC, C–O	Com	N	–	20	21–44
de Quervain et al 2000 [95]	RCT, DB, PC, C–O	Com	N	–	36	20–40

Follow-up time	Intervention	Primary outcome measures	Results	Quality of study
11 d	Dexamethasone 0.5, 1, 1, 1 mg/ placebo, for 4 days	Verbal declarative memory performance, attention, vigilance and visuoperceptual function	Impairment of verbal declarative memory performance (paragraph recall test) in dexamethasone treated	High
30 min	Hydrocortisone 10 mg/placebo	Procedural, declarative memory and spatial thinking	Impairment of declarative memory and spatial thinking in cortisol treated	High
6 d	Cortisol 40, 160 mg/ placebo for 4 days	Paragraph recall, Stroop CW test, verbal fluency etc	Impairment of verbal declarative memory with higher cortisol dose	High
8 d	Prednisone 160 mg/placebo for 4 days	EEG, mood rating, attention task, memory recall	Greater increase in negative emotion, recalled fewer objects, greater frontal EEG alpha act	High
4 w	Hydrocortisone twice daily for 10 days/placebo	Cambridge Neuropsychological Test Automated Battery	Impairments of visuospatial memory and paired associate learning subtest	High
1 h	Cortisone 25 mg/placebo	Free recall test and recognition test	Impaired free recall but not recognition	High

The table continues on the next page

Table 26.10 *continued*

Author Year Reference	Type of study	Setting	Disease diagnosis	Severity	No of individuals	Age-groups
TBCDS 1972 [94]	Pro	Com	–	–	700	–

Com = Community dwelling; C–O = Crossover; Co = Cohort study; CRT = Choice reaction time; CS = Cross-sectional; DB = Double-blind; MMSE = Mini-mental state examination; N = Normal subjects; ns = Not stated; NSAID = Non-steroidal anti-inflammatory drug; PC = Placebo-controlled; PCA = patient-controlled analgesia; Pro = Prospective study; RCT = Randomised controlled trial; VAS = Visual analogue scale; WAIS = Wechsler adult intelligence scale

	Follow-up time	Intervention	Primary outcome measures	Results	Quality of study
	–	–		Significantly more psychiatric disturbances in prednisolone treated	Low

Table 26.11 *Anti-ulcer agents.*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Oslin et al 1999 [107]	RCT, DB, PC, C–O	Com	N	–	12	Mean 71.2
Slugg et al 1992 [109]	Pro	Ho	Various medical and surgical	–	41 using ranitidine	Mean 62.4 68.4

CNS–ADR = Central nervous system-adverse drug reactions; C-O = Crossover;
Com = Community dwelling; DB = Double-blind; Ho = Hospital; ns = Not stated;
PC = Placebo-controlled; Pro = Prospective study; RCT = Randomised controlled trial

	Follow-up time	Intervention	Primary outcome measures	Results	Quality of study
	2.5 h	Cimetidine 400–1 600 mg in increasing doses/placebo	Cognitive test battery	No observable decrements	Moderate
	ns	–	CNS-ADR evaluated by Naranjo rating system	Confusion, disorientation etc more frequent in renal impairment and higher plasma levels	Low

Table 26.12 *Beta-receptor blocking agents.*

Author Year Reference	Type of study	Setting	Disease/ diagnosis	Severity	No of individuals	Age-groups
Perez-Stable et al 2000 [121]	RCT, DB, PC	Com	Hyper-tension	–	312	22–59
Muldoon et al 2002 [122]	RCT, DB, PC, C–O	Com	Hyperten-sion + nor-motensive	–	98 + 32	25–55

C-O = Crossover; Com = Community dwelling; DB = Double-blind; PC = Placebo-controlled; RCT = Randomised controlled trial

Follow-up time	Intervention	Primary outcome measures	Results	Quality of study
12 m	Propranolol 80–400 mg/d/placebo	Cognitive test battery with digital symbol substitution Californian verbal learning test etc	No significant difference in 11 out of 13 tests	High
8 w	Atenolol, metoprolol, hydrochlorothiazide, methyldopa, enalapril and verapamil	In-depth neuropsychological assessments	Reduction of simple motor speed slowed completion of two tests measuring perceptuomotor speed and mental flexibility. Favorably affected performance on several tests requiring working memory	High

References

1. Moore AR, O'Keeffe ST. Drug-induced cognitive impairment in the elderly. Drugs Aging 1999;15:15-28.

2. Larson EB, Kukull WA, Buchner D, Reifler BV. Adverse drug reactions associated with global cognitive impairment in elderly persons. Ann Intern Med 1987; 107:169-73.

3. Katz IR, Parmelee P, Brubaker K. Toxic and metabolic encephalopathies in long-term care patients. Int Psychogeriatr 1991;3:337-47.

4. Starr JM, Whalley LJ. Drug-induced dementia. Incidence, management and prevention. Drug Saf 1994;11:310-7.

5. Zemishlany Z, Thorne AE. Anticholinergic challenge and cognitive functions: a comparison between young and elderly normal subjects. Isr J Psychiatry Relat Sci 1991;28:32-41.

6. Flicker C, Ferris SH, Serby M. Hypersensitivity to scopolamine in the elderly. Psychopharmacology (Berl) 1992;107: 437-41.

7. Sunderland T, Tariot PN, Cohen RM, Weingartner H, Mueller EA, 3rd, Murphy DL. Anticholinergic sensitivity in patients with dementia of the Alzheimer type and age-matched controls. A dose-response study. Arch Gen Psychiatry 1987;44:418-26.

8. Tune LE, Damlouji NF, Holland A, Gardner TJ, Folstein MF, Coyle JT. Association of postoperative delirium with raised serum levels of anticholinergic drugs. Lancet 1981;2:651-3.

9. Miller PS, Richardson JS, Jyu CA, Lemay JS, Hiscock M, Keegan DL. Association of low serum anticholinergic levels and cognitive impairment in elderly presurgical patients. Am J Psychiatry 1988;145:342-5.

10. Rovner BW, David A, Lucas-Blaustein MJ, Conklin B, Filipp L, Tune L. Self-care capacity and anticholinergic drug levels in nursing home patients. Am J Psychiatry 1988; 145:107-9.

11. Hanlon JT, Horner RD, Schmader KE, Fillenbaum GG, Lewis IK, Wall WE, Jr, et al. Benzodiazepine use and cognitive function among community-dwelling elderly. Clin Pharmacol Ther 1998; 64: 684-92.

12. Greenblatt DJ, Allen MD. Toxicity of nitrazepam in the elderly: a report from the Boston Collaborative Drug Surveillance Program. Br J Clin Pharmacol 1978;5:407-13.

13. Greenblatt DJ, Allen MD, Shader RI. Toxicity of high-dose flurazepam in the elderly. Clin Pharmacol Ther 1977;21: 355-61.

14. Pomara N, Stanley B, Block R, Guido J, Russ D, Berchou R, et al. Adverse effects of single therapeutic doses of diazepam on performance in normal geriatric subjects: relationship to plasma concentrations. Psychopharmacology (Berl) 1984;84: 342-6.

15. Pomara N, Stanley B, Block R, Guido J, Stanley M, Greenblatt DJ, et al. Diazepam impairs performance in normal

elderly subjects. Psychopharmacol Bull 1984;20:137-9.

16. Hinrichs JV, Ghoneim MM. Diazepam, behavior, and aging: increased sensitivity or lower baseline performance? Psychopharmacology (Berl) 1987; 92:100-5.

17. Patterson JF. Triazolam syndrome in the elderly. South Med J 1987;80:1425-6.

18. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs 2004;18:37-48.

19. Fairweather DB, Kerr JS, Hindmarch I. The effects of acute and repeated doses of zolpidem on subjective sleep, psychomotor performance and cognitive function in elderly volunteers. Eur J Clin Pharmacol 1992;43:597-601.

20. Hemmeter U, Muller M, Bischof R, Annen B, Holsboer-Trachsler E. Effect of zopiclone and temazepam on sleep EEG parameters, psychomotor and memory functions in healthy elderly volunteers. Psychopharmacology (Berl) 2000;147: 384-96.

21. Allain H, Tessier C, Bentue-Ferrer D, Tarral A, Le Breton S, Gandon M, et al. Effects of risperidone on psychometric and cognitive functions in healthy elderly volunteers. Psychopharmacology (Berl) 2003;165:419-29.

22. Hill KP, Oberstar JV, Dunn ER. Zolpidem-induced delirium with mania in an elderly woman. Psychosomatics 2004;45:88-9.

23. Brodeur MR, Stirling AL. Delirium associated with zolpidem. Ann Pharmacother 2001;35:1562-4.

24. Freudenreich O, Menza M. Zolpidem-related delirium: a case report. J Clin Psychiatry 2000;61:449-50.

25. Steele C, Lucas MJ, Tune L. Haloperidol versus thioridazine in the treatment of behavioral symptoms in senile dementia of the Alzheimer's type: preliminary findings. J Clin Psychiatry 1986;47:310-2.

26. Devanand DP, Sackeim HA, Brown RP, Mayeux R. A pilot study of haloperidol treatment of psychosis and behavioral disturbance in Alzheimer's disease. Arch Neurol 1989;46:854-7.

27. Devanand DP, Marder K, Michaels KS, Sackeim HA, Bell K, Sullivan MA, et al. A randomised, placebo-controlled dose-comparison trial of haloperidol for psychosis and disruptive behaviors in Alzheimer's disease. Am J Psychiatry 1998;155:1512-20.

28. Legangneux E, McEwen J, Wesnes KA, Bergougnan L, Miget N, Canal M, et al. The acute effects of amisulpride (50 mg and 200 mg) and haloperidol (2 mg) on cognitive function in healthy elderly volunteers. J Psychopharmacol 2000;14:164-71.

29. Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomised, double-blind trial. Risperidone Study Group. J Clin Psychiatry 1999;60:107-15.

30. De Deyn PP, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PL, Eriksson S, et al. A randomised trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 1999;53:946-55.

31. Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomised, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry 2000; 57:968-76.

32. Sajatovic M, Perez D, Brescan D, Ramirez LF. Olanzapine therapy in elderly patients with schizophrenia. Psychopharmacol Bull 1998;34:819-23.

33. Beuzen JN, Taylor N, Wesnes K, Wood A. A comparison of the effects of olanzapine, haloperidol and placebo on cognitive and psychomotor functions in healthy elderly volunteers. J Psychopharmacol 1999;13:152-8.

34. Ravona-Springer R, Dolberg OT, Hirschmann S, Grunhaus L. Delirium in elderly patients treated with risperidone: a report of three cases. J Clin Psychopharmacol 1998;18:171-2.

35. Tavcar R, Dernovsek MZ. Risperidone-induced delirium. Can J Psychiatry 1998;43:194.

36. Morikawa M, Kishimoto T. Probable dementia with Lewy bodies and risperidone-induced delirium. Can J Psychiatry 2002;47:976.

37. Samuels S, Fang M. Olanzapine may cause delirium in geriatric patients. J Clin Psychiatry 2004;65:582-3.

38. Schuster P, Gabriel E, Kufferle B, Strobl G, Karobath M. Reversal by physostigmine of clozapine-induced delirium. Clin Toxicol 1977;10:437-41.

39. Centorrino F, Albert MJ, Drago-Ferrante G, Koukopoulos AE, Berry JM, Baldessarini RJ. Delirium during clozapine treatment: incidence and associated risk factors. Pharmacopsychiatry 2003; 36:156-60.

40. Jackson CW, Markowitz JS, Brewerton TD. Delirium associated with clozapine and benzodiazepine combinations. Ann Clin Psychiatry 1995;7:139-41.

41. McShane R, Keene J, Gedling K, Fairburn C, Jacoby R, Hope T. Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up. BMJ 1997;314:266-70.

42. DePaulo JR, Jr., Folstein MF, Correa EI. The course of delirium due to lithium intoxication. J Clin Psychiatry 1982;43:447-9.

43. Bartha L, Marksteiner J, Bauer G, Benke T. Persistent cognitive deficits associated with lithium intoxication: a neuropsychological case description. Cortex 2002;38:743-52.

44. Honig A, Arts BM, Ponds RW, Riedel WJ. Lithium induced cognitive side-effects in bipolar disorder: a qualitative analysis and implications for daily practice. Int Clin Psychopharmacol 1999;14:167-71.

45. Branconnier RJ, DeVitt DR, Cole JO, Spera KF. Amitriptyline selectively disrupts verbal recall from secondary memory of the normal aged. Neurobiol Aging 1982;3: 55-9.

46. Moskowitz H, Burns MM. Cognitive performance in geriatric subjects after acute treatment with antidepressants. Neuropsychobiology 1986;15 Suppl 1: 38-43.

47. Ogura C, Kishimoto A, Mizukawa R, Kunimoto N, Hazama H, Ryoke K, et al. Influence of single doses of dothiepin and amitriptyline on physiological measures and psychomotor performance in normal young and elderly volunteers. Neuropsychobiology 1983;10:103-7.

48. Ghose K, Sedman E. A double-blind comparison of the pharmacodynamic effects of single doses of lofepramine, amitriptyline and placebo in elderly subjects. Eur J Clin Pharmacol 1987;33:505-9.

49. Marcopulos BA, Graves RE. Antidepressant effect on memory in depressed older persons. J Clin Exp Neuropsychol 1990;12:655-63.

50. Kerr JS, Fairweather DB, Hindmarch I. Effects of fluoxetine on psychomotor performance, cognitive function and sleep in depressed patients. Int Clin Psychopharmacol 1993;8:341-3.

51. Legg JF, Stiff MP. Drug-related test patterns of depressed patients. Psychopharmacology (Berl) 1976;50: 205-10.

52. Glass RM, Uhlenhuth EH, Hartel FW, Matuzas W, Fischman MW. Cognitive dysfunction and imipramine in outpatient depressive. Arch Gen Psychiatry 1981;38:1048-51.

53. Siegfried K, O'Connolly M. Cognitive and psychomotor effects of different antidepressants in the treatment of old age depression. Int Clin Psychopharmacol 1986;1:231-43.

54. Georgotas A, McCue RE, Reisberg B, Ferris SH, Nagachandran N, Chang I, et al. The effects of mood changes and antidepressants on the cognitive capacity of elderly depressed patients. Int Psychogeriatr 1989;1:135-43.

55. Young RC, Mattis S, Alexopoulos GS, Meyers BS, Shindledecker RD, Dhar AK. Verbal memory and plasma drug concentrations in elderly depressives treated with nortriptyline. Psychopharmacol Bull 1991;27:291-4.

56. Hindmarch I, Shillingford J, Shillingford C. The effects of sertraline on psychomotor performance in elderly volunteers. J Clin Psychiatry 1990;51 Suppl B:34-6.

57. Branconnier RJ, Cole JO, Ghazvinian S, Rosenthal S. Treating the depressed elderly patient: the comparative behavioral pharmacology of mianserin and amitriptyline. Adv Biochem Psychopharmacol 1982;32:195-212.

58. Bailer U, Fischer P, Kufferle B, Stastny J, Kasper S. Occurrence of mirtazapine-induced delirium in organic brain disorder. Int Clin Psychopharmacol 2000;15:239-43.

59. McEvoy JP, McCue M, Spring B, Mohs RC, Lavori PW, Farr RM. Effects of amantadine and trihexyphenidyl on memory in

elderly normal volunteers. Am J Psychiatry 1987;144:573-7.

60. Van Spaendonck KP, Berger HJ, Horstink MW, Buytenhuijs EL, Cools AR. Impaired cognitive shifting in parkinsonian patients on anticholinergic therapy. Neuropsychologia 1993;31:407-11.

61. Meco G, Casacchia M, Lazzari R, Franzese A, Castellana F, Carta A, et al. Mental impairment in Parkinson's disease. The role of anticholinergic drugs. Acta Psychiatr Belg 1984;84:325-35.

62. Growdon JH, Kieburtz K, McDermott MP, Panisset M, Friedman JH. Levodopa improves motor function without impairing cognition in mild non-demented Parkinson's disease patients. Parkinson Study Group. Neurology 1998;50:1327-31.

63. Müller T, Benz S, Bornke C. Delay of simple reaction time after levodopa intake. Clin Neurophysiol 2001;112:2133-7.

64. Goetz CG, Leurgans S, Pappert EJ, Raman R, Stemer AB. Prospective longitudinal assessment of hallucinations in Parkinson's disease. Neurology 2001;57:2078-82.

65. Bush DF, Liss CL, Morton A. An open multicenter long-term treatment evaluation of Sinemet CR. Sinemet CR Multicenter Study Group. Neurology 1989;39(11 Suppl 2):101-4; discussion 105.

66. Serby M, Angrist B, Lieberman A. Psychiatric effects of bromocriptine and lergotrile in Parkinsonian patients. Adv Biochem Psychopharmacol 1980;23: 287-92.

67. Portin R, Rinne UK. The effect of deprenyl (selegiline) on cognition and emotion in parkinsonian patients undergoing long-term levodopa treatment. Acta Neurol Scand Suppl 1983;95:135-44.

68. Hindmarch I, Shamsi Z. Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects. Clin Exp Allergy 1999;29 Suppl 3:133-42.

69. Devinsky O. Cognitive and behavioral effects of antiepileptic drugs. Epilepsia 1995;36 Suppl 2:S46-65.

70. Smith DB, Mattson RH, Cramer JA, Collins JF, Novelly RA, Craft B. Results of a nationwide Veterans Administration Cooperative Study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. Epilepsia 1987;28 Suppl 3:S50-8.

71. Meador KJ, Loring DW, Allen ME, Zamrini EY, Moore EE, Abney OL, et al. Comparative cognitive effects of carbamazepine and phenytoin in healthy adults. Neurology 1991;41:1537-40.

72. Dodrill CB, Troupin AS. Neuropsychological effects of carbamazepine and phenytoin: a reanalysis. Neurology 1991;41:141-3.

73. Meador KJ, Loring DW, Huh K, Gallagher BB, King DW. Comparative cognitive effects of anticonvulsants. Neurology 1990;40(3 Pt 1):391-4.

74. Meador KJ, Loring DW, Moore EE, Thompson WO, Nichols ME, Oberzan RE, et al. Comparative cognitive effects of phenobarbital, phenytoin, and valproate in healthy adults. Neurology 1995;45:1494-9.

75. Gillham RA, Blacklaw J, McKee PJ, Brodie MJ. Effect of vigabatrin on sedation

and cognitive function in patients with refractory epilepsy. J Neurol Neurosurg Psychiatry 1993;56:1271-5.

76. Grünewald RA, Thompson PJ, Corcoran R, Corden Z, Jackson GD, Duncan JS. Effects of vigabatrin on partial seizures and cognitive function J Neurol Neurosurg Psychiatry 1994; 57:1057-63.

77. Lawlor PG. The panorama of opioid-related cognitive dysfunction in patients with cancer: a critical literature appraisal. Cancer 2002;94:1836-53.

78. Hanks GW, O'Neill WM, Simpson P, Wesnes K. The cognitive and psychomotor effects of opioid analgesics. II. A randomised controlled trial of single doses of morphine, lorazepam and placebo in healthy subjects. Eur J Clin Pharmacol 1995;48:455-60.

79. O'Neill WM, Hanks GW, Simpson P, Fallon MT, Jenkins E, Wesnes K. The cognitive and psychomotor effects of morphine in healthy subjects: a randomised controlled trial of repeated (four) oral doses of dextropropoxyphene, morphine, lorazepam and placebo. Pain 2000;85: 209-15.

80. Zacny JP, Lichtor JL, Flemming D, Coalson DW, Thompson WK. A dose-response analysis of the subjective, psychomotor and physiological effects of intravenous morphine in healthy volunteers. J Pharmacol Exp Ther 1994;268:1-9.

81. Walker DJ, Zacny JP. Subjective, psychomotor, and physiological effects of cumulative doses of opioid mu agonists in healthy volunteers. J Pharmacol Exp Ther 1999;289:1454-64.

82. Saarialho-Kere U, Mattila MJ, Seppala T. Psychomotor, respiratory and neuroendocrinological effects of a mu-opioid receptor agonist (oxycodone) in healthy volunteers. Pharmacol Toxicol 1989;65:252-7.

83. Moulin DE, Iezzi A, Amireh R, Sharpe WK, Boyd D, Merskey H. Randomised trial of oral morphine for chronic non-cancer pain. Lancet 1996;347:143-7.

84. Banning A, Sjogren P, Kaiser F. Reaction time in cancer patients receiving peripherally acting analgesics alone or in combination with opioids. Acta Anaesthesiol Scand 1992;36:480-2.

85. Sjögren P, Olsen AK, Thomsen AB, Dalberg J. Neuropsychological performance in cancer patients: the role of oral opioids, pain and performance status. Pain 2000;86:237-45.

86. Schor JD, Levkoff SE, Lipsitz LA, Reilly CH, Cleary PD, Rowe JW, et al. Risk factors for delirium in hospitalized elderly. JAMA 1992;267:827-31.

87. Egbert AM, Parks LH, Short LM, Burnett ML. Randomised trial of postoperative patient-controlled analgesia vs intramuscular narcotics in frail elderly men. Arch Intern Med 1990;150:1897-903.

88. Wysenbeek AJ, Klein Z, Nakar S, Mane R. Assessment of cognitive function in elderly patients treated with naproxen. A prospective study. Clin Exp Rheumatol 1988;6:399-400.

89. Hanlon JT, Schmader KE, Landerman LR, Horner RD, Fillenbaum GG, Pieper CF, et al. Relation of prescription nonsteroidal antiinflammatory drug use to cogni-

tive function among community-dwelling elderly. Ann Epidemiol 1997;7:87-94.

90. Saag KG, Rubenstein LM, Chrischilles EA, Wallace RB. Nonsteroidal antiinflammatory drugs and cognitive decline in the elderly. J Rheumatol 1995;22:2142-7.

91. May FE, Moore MT, Stewart RB, Hale WE. Lack of association of nonsteroidal anti-inflammatory drug use and cognitive decline in the elderly. Gerontology 1992;38:275-9.

92. Bruce-Jones PN, Crome P, Kalra L. Indomethacin and cognitive function in healthy elderly volunteers. Br J Clin Pharmacol 1994;38:45-51.

93. Belanoff JK, Gross K, Yager A, Schatzberg AF. Corticosteroids and cognition. J Psychiatr Res 2001;35: 127-45.

94. Program TBCDS. Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol Ther 1972;13: 694-8.

95. de Quervain DJ, Roozendaal B, Nitsch RM, McGaugh JL, Hock C. Acute cortisone administration impairs retrieval of long-term declarative memory in humans. Nat Neurosci 2000;3:313-4.

96. Newcomer JW, Craft S, Hershey T, Askins K, Bardgett ME. Glucocorticoid-induced impairment in declarative memory performance in adult humans. J Neurosci 1994;14:2047-53.

97. Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K, et al. Decreased memory performance in healthy humans induced by stress-level cortisol treatment. Arch Gen Psychiatry 1999;56:527-33.

98. Schmidt LA, Fox NA, Goldberg MC, Smith CC, Schulkin J. Effects of acute prednisone administration on memory, attention and emotion in healthy human adults. Psychoneuroendocrinology 1999; 24:461-83.

99. Kirschbaum C, Wolf OT, May M, Wippich W, Hellhammer DH. Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. Life Sci 1996;58:1475-83.

100. Wolkowitz OM, Reus VI, Weingartner H, Thompson K, Breier A, Doran A, et al. Cognitive effects of corticosteroids. Am J Psychiatry 1990;147: 1297-303.

101. Young AH, Sahakian BJ, Robbins TW, Cowen PJ. The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. Psychopharmacology (Berl) 1999;145: 260-6.

102. Hall RC, Popkin MK, Stickney SK, Gardner ER. Presentation of the steroid psychoses. J Nerv Ment Dis 1979;167: 229-36.

103. Keenan PA, Jacobson MW, Soleymani RM, Newcomer JW. Commonly used therapeutic doses of glucocorticoids impair explicit memory. Ann N Y Acad Sci 1995;761:400-2.

104. Varney NR, Alexander B, MacIndoe JH. Reversible steroid dementia in patients without steroid psychosis. Am J Psychiatry 1984;141:369-72.

105. Cantu TG, Korek JS. Central nervous system reactions to histamine-2 receptor blockers. Ann Intern Med 1991; 114:1027-34.

106. Catalano G, Catalano MC, Alberts VA. Famotidine-associated delirium. A series of six cases. Psychosomatics 1996;37:349-55.

107. Oslin DW, Katz IR, Sands LP, Bilker W, DiFilippo SD, D'Angelo K. Examination of the cognitive effects of cimetidine in normal elderly volunteers. Am J Geriatr Psychiatry 1999;7:160-5.

108. Schentag JJ, Cerra FB, Calleri G, DeGlopper E, Rose JQ, Bernhard H. Pharmacokinetic and clinical studies in patients with cimetidine-associated mental confusion. Lancet 1979;1:177-81.

109. Slugg PH, Haug MT, 3rd, Pippenger CE. Ranitidine pharmacokinetics and adverse central nervous system reactions. Arch Intern Med 1992;152:2325-9.

110. Jenike MA, Levy JC. Physostigmine reversal of cimetidine-induced delirium and agitation. J Clin Psychopharmacol 1983;3:43-4.

111. Fireman Z, Kopelman Y, Sternberg A. Central nervous system side effects after proton pump inhibitor treatment. J Clin Gastroenterol 1997;25:718.

112. Heckmann JG, Birklein F, Neundorfer B. Omeprazole-induced delirium. J Neurol 2000;247:56-7.

113. Morton MR, Robbins ME. Delirium in an elderly woman possibly associated with administration of misoprostol. Dicp 1991;25:133-4.

114. Pahor M, Guralnik JM, Gambassi G, Bernabei R, Carosella L, Carbonin P. The impact of age on risk of adverse drug reactions to digoxin. For The Gruppo Italiano di Farmacovigilanza nell' Anziano. J Clin Epidemiol 1993; 46:1305-14.

115. Gray SL, Lai KV, Larson EB. Drug-induced cognition disorders in the elderly: incidence, prevention and management. Drug Saf 1999;21:101-22.

116. Cooke DM. The use of central nervous system manifestations in the early detection of digitalis toxicity. Heart Lung 1993;22:477-81.

117. Lely AH, van Enter C. Non-cardiac symptoms of digitalis intoxication. Am Heart J 1972;83:149-52.

118. Eisendrath SJ, Sweeney MA. Toxic neuropsychiatric effects of digoxin at therapeutic serum concentrations. Am J Psychiatry 1987;144:506-7.

119. Eisenman DP, McKegney FP. Delirium at therapeutic serum concentrations of digoxin and quinidine. Psychosomatics 1994;35:91-3.

120. Dimsdale JE, Newton RP, Joist T. Neuropsychological side effects of beta-blockers. Arch Intern Med 1989;149: 514-25.

121. Perez-Stable EJ, Halliday R, Gardiner PS, Baron RB, Hauck WW, Acree M, et al. The effects of proprano-

lol on cognitive function and quality of life: a randomised trial among patients with diastolic hypertension. Am J Med 2000;108:359-65.

122. Muldoon M, Waldstein SR et al. Effects of six anti-hypertensive medications on cognitive performance. J Hypertens 2002;20:1643-52.

123. Rogers TK, Bowman CE. Cognitive impairment associated with beta-blockade in the elderly. Postgrad Med J 1990;66:1050-2.

124. Fisher CM. Amnestic syndrome associated with propranolol toxicity: a case report. Clin Neuropharmacol 1992;15:397-403.

125. Westerlund A. Central nervous system side-effects with hydrophilic and lipophilic beta-blockers. Eur J Clin Pharmacol 1985;28 Suppl:73-6.

126. Nygaard HA, Hovding G. [Adverse effects of local use of beta-blockaders in glaucoma. A literature review and a survey of reports to the adverse drug reaction authority 1986–95]. Tidsskr Nor Laegeforen 1997;117:2019-21.

127. Bagon JA. Neuropsychiatric complications following quinolone overdose in renal failure. Nephrol Dial Transplant 1999;14:1337.

128. Dasgupta R, Mukhopadhyay S, Ganguly S. Adverse effects of quinolone antibiotics. J Assoc Physicians India 1994; 42:348.

129. Jay GT, Fitzgerald JM. Ciprofloxacin-induced delirium. Ann Pharmacother 1997;31:252.

130. McDermott JL, Gideonse N, Campbell JW. Acute delirium associated with ciprofloxacin administration in a hospitalized elderly patient. J Am Geriatr Soc 1991;39:909-10.

131. Mermelstein HT. Clarithromycin-induced delirium in a general hospital. Psychosomatics 1998;39:540-2.

132. Cone LA, Padilla L, Potts BE. Delirium in the elderly resulting from azithromycin therapy. Surg Neurol 2003; 59:509-11.

133. Pollak PT, Sketris IS, MacKenzie SL, Hewlett TJ. Delirium probably induced by clarithromycin in a patient receiving fluoxetine. Ann Pharmacother 1995;29: 486-8.

134. Gregor JC, Zilli CA, Gotlib IH. Acute psychosis associated with oral trimethoprim-sulfamethoxazole therapy. Can J Psychiatry 1993;38:56-8.

135. Gales BJ, Gales MA. Confusion and bradykinesia associated with famciclovir therapy for herpes zoster. Am J Health Syst Pharm 1996;53:1454, 1456.

136. Johnson GL, Limon L, Trikha G, Wall H. Acute renal failure and neurotoxicity following oral acyclovir. Ann Pharmacother 1994;28:460-3.

137. Southworth MR, Dunlap SH. Psychotic symptoms and confusion associated with intravenous ganciclovir in a heart transplant recipient. Pharmacotherapy 2000;20:479-83.

138. Ahles TA, Saykin AJ. Breastcancer chemotherapy-related cognitive dysfunc-

tion. Clin Breast Cancer 2002;3 Suppl 3: S84-90.

139. Ahles TA, Saykin AJ, Furstenberg CT, Cole B, Mott LA, Skalla K, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and ymphoma. J Clin Oncol 2002;20: 485-93.

27. **Non-established Pharmacological Treatments for Dementia Disorders**

Conclusions

Table 27.1 summarizes the current scientific evidence for the effects of various kinds of non-established treatments on cognitive function in dementia disorders. There is limited evidence for Ginkgo biloba and for propentophylline. Small effects have been observed for vitamin E and estrogen, but the evidence is insufficient. No RCTs have been reported for a number of treatments, including dehydroepiandrosterone, alpha lipoic acid, aspirin, statins and vaccine. Thus, there is no evidence either for or against an effect in the case of these drugs. On the other hand, two or more RCTs have been conducted that provide evidence of no effect on cognitive function when it comes to certain substances, including lecithin, vitamin B_{12}, folate, piracetam and NSAIDs.

Background

Apart from the established treatments for AD (Alzheimer's disease), several other drugs have been reported to have beneficial effects in dementia disorders, either by alleviating the symptoms of cognitive decline or modifying the pathological process. The evidence for some of the drugs is weak. For some, most results are from epidemiological studies. For others, RCTs have been conducted but the results are in some cases contradictory. This chapter reviews the most important non-established pharmacological treatments for AD and other dementia disorders. Because vaccine treatment of AD has received considerable attention, a description of those data is also provided.

Method

The data presented is based primary on systematic reviews from the Cochrane Institute. An updated Medline literature search of published studies and systematic reviews through July 2004 changed none of the conclusions.

Individual drugs

Lecithin

Lecithin is a major dietary source of choline, which is part of the acetylcholine molecule. Since AD patients are reported to have a deficiency of the enzyme that converts choline to acetylcholine in the brain, lecithin supplementation could conceivably slow the progression of the disease.

The Cochrane Collaboration conducted a systematic review to determine the efficacy of lecithin in treating dementia or cognitive impairment [1] (Table 27.1). The review included all unconfounded, randomised trials that compared lecithin with placebo for treating patients with Alzheimer-type dementia, VaD, mixed AD and VaD, unclassified or other dementia, as well as unclassified cognitive impairment.

Twelve randomised trials were identified, including patients with AD (n = 265), parkinsonian dementia (n = 21) and subjective memory problems (n = 90). None of the trials reported a clear clinical benefit of lecithin in treating AD. However, lecithin produced a dramatic improvement in a trial that included subjects with subjective memory problems.

The conclusion was that evidence from randomised trials does not support the use of lecithin in treating patients with dementia.

Vitamin B_{12}

Cobalamin (vitamin B_{12}) deficiency, which has been found to be present in 5–15% of the elderly population, is even more common in dementia conditions [2]. Vitamin B_{12} deficiency as measured by either low levels

of vitamin B_{12} [3] or increased levels of plasma Hcyb [4] has been discussed as a risk factor for developing dementia.

Because vitamin B_{12} is a common treatment for dementia and cognitive symptoms, the literature was searched for evidence of its effectiveness [5]. The Cochrane Collaboration examined the effect of B_{12} supplementation on the cognitive function of healthy elderly subjects and those with dementia in terms of preventing the onset or slowing the progression of cognitive impairment or dementia [6]. In September 2002, the Cochrane group searched for all available randomised double-blind trials in which vitamin B_{12} of any dose was compared to placebo. Only two studies were found [6,7]. The meta-analysis of data from the two studies on patients with dementia and low serum vitamin B_{12} levels showed no statistically significant evidence of effects on cognitive function when vitamin B_{12} was compared with placebo.

Thus, despite several indications of the relation between vitamin B_{12} deficiency and the development of cognitive symptoms or dementia, no prospective double-blind studies on people without dementia were found. Neither of the placebo-controlled studies on dementia and low serum B_{12} levels offered evidence that cognitive function improved.

Folic acid

Homocysteine, vitamin B_{12} (cobalamin) and folate are all involved in the one-carbon cycle. Normal functioning of the cycle is essential for proper development and maintenance of the CNS. Folate acts as a methyl-group donator in a reaction catalyzed by the enzyme methionine synthase to produce the methylcoboloamin needed for the methylation of homocysteine to methionine. As a result, folate deficiency may – in addition to impairing one-carbon metabolism – cause high homocysteine levels in the blood and cells. That is a risk factor for atherosclerosis and cerebrovascular disease.

In light of the above considerations, a Cochrane report investigated the effects of folic acid supplementation – with or without vitamin B_{12} – on healthy elderly and those with dementia for the purpose of preventing cognitive impairment or retarding its progression [8].

All double-blind placebo-controlled randomised trials were included. Four randomised trials were found [9,10].

The reviewer concluded that the available studies were limited in size and provided no evidence that folic acid – with or without vitamin B_{12} – had any beneficial effect on cognitive function or mood in either healthy subjects or those with cognitive impairment or dementia.

Vitamin E

Vitamin E is a group of naturally occurring chemical derivatives of tocopherol and tocotrienol. Vitamin E occurs in oils, fats, nuts and other seeds. The biological function of vitamin E is that of an antioxidant, neutralizing the effects of peroxide and free radicals in the cell that would otherwise damage proteins, DNA and cell membranes. Since free radical damage is a potential mechanism in the degeneration of neurons in AD, etc, antioxidants like vitamin E might be expected to either prevent the disease or delay its progression. Therefore, a Cochrane report focused on vitamin E for the prevention and treatment of AD [11].

All double-blind, placebo-controlled randomised studies with any dose of vitamin E were included. Only one study met all of the inclusion criteria [12]. Vitamin E appeared to produce some benefit – fewer participants reached 1 out of 4 endpoints (death, institutionalization, loss of 2 out of 3 basic activities or severe dementia). However, more participants who took vitamin E suffered from falls.

The conclusion was that the evidence on vitamin E sufficed to justify further study but that evidence of its efficacy in the treatment of AD was inadequate.

Piracetam

Piracetam is believed to have properties that enhance memory and other intellectual functions. However, the mechanism of action is not well known. Piracetam has been suggested to act by increasing oxygen and glucose utilization. At higher doses, it is also believed to enhance

microcirculation and antithrombotic properties by affecting platelets and erythrocytes. The effects on AD and other types of dementia remain uncertain, although larger trials have shown some positive results.

A Cochrane review was carried out to determine the clinical efficacy of piracetam for the features of dementia or cognitive impairment classified according to the major subtypes of AD, mixed AD and VaD, unclassified dementia or cognitive impairment that failed to meet the criteria for dementia [13].

Apart from searching the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group, several studies (many of which unpublished) were obtained from UCB Pharma, the pharmaceutical company responsible for marketing most piracetam worldwide. All unconfounded, randomised trials were included in which piracetam was administered for more than 1 day and compared with placebo, in patients with Alzheimer-type dementia, VaD, mixed AD and VaD, unclassified dementia or cognitive impairment that failed to meet the criteria for dementia. Whenever feasible, studies were pooled, and the pooled odds ratios or average differences were estimated. Intention-to-treat analyses were performed wherever possible.

A total of 68 studies were reviewed. Many were crossover studies, and first-phase data were unavailable or could not be extracted. Only 3 studies had a treatment duration of more than three months. Global Impression of Change was the only outcome with a significant amount of evidence from the pooled data. Using a fixed effects model, the odds ratio for improvement in the piracetam group compared with the placebo group was 3.55 (95% CI 2.45–5.16). Using a random effects model, the odds ratio was 3.47 (1.29–9.30). The evidence of effects on cognition and other measures was inconclusive.

The reviewers concluded that available evidence did not support the use of piracetam in treating people with either dementia or cognitive impairment. Although effects were found on global impression of change, no benefit was shown from any of the more specific measures.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) and its sulphate form (DHEA/S) are the most abundant hormones in both men and women. Each hormone is found in the brain and adrenal gland. The hormones have been shown to increase the effect of the excitatory transmitter glutamate and to decrease the effect of the inhibitory transmitter GABA. They also appear to have neuroprotective properties and stimulate the immune system. Both hormones possess strong antiglucocorticoid action, possibly explaining their neuroprotective effects. Some evidence from epidemiological studies suggests that DHEA may protect against heart disease and increase longevity. Dementia patients have been reported to have lower levels of DHEA.

Thus there is a theoretical basis, but very little evidence, for believing that DHEA may have beneficial effects. Nevertheless, health food stores in many countries sell DHEA as a possible enhancer of cognitive function in aging and dementia.

The Cochrane Collaboration undertook a review of well-executed studies in the pursuit of evidence that cognitive function improved or cognitive decline slowed in the healthy older adults or those with dementia [14]. Another aim was to provide a scientific basis for effective dosage, acceptable route and duration of administration, and side-effect profiles. All relevant RCTs concerning the effect of DHEA/S on cognition in older adults were searched among relevant electronic databases, journals, personal communications and conference abstracts.

Four studies were found. Three addressed cognition in healthy older people and one in perimenopausal women with decreased well-being, but none in people with dementia. Some significant findings were identified. One crossover trial reported significant improvement after 2 weeks of treatment with both DHEA and placebo, following DHEA compared with placebo in both immediate recall (MD 0.8, 95% CI 0.16–1.44) and delayed recall (MD 0.9; 0.09–1.71) for a visual memory test in women. However, there was no significant improvement in men, or a significant effect on a verbal memory test or four other cognitive tests. Another study showed that placebo group performance deteriorated significantly

on a test of selective attention following a psychosocial stressor ($p < 0.05$). But that was not observed in the DHEA group ($p = 0.85$) after 2 weeks of treatment. However, DHEA led to significant impairment on a visual memory test and no significant effect was detected on a third cognitive task. A third study found no significant effect of DHEA compared with placebo on 3 cognitive measures after 3 months. The findings to date suggest that DHEA has no significant side-effects.

The reviewers concluded that there was no support for improved memory or other aspects of cognitive function following DHEA treatment in healthy older people. But since it is possible that any neuroprotective effect of DHEA/S may be evident only in the long term, they identified a need for trials on DHEA treatment for longer than 1 year. Recently completed trials on DHEA supplementation in AD patients (United States), postmenopausal women (United States), healthy older men (United Kingdom), and healthy older adults (France – 1-year) will be reviewed and included as soon as the results are available.

Propentophylline

Propentophylline is a dementia drug with a unique mechanism of action. At the molecular level, it blocks the uptake of adenosine and inhibits the enzyme phosphodiesterase. In vitro and in vivo, it both inhibits the production of free radicals and reduces the activation of microglial cells. Thus, propentophylline interacts with inflammatory processes that are believed to contribute to dementia. As a result, it might be a disease-modifying agent.

A Cochrane review was conducted to determine the clinical efficacy and safety of propentophylline in people with dementia [15]. Trials were searched in the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group. In addition, Aventis, the manufacturer, was asked for data from unpublished studies. All 9 unconfounded, double-blind RCTs of propentophylline compared with placebo or another treatment group, were included. Detailed reports were found for only 4 of them. The efficacy of propentophylline was reviewed for undifferentiated dementia, given that the data were insufficient to analyze the individual types.

Several significant treatment effects favoring propentophylline were reported: cognition at 3, 6, and 12 months, including MMSE at 12 months (MD 1.2, 95% CI 0.12 to 2.28, p = 0.03); severity of dementia at 3, 6, and 12 months, including CGI at 12 months (MD −0.21, −0.39; −0.03, p = 0.03), ADL (NAB) at 6 and 12 months (MD −1.20, −2.22; −0.18, p = 0.02), and Global Assessment (CGI) at 3 months (MD −0.48, −0.75 to −0.21, p = 0.0006) but not afterwards.

The reviewers concluded that there is limited evidence that propentophylline benefits cognition, global function, and ADL in people with AD and/or VaD. Considering that there is unpublished data on another 1 200 patients in randomised trials, the meta-analyses did not satisfactorily summarize the efficacy of propentophylline. Unfortunately, Aventis representatives were unwilling to correspond with the authors. According to the authors, that significantly limited the scope of the review.

Estrogen

Estrogen has several effects on the CNS – including modulation of neurotransmitter systems, regulation of synaptogenesis, neuroprotection, increased cerebral blood flow, anti-inflammatory actions and antioxidant properties – that may have implications for neurodegenerative disorders.

A reasonable assumption is that maintaining estrogen levels in postmenopausal women by means of estrogen replacement therapy (ERT) could protect against cognitive decline and the development of AD or other types of dementia.

The Cochrane Collaboration conducted a review aimed at investigating the effects of ERT (estrogens only) or hormone replacement therapy (HRT – estrogens combined with a progestagen) compared with placebo in RCTs on the cognitive function of postmenopausal women with dementia [16]. The CDCIG Specialized Register, Medline, EMBASE, and PsycInfo were searched for all double-blind RCTs concerning the effect of ERT or HRT on cognitive function that included treatment of at least 2 weeks in postmenopausal women with AD or other types of dementia.

At total of 5 trials that included 210 women were analyzed. Meta-analyses showed a small positive effect from a low dosage of conjugated equine estrogens (CEE, 0.625 mg once daily) but not from higher doses (1.25 mg once daily) on the MMSE after 2 months (WMD = 1.28, 95% CI 0.26–2.30, z = 2.45, p <0.01). However, the effect disappeared after 3, 6, and 12 months of treatment. The effect was small (1 point on the MMSE compared to placebo). In addition, there were short-term effects of 1.25 mg from CEE on tests of concentration and executive function. When it came to memory tests, only cued delayed recall of a word list was positively affected by 2 months of transdermal diestradiol (E2) (WMD = 6.50, 95% CI 4.04–8.96, z = 5.19, p <0.0001). No effects were observed on language functions, most speeded tests, clinical rating scales or depression. Controls scored better on a dementia rating scale (CDR, overall WMD = 0.35, 95% CI 0.01–0.69, z = 1.99, p <0.05). According to the authors, the positive findings might have been random effects caused by multiple analyses. After correction for multiple testing, only the short-term positive treatment effect of E2 on memory remained.

The reviewers concluded that neither HRT nor ERT is indicated for cognitive improvement or maintenance in women with AD. Other types of dementia remain to be investigated. It is also possible that different types or preparations of ERT and HRT, as well as other durations of treatment, would have different effects. Another question is whether ERT or HRT can delay the time to onset of dementia. Studies addressing this question are under way in the United Kingdom, United States and Canada.

Non-steroidal anti-inflammatory drugs

Several lines of evidence suggest that inflammatory processes play a role in the pathogenesis of AD. One of the immune responses in the brain is the activation of the prostaglandin pathways. Non-steroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the cyclooxygenase (COX) involved in prostaglandin synthesis. Thus, they could conceivably have protective effects against the development of AD, and several epidemiological studies suggest that this may be the case. However, the results of many clinical trials have been discouraging.

In light of these conflicting results, two Cochrane reviews were carried out to examine the efficacy of the NSAIDs indomethacin and ibuprofen in treating patients with AD [17,18]. Searches were conducted in the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group. Additional searches involved other relevant computerized databases, websites, manual techniques and additional references from selected papers. Furthermore, an effort was made to find data from ongoing trials. Single-center or multicenter, placebo-controlled, randomised trials examining the efficacy of indomethacin or ibuprofen in patients diagnosed with AD were included.

Only one study was selected for indomethacin. No significant difference was found between indomethacin treatment and placebo for the individual cognitive tests of MMSE, Alzheimer's Disease Assessment Scale (ADAS), Boston Naming Test (BNT) or Token Test (TK). The dropout rate was higher and the gastrointestinal side-effects more prevalent in the indomethacin group. There was no statistically significant difference in mortality. No completed randomised, double-blind, placebo-controlled trial on ibuprofen met the inclusion criteria for review.

The reviewers concluded that there was no evidence to recommend indomethacin for the treatment of mild to moderate AD. At doses of 100 to 150 mg daily, serious side-effects limit its use. There are no data yet available from RCTs on ibuprofen. Studies on other NSAIDs are ongoing. However, the use of NSAIDs carries a significant risk of potentially serious side-effects such as gastrointestinal bleeding that must be weighed against any beneficial effect in the treatment of AD.

After the Cochrane review, one RCT has been published on the effect of rofecoxib for slowing the progression of dementia in 692 patients with established AD. Four hundred eighty-one patients (70%) completed assessments and remained on treatment at 12 months. No significant differences between treatments were found in terms of mean change from the baseline error score for the ADAS-cog or the mean score on the CIBIC+ [19].

Ginkgo biloba

Ginkgo biloba contains extracts of the leaves of the maidenhair tree. It has long been used in China for various health disorders. Ginkgo biloba is also widely prescribed in Germany and France for several conditions, including memory and concentration problems, confusion, depression, anxiety, dizziness, tinnitus and headache. The extract is believed to act by dilating blood vessels, thereby increasing blood supply, reducing blood viscosity, modifying neurotransmitter systems and reducing oxygen-free radicals.

A Cochrane review investigated the efficacy and safety of Ginkgo biloba in treating dementia or cognitive decline [20]. A search was conducted of the CDCIG Specialized Register which contains records from all main medical databases (Medline, EMBASE, Cinahl, PsycInfo, Sigle, Lilacs), databases of ongoing trials, such as Clinicaltrials.gov and Current Controlled Trials, and several other sources. All relevant, unconfounded, randomised, double-blind controlled studies were included in which extracts of Ginkgo biloba (at any strength and over any period of time) were compared with placebo for the effects on people with acquired cognitive impairment, including dementia (at any degree of severity). Meta-analyses were based on reported summary statistics for each study. Both intention-to-treat analyses (ITT) and analyses of completers were performed. Because there were few attempts at ITT analyses, only completers were analyzed.

A total 33 studies with a treatment duration of 3–52 weeks were reviewed. Benefits were associated with Ginkgo (<200 mg daily) compared with placebo at less than 12 weeks and with Ginkgo (>200 mg daily) at 24 weeks. Cognition benefited from Ginkgo (at both less than and more than 200 mg daily) compared with placebo at 12 weeks and at 24 weeks, as well as for Ginkgo less than 200 mg daily at 52 weeks. ADL benefited from Ginkgo (<200 mg daily) compared with placebo at 12, 24, and 52 weeks. Measures of mood and emotional function benefited from Ginkgo (<200 mg daily) compared with placebo at less than 12 weeks and at 12 weeks. Overall, there were no significant differences between Ginkgo and placebo with respect to the percentage of participants experiencing adverse events.

The reviewers concluded that Ginkgo biloba does not appear to have more side-effects than placebo. Generally speaking, there is promising evidence of improvement in cognition and function associated with Ginkgo biloba. However, the three more recent trials showed inconsistent results. There is a need for a large trial that uses the latest methodology and permits ITT analysis.

After the Cochrane review, a 24-week, multicenter, double-blind, placebo-controlled, randomised trial has been published on the effects of the special Ginkgo biloba extract EGb 761 (240 mg daily) in outpatients with Alzheimer-type dementia and multi-infarct dementia of mild to moderate severity. An ITT analysis showed a significant decrease in Syndrom-Kurztest (SKT) and estimated ADAS-cog scores, while there was only a minimal change in the placebo group, indicating that EGb 761 improved cognitive function in dementia patients [21].

We performed a meta-analysis of the latter study [21] together with a previous RCT [22] using ADAS-Cog as evaluation instrument. Both studies made an ITT analysis of the effects of treatment with Egb 761 (240 mg/day for 24 weeks and 120 mg/day for 26 weeks respectively) on cognitive function in dementia. This meta-analysis showed a mean improvement compared to placebo of 1.3 points (–1.3 (95% CI –2,0; –0.6)).

In conclusion, the Cochrane review and our meta-analysis of two larger RCTs would provide at least a moderately strong support for an effect of Ginkgo Biloba on cognition in dementia. However, overall, the studies on Ginkgo have used a range of different instruments to measure the outcome, and very few of them were ADAS-Cog. There are also numerous other variations, in for example diagnostic criteria and treatment doses. In addition, some of the more recent studies show conflicting results. Altogether this decreases the level of evidence.

Alpha lipoic acid and dementia

Alpha lipoic acid (ALA) is a potent antioxidant that is intimately connected to cell metabolism and the redox state. It is essential to oxidative metabolism and serves as a co-factor in mitochondrial dehydrogenase

reactions. ALA can also chelate metals that may be involved in oxidative reactions [23,24]. Because oxidative stress and free radicals can be part of the disease mechanism of degenerative disorders, ALA may also be of value in the treatment or prevention of dementia [25].

Thus, a Cochrane report was published on ALA and dementia [26]. All double-blind randomised placebo-controlled trials examining ALA in dementia were reviewed. However, no trials that met the inclusion criteria were identified. The reviewers concluded that in the absence of evidence of the potential effects of ALA in dementia, it cannot be recommended as treatment.

Aspirin

A key mechanism in the pathogenesis of dementia is ischemia of the brain tissue. Ischemia has been described in AD, as well as mixed AD and VaD, and is the major pathogenic mechanism in VaD. When it comes to clinical practice, separating different pathogenic mechanisms in individual cases is often very difficult given that several may contribute to the condition [27]. Aspirin reduces the risk of ischemic stroke [28]. Because different ischemic mechanisms may contribute to dementia, aspirin has been widely prescribed for patients with a diagnosis of VaD, as well as for those with dementia and vascular risk factors.

However, two overriding questions remain to be answered in terms of treating dementia with aspirin. First, is there sufficient evidence supporting the clinical efficacy of aspirin for preventing the further progress of VaD or improving cognitive function? Second, are the risks of aspirin treatment, such as cerebral and gastrointestinal hemorrhage, acceptable in view of the possible treatment effects?

In order to address these questions, a Cochrane report assessed the evidence of the efficacy of aspirin for treating VaD [29]. The report was most recently amended in November 2003.

All RCTs investigating the efficacy of aspirin for treating VaD were searched. However, no trials eligible for inclusion were found. Thus, there

appears to be no evidence that aspirin is effective in treating patients with VaD. Further research must be conducted to generate evidence for the current medical practice of using aspirin to treat VaD.

Statins

Statins have been investigated for their preventive effect on dementia. Statins have also been investigated for their clinical effect in the treatment of patients with AD and normal serum lipids. Apart from some studies on biochemical measurements, no data have been published on the clinical efficacy of statins (simvastatin, pravastatin, atorvastatin or fluvastatin) in the treatment of AD.

Thus, there does not appear to be any evidence for statins in treating patients with AD and normal serum lipids.

Vaccine treatment

No placebo-controlled data have been published on vaccine treatment of AD. But since the treatment attempts that have been made suggest a new approach, a brief overview of the literature is provided.

Because formation of fibrillar beta-amyloid (Aβ) and neuritic plaques is believed to play a key role in the pathogenesis of AD, one therapeutic approach would be to develop antibodies against the Aβ protein. It was shown that active immunization against the Aβ protein could decrease Aβ deposition in the brains of a mouse model [30]. That, as well as other findings, preceded the development of a synthetic Aβ 1–42 (AN–1792) protein for use in human vaccination trials. A phase 1 study showed that some of the 70 patients produced measurable antibodies against the vaccine [31]. A subsequent phase 2 study that immunized 300 out of 375 patients with 225 βgAN–1792 at baseline and different time points thereafter found that a subgroup (19 patients, 6%) of the immunized patients developed a meningoencephalitis. The study was discontinued after only a few months [32]. A postmortem follow-up of one of the patients

indicated clearance of Aβ plaques, as well as a T-lymphocyte meningoencephalitis that had been identified as a side-effect in some of the other patients [33]. A major obstacle to vaccination with Aβ protein analogues is that the immune response is directed against a naturally occurring target (like Aβ protein) that is present in healthy tissue. That could trigger a more unwanted, generalized immune response [34].

Table 27.1 *Scientific evidence for the effect of different types of non-established treatments on cognitive function in dementia disorders.*

Author Year, reference	**Compound**	**Population**
Higgins et al 2003 [1]	Lecithin	Alzheimer/Parkinsonian dementia
Malouf et al 2003 [6]	Vitamin B_{12}	Dementia/Alzheimer
Malouf et al 2004 [8]	Folic acid	Dementia
Tabet et al 2002 [17]	Vitamin E	Alzheimer
Flicker et al 2003 [13]	Piracetam	Dementia
Huppert et al 2003 [14]	Dehydroepiandrosterone	Dementia
Frampton et al 2003 [15]	Propentophylline	Dementia
Hogervorst et al 2003 [16]	Estrogen	Alzheimer
Tabet et al 2003 [18]	NSAIDs	Alzheimer

No of RCTs	Conclusion	Scientific evidence
12	No study reported clear benefit in AD. Dramatic result in subjective memory problems	Insufficient
2	Insufficient evidence for benefits of Vitamin B_{12} supplementation on cognitive function	Insufficient
3	Folic acid with or without vitamin B_{12} gave no benefits on cognitive function, but was effective in reducing serum homocysteine.	Insufficient
1	Insufficient evidence of efficacy	Insufficient
3 (>3 months)	Effects on global impression of change but not on more specific measures	Insufficient
0	No study in dementia. No evidence for effect in normal old people	No
4	Limited evidence of effects on cognition, global function and ADL	Limited
5	Small positive effect of short-term treatment with E2 on memory	Insufficient
2	No evidence for effect on cognitive function	Insufficient

The table continues on the next page

Table 27.1 *continued*

Author Year, reference	**Compound**	**Population**
Reines et al 2004 [19]	Ginkgo biloba	Dementia
Sauer et al 2004 [26]	Alpha lipoic acid	Dementia
Rands 2004 [29]	Aspirin	Vascular dementia
Ongoing studies	Statins	Alzheimer
Ongoing studier	Vaccine	Alzheimer

AD = Alzheimer's disease; ADL = Activities of daily living; NSAIDs = non-steroidal anti-inflammatory drug; RCT = Randomised controlled trial

	No of RCTs	Conclusion	Scientific evidence
	34	Promising evidence of improvement of cognition and function. However variations in study design, and some conflicting results	Limited
	0	No data available	No
	0	No data available	No
	0	No data available	No
	0	No data available	No

References

1. Higgins J, Flicker, L. Lecithin for dementia and cognitive impairment. Cochrane Methodology Review 2003(4).

2. Nagga K, Rajani R, Mardh E, Borch K, Mardh S, Marcusson J. Cobalamin, folate, methylmalonic acid, homocysteine, and gastritis markers in dementia. Dement Geriatr Cogn Disord 2003;16:269-75.

3. Wang HX, Wahlin A, Basun H, Fastbom J, Winblad B, Fratiglioni L. Vitamin B(12) and folate in relation to the development of Alzheimer's disease. Neurology 2001;56:1188-94.

4. Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346:476-83.

5. Nagga AK, Marcusson J. Associated physical disease in a demented population. Aging (Milano) 1998;10:440-4.

6. Malouf R, Areosa Sastre A. Vitamin B12 for cognition. Cochrane Database Syst Rev 2003:CD004326.

7. Seal EC, Metz J, Flicker L, Melny J. A randomised, double-blind, placebo-controlled study of oral vitamin B12 supplementation in older patients with subnormal or borderline serum vitamin B12 concentrations. J Am Geriatr Soc 2002;50:146-51.

8. Malouf R, Grimley, Evans J, Aerosa Sastre, A. Folic acid with or without vitamin B12 for cognition and dementia. The Cochrane Library 2004(1).

9. Bryan J, Calvaresi E, Hughes D. Short-term folate, vitamin B-12 or vitamin B-6 supplementation slightly affects memory performance but not mood in women of various ages. J Nutr 2002;132:1345-56.

10. Sommer BR, Hoff AL, Costa M. Folic acid supplementation in dementia: a preliminary report. J Geriatr Psychiatry Neurol 2003;16:156-9.

11. Tabet N, Birks, J, Grimley Evans, J, Orrel, M, Spector, A. Vitamin E for Alzheimer's disease (Cochrane Review). The Cochrane Library 2004(1).

12. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997;336:216-22.

13. Flicker L, Grimley Evans, J. Piracetam for dementia or cognitive impairment. Cochrane Methodology Review 2003(4).

14. Huppert F, van Niekerk, JK. Dehydroepiandrosterone (DHEA) supplementation for cognitive function. Cochrane Methodology Review 2003(4).

15. Frampton M, Harvey, RJ, Kirchner, V. Propentofylline for dementia. Cochrane Methodology Review 2003(4).

16. Hogervorst E, Yaffe, K, Richards, M, Huppert, F. Hormone replacement therapy to maintain cognitive function in women with dementia. Cochrane Methodology Review 2003(4).

17. Tabet N, Feldman, H. Indomethacin for Alzheimer's disease. The Cochrane Database of Systematic Reviews 2002(2).

18. Tabet N, Feldman, H. Ibuprofen for Alzheimer's disease. The Cochrane Database of Systematic Reviews 2003(2).

19. Reines S, Block GA, et al. Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomised, blinded, controlled study. Neurology 2004;62:66-71.

20. Birks J, Grimley Evans, J, van Dongen, M. Ginkgo biloba for Cognitive Impairment and Dementia. Cochrane Methodology Review 2003(4).

21. Kanowski S, Hoerr, R. Ginkgo biloba extract EGb 761 in dementia: intent-to-treat analyses of a 24-week, multicenter, double-blind, placebo-controlled, randomised trial. Pharmacopsychiatry 2003;36:297-303.

22. Le Bars PL, Kieser M, Itil KZ. A 26-week analysis of a double-blind, placebo-controlled trial of the Ginkgo biloba extract EGb 761 in dementia. Dement Geriatr Cogn Disord 2000;11:230-7.

23. Moini H, Packer L, Saris NE. Antioxidant and prooxidant activities of alpha-lipoic acid and dihydrolipoic acid. Toxicol Appl Pharmacol 2002;182:84-90.

24. Bast A, Haenen GR. Lipoic acid: a multifunctional antioxidant. Biofactors 2003;17:207-13.

25. Brunk UT, Terman A. The mitochondrial-lysosomal axis theory of aging: accumulation of damaged mitochondria as a result of imperfect autophagocytosis. Eur J Biochem 2002;269:1996-2002.

26. Sauer J, Tabet N, Howard R. Alpha lipoic acid for dementia. Cochrane Database Syst Rev 2004(1):CD004244.

27. Nägga K, Rådberg, C, Marcusson, J. CT brain findings in clinical dementia investigation – underestimation of mixed dementia. Dement Geriatr Cogn Disord 2004;18:59-66.

28. Sandercock P, Gubitz G, Foley P, Counsell C. Antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev 2003(2):CD000029.

29. Rands G, Orrel, M, Spector, A, Williams, P. Aspirin for vascular dementia (Cochrane Review). The Cochrane Library 2004(1).

30. Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 1999;400: 173-7.

31. Schenk D. Amyloid-beta immunotherapy for Alzheimer's disease: the end of the beginning. Nat Rev Neurosci 2002;3:824-8.

32. Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, et al. Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. Neurology 2003;61:46-54.

33. Nicoll JA, Wilkinson D, Holmes C, Steart P, Markham H, Weller RO. Neuropathology of human Alzheimer disease after immunization with amyloid-beta peptide: a case report. Nat Med 2003;9:448-52.

34. Robinson SR, Bishop GM, Lee HG, Munch G. Lessons from the AN 1792 Alzheimer vaccine: lest we forget. Neurobiol Aging 2004;25:609-15.

28. **Dementia and Quality of Life**

Conclusions

There is moderately strong scientific evidence that treatment with rofecoxib or naproxen has no significant effect on quality of life (QoL) for a period of 12 months in patients with mild to moderate AD (Evidence Grade 2).

There is no scientific evidence that donepezil has any significant effect on quality of life (QoL) in patients with AD. No QoL studies QoL have been published on the other CHEIs or memantine.

There is no scientific evidence for any other QoL interventions.

Questions of interest

- What are the effects of pharmacological treatment in terms of quality of life (QoL)?
- What impact do various intervention programs at a community and individual level have on QoL?

Background

QOL is regarded as one of the most important and clinically relevant outcomes when analyzing interventions in dementia [1].

Among the variables that the QoL dimension encompasses are physical, psychological and cognitive health, as well as functional status and social well-being [2]. Evaluating QoL in dementia poses difficulties of its own. Assessments of QoL are normally self-rated, but that is often impossible

when it comes to dementia. Thus, results – such as the subjective well-being of the patient as compared to the views of proxies – may be unreliable [3]. The use of proxies often produces different ratings than what the patient may be able to offer [3,4]. The patient's behavior may serve as an alternative or complement [5].

Two types of approaches can be used to assess QoL. Generic scales are applied to all kinds of patients, independently of their disease. Such instruments are exemplified by the sickness impact profile [6], the QLA scale [7], the Short Form 36 (SF-36) [8], the Health Utilities Index (HUI) [9,10], the EuroQoL/EQ-5D [11] and the Index of well-being quality of wellbeing scale (QWBS) [12]. HUI, EQ-5D and QWBS can be used to calculate Quality Adjusted Life Years (QALYs) [13]. The caregiver quality of life index (CQLI) [14] calculates QALYs (effects on caregivers are the focus of an upcoming SBU report).

Scales are customized to analyze the specific disease of interest, dementia in this case. Several dementia-specific scales, generally with proxies, have been used for the assessment of QoL [15,16]. Among them are the Dementia Quality of Life Instrument (DQoL) [17], the Quality of Life – AD (QoL-AD) [18,19], the Progressive Deterioration scale (PDS) [20] (which is not included here because it is an ADL rather than a QoL instrument) and Dementia Care Mapping [21]. The Dementia Quality of Life Instrument (DQoL) [17,72] has emerged recently to assess QoL directly from the patient.

Search strategy

The search focused on controlled clinical trials that employed the concept of QoL. PubMed, Ingenta, Cochrane Library, NHSEED/THA, HEED, PsycInfo, ERIC, Societal services abstracts and Sociological abstracts were search for studies published in English. The search period was from 1960 (with slight variations depending on the database) to July 31, 2004.

Papers with other concepts such as well-being were not included in the final analysis. Cost-effectiveness/cost utility studies that contained empirical data and identified QALYs/quality of life measurements were

reviewed. The scales mentioned above were also used as search terms in PubMed. The other search terms/MeSH terms/subheadings were dementia/Alzheimer's disease/Alzheimer disease/Alzheimer and controlled clinical trial.

Studies in the database of this dementia project containing assessments of QoL were also reviewed. Each abstract was reviewed by two people. A total of 2 614 hits were identified in the first round among various databases and 341 in a second, narrower round (duplicates not excluded). For the search terms and results, see Appendix 28.1.

Of the 32 studies that were assessed for quality, 10 were ultimately included (6 regarding programs and 4 regarding drug interventions). Table 28.3 lists the papers that were excluded.

Results

What are the effects of pharmacological treatment in terms of QoL?

Four studies, three on donepezil and one on coxiber, used the same QoL instrument (Table 28.1) [7]. The 3 donepezil studies were considered to be of low quality, given that the appropriateness of the QoL instrument for AD was questionable. Variability was high. Although there were some indications of improved QoL, the results were inconclusive. The study on coxiber was well conducted and showed no significant difference between the groups [22]. While employed by some studies, the PDS scale is not regarded as a QoL instrument (see above) [20]. Thus, such studies were not included.

What are the effects of intervention programs on QoL at the individual and community level?

Six studies were identified – five that was low quality and concerned the present research question, and one that was of medium quality. Four studies were randomised. Generally speaking, the study groups were rather small and thus of low power (Table 28.2). The study by Spector et al was well designed, but the duration and evaluation period were short (7 weeks) [23].

Evidence grade

Pharmacological treatment

There is moderately strong scientific evidence that treatment with rofecoxib or naproxen has no significant effect on QoL for a period of 12 months in patients with mild to moderate AD (Evidence Grade 2).

There is no evidence, mainly due to the lack of sufficient studies, that donepezil has any significant effect on QoL in patients with AD. No studies have been published on QoL with either the other CHEIs or memantine.

Programs

The evidence is insufficient when it comes to the effects of cognitive stimulation on QoL.

The evidence is insufficient with respect to the effect of other programs (not enough studies) on QoL.

Discussion

Scientific evidence offers no support that pharmacological treatments or intervention programs improve QoL in dementia, probably due to methodological issues and the lack of publications in the field. Almost everyone engaged in dementia research stresses the importance of QoL, while not neglecting methodological issues [1,15,16,24–32]. Nevertheless, the number of controlled clinical studies in which QoL was examined is quite limited. However, QoL evaluations are more common in connection with various models.

The focus of pharmacological trials is on efficacy outcomes that are important for approval, and perhaps on reimbursement issues (including cognition and global judgments such as CIBIC). Because QoL is not included in these formal requirements, the number of studies with QoL assessments is limited.

Most drug trials are well-designed and based on established principles with regard to efficacy, safety and ethics. The internal validity of such studies is generally high. Discussions about drug trials focus mainly on external validity (generalizability and inclusion/exclusion criteria) and the presentation of results (such as principles for ITT analysis).

Due primarily to methodological issues, programs in the broad sense of the word face many more problems than pharmacologic interventions. For practical reasons, it may be difficult to include a sufficient number of patients (causing low power), the studied intervention may be contaminated by other interventions, drop-ins and drop-outs may be frequent, the intervention may be difficult to operationalize, and it may be hard to demonstrate the extent to which the program has been completed. Blindness is problematic (single-blinded at best), and randomization is not always possible. Thus, even though a program has certain advantages, it may be difficult to satisfy the evidentiary criteria.

Recommendations for future research

There is a need for methodological development (both generic and diagnosis-specific instruments) regarding the assessment of QoL in dementia.

There is a need for studies with combined approaches (such as drugs and programs) and for comparative studies (different CHEIs and CHEIs with other drugs).

The database on programs in general is limited and RCTs are badly needed.

Table 28.1 *Studies focusing on effects of pharmacological interventions on quality of life.*

Author Year Reference Country	Type of study	Setting	Dementia/ Diagnosis	Severity of dementia	Patients (n) included (attrition). Active treatment first (treatment(s), placebo)	Age-groups Mean/Range (SD) (treatment(s), placebo)
Rogers et al 1998 [33] USA	RCT	Community?	Alzheimer's disease (NINCDS, DSM-III-R)	Mild-moderate	162+154 +157 (20%, 15%, 32%)	72.6 (56–88), 72.9 (51–86), 74.6 (53–94)
Rogers et al 1998 [34] USA	RCT	Community?	Alzheimer's disease (NINCDS, DSM-III-R)	Mild-moderate	157+158+153 (11%, 24%, 12%)	73.8 (50–94), 73.4 (50–92), 74.0 (50–92)
Burns et al 1999 [35] United Kingdom	RCT	Community	Alzheimer's disease (NINCDS, DSM-III-R)	Mild-moderate	271+273+274 (22%, 26%, 20%)	71 (50–90), 72 (51–91), 72 (53–93)
Aisen et al 2003 [22] USA	RCT	Community	Alzheimer's disease (NINCDS, DSM-III-R)	Mild-moderate	118+122+111 (24%, 27%, 21%)	73.7 (7.2), 74.1 (7.8), 73.8 (8.0)

* From the perspective of this analysis, these outcomes may be secondary in original trials.
** Chi2 test own calculations.
*** Based on study population in original publication [36].
Study quality: 1 = Limited study quality; 2 = Moderately high study quality; 3 = High study quality.

DSM = Diagnostic and statistical manual; NINCDS = National institute of neurological and communicable diseases; ns = Not stated; QoL = Quality of Life; QoLAD = Quality of life Alzheimer's disease; RCT = Randomised controlled trial; SD = Standard deviation

Study period	Drug	Primary outcome*	Effects (end)	Remarks from reviewer	Quality of study
6 months	Donepezil, 5 mg, 10 mg, placebo	Patient rated QoL (well-being scale; not specified, but with reference [7])	NS (but rend for donepezil 5 mg at week 24: p = 0.05)	Rather high attrition in 10 mg group	1
15 weeks	Donepezil, 5 mg, 10 mg, placebo	Patient rated QoL (well-being scale; not specified, but with reference [7])	At week 12, QoL better for placebo and donepezil 5 mg vs donepezil 10 mg ($p<0.05$)	Short duration. QoL effects due to side-effects of 10 mg?	1
6 months	Donepezil	Patient rated QoL (well-being scale; not specified, but with reference(7])	NS	Placebo, 5, 10 mg donepezil. Rather high attrition in donepezil 10 mg. Great variability	1
12 months	Naproxen, rofecoxib, placebo	QoLAD	NS	Well conducted study	3

Table 28.2 *Studies focusing on effects of "programs" on quality of life.*

Author Year, reference Country	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition)	Age-groups (patients) Mean (range or SD)
Wimo et al 1995 [37] Sweden	Quasi-experi-mental	Institution (group living)	Clinical (geriatrician)	Mild-moderate-severe	46+62 (0%, 0%)	79 (7), 79 (6)
Wimo et al 1994 [39] Sweden	Quasi-experi-mental	Com-munity	Clinical (geriatrician)	Moderate	55+45 (0%)	78 (76–80), 79 (77–81)
Davis et al 2001 [41] USA	RCT	Com-munity (?)	Alzheimer's disease (NINCDS)	Mild-moderate	19+18 (0%)	68.7 (3.9), 72.6 (7.6)
Teri et al 2003 [42] USA	RCT	Com-munity	Alzheimer's disease (NINCDS)	Moderate-severe	76+77 (41%, 43%)	78 (6), 78 (8)
Spector et al 2003 [23] United Kingdom	RCT	Com-munity	DSM-IV	Mild-moderate	115+86 (16%, 19%)	85.7 (6.2), 84.7 (7.9)
Politis et al 2004 [43] USA	RCT	Institution	DSM-IV	Moderate (GDS 3–5)	18+18 (1/37)	84.4 (4.5), 83.5 (4.9)

* From the perspective of this analysis, these outcomes may be secondary in original trials.
Study quality: 1 = Limited study quality; 2 = Moderately high study quality; 3 = High study quality.

Study period	Intervention (end)	Primary outcome*	Effects (end)	Remarks from reviewer	Quality of study
1 year	Group living	QALYs (Index of well-being [12], mapped from GDS [38])	GL less deterioration in QALYs than controls, but no significant calculation given	Empirical part of model. Non-randomised	1
1 year	Day care	QALYs (index of well-being [12] and Rosser index [40], mapped from different scales	NS	Non-randomised, low power	1
5 weeks	Cognitive stimulation	QLA-P [7]	NS	Small sample-low power, short duration, difference in age between groups	1
2 years	BPSD + training	SF-36 (part)	SF 36 better in program group at 3 months (ITT; $p<0.001$). After 2 years (completers) SF 36 still better in program group ($p<0.01$)	Rather low power. Proxy rated SF-36 (by caregivers). 2 years results doubtful due to attrition (eg institutionalized were excluded)	1
7 weeks	Cognitive stimulation	QoL-AD	Treatment group better ($p = 0.028$) than controls	Short duration	2
4 weeks	Activity therapy	ADQRL	NS	Low power, short duration	1

AD = Alzheimer's disease; DSM = Diagnostic and statistical manual; GDS = Global deterioration scale; GL = Group living; ITT = Intention to treat; NINCDS = National institute of neurological and communicable diseases; ns = Not stated; QoL = Quality of life; RCT = Randomised controlled trial; SF = Short form

Table 28.3 *Excluded papers*.*

Author, year, reference	Exclusion reason 1	Exclusion reason 2	Exclusion reason 3
Ballard et al, 2002 [44]	3		
Ballard et al, 2004 [45]	3		
Bottini et al, 1992 [46]	4		
Brodaty et al, 2004 [47]	4	1	
Challis et al, 2002 [48]	3		
Fontaine et al, 2003 [49]	4	1	
Knapp et al, 1994 [50]	3		
Lawton et al, 1989 [51]	3		
Reimer et al, 2004 [52]	3		
Sano et al, 1992 [53]	1		
Thorgrimsen et al, 2002 [54]	4	1	
Wesnes et al, 1987 [55]	2	3	

* Furthermore, 4 papers were excluded due to exclusion class 0 (not relevant for the question of interest) and 6 due to exclusion class 9 (no original data presented), a total of 10 papers excluded due to these reasons.
See Appendix 2 The Exclusion list.

References

1. Winblad B, Hill S, Beermann B, Post SG, Wimo A. Issues in the economic evaluation of treatment for dementia. Position paper from the International Working Group on Harmonization of Dementia Drug Guidelines. Alzheimer Dis Assoc Disord 1997;11:39-45.

2. Winblad B, Wimo A, Almkvist O. Outcome measures in Alzheimer's disease: do they go far enough? Dement Geriatr Cogn Disord 2000;11 Suppl 1:3-10.

3. Jönsson L. Economic evaluation of treatments for Alzheimer's disease. Stockholm: Karolinska Institutet; 2003.

4. Sands LP, Ferreira P, Stewart AL, Brod M, Yaffe K. What explains differences between dementia patients' and their caregivers' ratings of patients' quality of life? Am J Geriatr Psychiatry 2004;12:272-80.

5. Albert SM, Del Castillo-Castaneda C, Sano M, Jacobs DM, Marder K, Bell K, et al. Quality of life in patients with Alzheimer's disease as reported by patient proxies. J Am Geriatr Soc 1996;44:1342-7.

6. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981;19:787-805.

7. Blau TH. Quality of Life, social indicators and criteria of change. Prof Psychol 1977;8:464-473.

8. Ware JE, Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.

9. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care 1996;34:702-22.

10. Neumann PJ, Sandberg EA, Araki SS, Kuntz KM, Feeny D, Weinstein MC. A comparison of HUI2 and HUI3 utility scores in Alzheimer's disease. Med Decis Making 2000;20:413-22.

11. Coucill W, Bryan S, Bentham P, Buckley A, Laight A. EQ-5D in patients with dementia: an investigation of inter-rater agreement. Med Care 2001;39:760-71.

12. Kerner DN, Patterson TL, Grant I, Kaplan RM. Validity of the Quality of Well-Being Scale for patients with Alzheimer's disease. J Aging Health 1998;10:44-61.

13. Torrance GW. Preferences for health outcomes and cost-utility analysis. Am J Manag Care 1997;3 Suppl:S8-20.

14. Mohide EA, Torrance GW, Streiner DL, Pringle DM, Gilbert R. Measuring the wellbeing of family caregivers using the time trade-off technique. J Clin Epidemiol 1988;41:475-82.

15. Walker MD, Salek SS, Bayer AJ. A review of quality of life in Alzheimer's disease. Part 1: Issues in assessing disease impact. Pharmacoeconomics 1998;14:499-530.

16. Salek SS, Walker MD, Bayer AJ. A review of quality of life in Alzheimer's

disease. Part 2: Issues in assessing drug effects. Pharmacoeconomics 1998;14:613-27.

17. Brod M, Stewart AL, Sands L, Walton P. Conceptualization and measurement of quality of life in dementia: the dementia quality of life instrument (DQoL). Gerontologist 1999;39:25-35.

18. Logsdon RG, Gibbons LE, McCurry SM, Teri L. Assessing quality of life in older adults with cognitive impairment. Psychosom Med 2002;64:510-9.

19. Selai C, Vaughan A, Harvey RJ, Logsdon R. Using the QOL-AD in the UK. Int J Geriatr Psychiatry 2001;16:537-8.

20. DeJong R, Osterlund OW, Roy GW. Measurement of quality-of-life changes in patients with Alzheimer's disease. Clin Ther 1989;11:545-54.

21. Fossey J, Lee L, Ballard C. Dementia Care Mapping as a research tool for measuring quality of life in care settings: psychometric properties. Int J Geriatr Psychiatry 2002;17:1064-70.

22. Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomised controlled trial. JAMA 2003;289:2819-26.

23. Spector A, Thorgrimsen L, Woods B, Royan L, Davies S, Butterworth M, et al. Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. Br J Psychiatry 2003;183: 248-54.

24. Howard K, Rockwood K. Quality of life in Alzheimer's disease. Dementia 1995;6:113-6.

25. Jonsson L, Jonsson B, Wimo A, Whitehouse P, Winblad B. Second international pharmacoeconomic conference on Alzheimer's disease. Alzheimer Dis Assoc Disord 2000;14:137-40.

26. Lawton MP. Assessing quality of life in Alzheimer disease research. Alzheimer Dis Assoc Disord 1997;11 Suppl 6:91-9.

27. Lawton MP. Quality of life in Alzheimer disease. Alzheimer Dis Assoc Disord 1994;8 Suppl 3:138-50.

28. Mack JL, Whitehouse PJ. Quality of Life in Dementia: state of the art – report of the International Working Group for Harmonization of Dementia Drug Guidelines and the Alzheimer's Society satellite meeting. Alzheimer Dis Assoc Disord 2001;15:69-71.

29. Adler C, Gunzelmann T, Machold C, Schumacher J, Wilz G. [Perception of stress by caregiving relatives of dementia patients]. Z Gerontol Geriatr 1996;29:143-9.

30. Selai C. Assessing quality of life in dementia. Med Care 2001;39:753-5.

31. Selai C. Assessing quality of life in dementia. Aging Ment Health 1999;3:101-11.

32. Whitehouse PJ, Winblad B, Shostak D, Bhattacharjya A, Brod M, Brodaty H, et al. First International Pharmacoeconomic Conference on Alzheimer's Disease: report and summary. Alzheimer Dis Assoc Disord 1998;12:266-80.

33. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 1998;50:136-45.

34. Rogers SL, Doody RS, Mohs RC, Friedhoff LT. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. Arch Intern Med 1998;158:1021-31.

35. Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Moller HJ, et al. The effects of donepezil in Alzheimer's disease – results from a multinational trial. Dement Geriatr Cogn Disord 1999;10:237-44.

36. Corey-Bloom J, Anand R, Veach J. A randomised trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholineesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. International Journal of Geriatric Psychopharmacology 1998;1:55-65.

37. Wimo A, Mattson B, Krakau I, Eriksson T, Nelvig A, Karlsson G. Cost-utility analysis of group living in dementia care. Int J Technol Assess Health Care 1995;11:49-65.

38. Reisberg B, Ferris SH, de Leon MJ, Crook T. Global Deterioration Scale (GDS). Psychopharmacol Bull 1988; 24:661-3.

39. Wimo A, Mattsson B, Krakau I, Eriksson T, Nelvig A. Cost-effectiveness analysis of day care for patients with dementia disorders. Health Econ 1994;3:395-404.

40. Kind P, Rosser R, Williams A. Valuation of quality of life: some psycho-metric evidence. In: Jones-Lee M, editor. The value of life and safety. Amsterdam-New York-Oxford: North-Holland Publishing; 1982.

41. Davis RN, Massman PJ, Doody RS. Cognitive intervention in Alzheimer disease: a randomised placebo-controlled study. Alzheimer Dis Assoc Disord 2001;15:1-9.

42. Teri L, Gibbons LE, McCurry SM, Logsdon RG, Buchner DM, Barlow WE, et al. Exercise plus behavioral management in patients with Alzheimer disease: a randomised controlled trial. JAMA 2003;290:2015-22.

43. Politis AM, Vozzella S, Mayer LS, Onyike CU, Baker AS, Lyketsos CG. A randomised, controlled, clinical trial of activity therapy for apathy in patients with dementia residing in long-term care. Int J Geriatr Psychiatry 2004;19:1087-94.

44. Ballard CG, O'Brien JT, Reichelt K, Perry EK. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. J Clin Psychiatry 2002;63:553-8.

45. Ballard CG, Thomas A, Fossey J, Lee L, Jacoby R, Lana MM, et al. A 3-month, randomised, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiat-

ric inventory median cutoff is a predictor of clinical outcome. J Clin Psychiatry 2004;65:114-9.

46. Bottini G, Vallar G, Cappa S, Monza GC, Scarpini E, Baron P, et al. Oxiracetam in dementia: a double-blind, placebo-controlled study. Acta Neurol Scand 1992;86:237-41.

47. Brodaty H, Low LF. Making Memories: pilot evaluation of a new program for people with dementia and their caregivers. Australas J Ageing 2004;23:144-6.

48. Challis D, von Abendorff R, Brown P, Chesterman J, Hughes J. Care management, dementia care and specialist mental health services: an evaluation. Int J Geriatr Psychiatry 2002;17:315-25.

49. Fontaine CS, Hynan LS, Koch K, Martin-Cook K, Svetlik D, Weiner MF. A double-blind comparison of olanzapine versus risperidone in the acute treatment of dementia-related behavioral disturbances in extended care facilities. J Clin Psychiatry 2003;64:726-30.

50. Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI. A 30-week randomised controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. JAMA 1994;271:985-91.

51. Lawton MP, Brody EM, Saperstein AR. A controlled study of respite service for caregivers of Alzheimer's patients. Gerontologist 1989;29:8-16.

52. Reimer MA, Slaughter S, Donaldson C, Currie G, Eliasziw M. Special care facility compared with traditional environments for dementia care: a longitudinal study of quality of life. J Am Geriatr Soc 2004;52:1085-92.

53. Sano M, Bell K, Cote L, Dooneief G, Lawton A, Legler L, et al. Double-blind parallel design pilot study of acetyl levocarnitine in patients with Alzheimer's disease. Arch Neurol 1992;49:1137-41.

54. Thorgrimsen L, Schweitzer P, Orrell M. Evaluating reminiscence for people with dementia: A pilot study. Arts in Psychotherapy 2002;29:93-7.

55. Wesnes K, Simmons D, Rook M, Simpson P. A double-blind placebo-controlled trial of Tanakan in the treatment of idiopathic cognitive impairment in the elderly. Human Psychopharmacology: Clinical & Experimental 1987; 2:159-69.

Appendices

Appendix 28.1 *Search strategy.*

Database	Search term 1	Search term 2
PubMed	Dementia (MeSH)	Quality of life (MeSH)
	Dementia (MeSH)	Controlled clinical trial (MeSH)
	Dementia (MeSH)	Controlled clinical trial (MeSH)
	Dementia	Quality of life
	Dementia (MeSH)	Quality of life (MeSH)
	Dementia (MeSH)	Quality-adjusted life years (MeSH)
	Dementia (MeSH)	Short form/SF-36/SF-20/SF-12
	Dementia (MeSH)	Health utilities index/HUI
	Dementia (MeSH)	EuroQol/EQ-5D
	Dementia (MeSH)	QWBS/Index of wellbeing/ quality of well-being scale
	Dementia (MeSH)	CQLI/Caregiver quality of life index
	Dementia (MeSH)	DQOL/Dementia Quality of Life Instrument
	Dementia (MeSH)	PDS/ Progressive Deterioration scale
	Dementia (MeSH)	QOL-AD/The Quality of Life AD
	Alzheimer Disease (MeSH)	Quality of life (MeSH)

	Search term 3	Results
		382 (only titles reviewed)
		525 (only titles reviewed)
	Treatment	491 (only titles reviewed)
	Controlled trial	13
	Controlled clinical trial (MeSH)	3
	Controlled clinical trial (MeSH)	0
	Controlled clinical trial (MeSH)	0
	Controlled clinical trial (MeSH)	0
	Controlled clinical trial (MeSH)	0
	Controlled clinical trial (MeSH)	0
	Controlled clinical trial (MeSH)	0
	Controlled clinical trial (MeSH)	0
	Controlled clinical trial (MeSH)	0
		249 (only titles reviewed)

The table continues on the next page

Appendix 28.1 *continued*

Database	Search term 1	Search term 2
	Alzheimer Disease (MeSH)	Controlled clinical trial (MeSH)
	Alzheimer Disease	Quality of life
	Alzheimer Disease (MeSH)	Quality of life
	Alzheimer Disease (MeSH)	Quality-adjusted life years (MeSH)
	Alzheimer Disease (MeSH)	Short form/SF-36/SF-20/SF-12
	Alzheimer Disease (MeSH)	Health utilities index/HUI
	Alzheimer Disease (MeSH)	EuroQol/EQ-5D
	Alzheimer Disease (MeSH)	QWBS/Index of wellbeing/ quality of well-being scale
	Alzheimer Disease (MeSH)	CQLI/Caregiver quality of life index
	Alzheimer Disease (MeSH)	DQOL/Dementia Quality of Life Instrument
	Alzheimer Disease (MeSH)	PDS/Progressive Deterioration scale
	Alzheimer Disease (MeSH)	QOL-AD/The Quality of Life – AD
PsycInfo	Dementia	Quality of life
	Dementia	Quality of life
	Alzheimer('s) (Disease)	Quality of life
	Alzheimer('s) (Disease)	Quality of life

Search term 3	Results
	315 (only titles reviewed)
Controlled trial	4
Controlled clinical trial (MeSH)	2
Controlled clinical trial (MeSH)	
Controlled clinical trial (MeSH)	0
Controlled clinical trial (MeSH)	0
Controlled clinical trial (MeSH)	0
Controlled clinical trial (MeSH)	0
Controlled clinical trial (MeSH)	0
Controlled clinical trial (MeSH)	0
Controlled clinical trial (MeSH)	0
Controlled clinical trial (MeSH)	3
	311 (titles reviewed, abstracts selected)
Controlled trial	6
	31
Controlled trial	3

The table continues on the next page

Appendix 28.1 *continued*

Database	Search term 1	Search term 2
CRD: NHSEED/ HTA	Dementia	Quality of life
	Alzheimer('s) (Disease)	Quality of life
	Alzheimer('s) (Disease)	Quality of life
Ingenta	Dementia	Quality of life
	Alzheimer('s) (Disease)	Quality of life
Cochrane	Dementia	Quality of life
	Alzheimer('s) (Disease)	Quality of life

Appendix 28.2 The exclusion list

0. Outside the research question, so quality is not assessed. The apparent irrelevance is a result of insufficient coding in databases or an insufficient search strategy
1. Insufficient number of subjects/low power
2. Inadequate description/selection of subjects, abstracts
3. Inadequate methods/instruments to measure outcomes/effects/ consequences

Search term 3	Results
	10
	12
	42
	125
	39
	2
	1

4. Inadequate design
5. Inadequate data collection/high attrition/drop-out/drop-in rate
6. Inadequate statistical methods/calculations
7. Inadequate ethics
8. Serious conflict of interest
9. No original data (such as reviews)
10. Miscellaneous.

29. **Dementia and Mortality**

Conclusions

There is moderately strong scientific evidence that interventions with acetylcholine esterase inhibitors, coxiber and memantine, as well as caregiver support programs, have no effect on mortality for a period of 6–12 months (Evidence Grade 2).

There is strong evidence that treatment with antipsychotics (as a group) carries a small risk of increased death (Evidence Grade 1).

Questions of interest

- Do pharmacological interventions have any effect on mortality in dementia?
- Do environmental interventions (programs) have any effect on mortality in dementia?

Background

Whether intervention effects on mortality (prolonging life) is a relevant clinical outcome in dementia care is a matter for discussion [1]. The outcomes discussed in other sections of this report – such as QoL, severity and institutionalization – may be regarded as more meaningful. Nevertheless, while mortality may be a traditional aspect of safety, prolonged survival also has implications for resource utilization, costs and outcome. As a definite end-point in any intervention, mortality influences long-term resource utilization and costs but is seldom presented as such in studies with short duration/follow-up. This section includes

only studies that contain empirical data on mortality and that lasted for 6 months or more. Models were not considered. The focus is on patient mortality. Because many studies did not regard mortality as the primary outcome, the statistical significance of the effect on mortality was often estimated on the basis of the reviewers' Chi-2 calculations. This review did not include studies on mild cognitive impairment (MCI).

Search results

PubMed, Ingenta, Cochrane Library, NHSEED/THA, HEED, PsycInfo, ERIC, Societal services abstracts and Sociological abstracts were searched for studies published in English. The search period was 1960 (or the years immediately before and after, depending on database) through July 31, 2004. For the search terms and results, see Appendix 29.1. A total of 286 hits were identified (excluding the first broad search). Mortality was seldom the main focus of the studies. Thus, mortality figures were extracted from the database of intervention studies (drug and interventions programs). Altogether, 39 studies (21 with drug treatment and 18 with programs) of acceptable quality and duration of 6 or more months were included. Due to the somewhat unsystematic search approach, it is not meaningful to list the excluded papers. However, since there have been reports of mortality when people with dementia were given atypical antipsychotic drugs, a recently published systematic review was included [2]. Furthermore, new searches in PubMed were undertaken with a focus on atypical antipsychotic drugs and antidepressive agents, second-generation (mainly SSRIs), with the following search terms:

"Dementia" [MeSH] AND "Antipsychotic Agents" [MeSH] AND "Mortality" [MeSH] (nine hits, none of interest).

"Dementia" [MeSH] AND "Mortality" [MeSH] AND "Antidepressive Agents, Second-Generation" [MeSH] (no hits).

Results

Pharmacological treatment

Effects on mortality were identified in 21 pharmacological studies with a duration of 6 months or more (Table 29.1). Seventeen of them were RCTs with a duration of 6–24 months. AD 2000 was a three-year study [3]. One study lasted for 2 years [4] and the others for 6–12 months. Few deaths occurred during a well conducted study on rofecoxib and naproxen vs placebo [5]. Different methods were used to postpone the observation period, and to create comparison groups, in the observational studies. Two of them were extensions of RCTs [6,7], while the other two were non-RCTs from the beginning [8,9]. All 4 observational studies may be characterized as low-quality. The RCTs showed any effects on survival. Fewer than 100 out of almost 7 000 patients died during the RCTs on cholinesterase inhibitors (some trials were published in more than one paper, making the calculations somewhat difficult), yielding a mortality rate of less than 1.5%. One observational study on nursing home residents showed that those treated with tacrine survived longer [8]. Two studies found indications of prolonged survival in certain analyzed CHEI treatment options [7,9]. The fourth study showed prolonged survival from tacrine treatment that was almost significant ($p = 0.06$) [6]. Two 6-month studies with memantine detected no effects on mortality.

The systematic review of atypical antipsychotic drug treatment (which focused on drugs marketed in the United States) included 15 trials (9 unpublished). The meta-analysis showed a small increased risk for death in those treated with the drugs as a group (odds ratio 1.54, 95% confidence interval 1.06–2.23) [2]. However, the results were not significant for individual drugs.

Programs

Eighteen studies on programs identified effects on mortality (Table 29.2). The observation periods were 6 to 39 months. Nine of these studies were RCTs and eight were quasi-experimental. Four studies were regarded as moderate quality and the others as low quality. Many of the studies had

rather small populations, leading to power problems. Only one study (of low quality) observed effects on mortality [10].

Evidence grades for effects on mortality

Pharmacological treatment: There is moderately strong scientific evidence (Evidence Grade 2) that pharmacological interventions with acetylcholine esterase inhibitors have no effect on mortality within the time span studied (6–12 months). No statement concerning evidence can be made for longer treatment periods.

There is moderately strong scientific evidence that pharmacological interventions with rofecoxib or naproxen have no effect on mortality for a period of one year (Evidence Grade 2).

There is moderately strong scientific evidence (Evidence Grade 2) that pharmacological interventions with memantine have no effect on mortality for a period of 6 months.

There is strong evidence that treatment with antipsychotics (as a group) carries a small risk of increased death (Evidence Grade 1).

Programs: There is moderately strong scientific evidence that caregiver support programs have no effect on mortality for a period of one year (Evidence Grade 2). No statement concerning evidence can be made for longer treatment periods or other programs.

Discussion

There is no support based on scientific evidence that pharmacological treatments or intervention programs either reduce or increase mortality in dementia care.

Mortality is generally not regarded as an outcome of interest per se, but most studies include information on mortality as a safety consideration (drug trials) or in flow charts of the way in which their populations changed over time. Mortality is likely to occur over a period of years.

Thus, it is not surprising (given that duration is often rather short) that the available information is limited. Long-term studies are difficult to conduct, and practical problems arise when it comes to collecting data over an extended period of time. It is also difficult to maintain an RCT design for several years. Thus, finding valid control groups/comparators is no easy task. That is unsatisfactory from a long-term resource utilization point of view. Because dementia disorders are expensive to treat, a prolonged period of survival as the result of any intervention may affect resource utilization and costs. This does not necessarily imply poorer cost effectiveness, given that the outcome may justify prolonged survival. Institutionalization and mortality interact in a complex manner – for instance, reduced mortality may increase the period of institutional care.

Recommendations for future research

There is a need for studies that focus on the long-term effects of different interventions on mortality.

Table 29.1 *Studies focusing on effects of pharmacological treatment on mortality.*

Author Year, reference Country	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition). Active treatment first (treatment(s), placebo)
Sano et al 1997 [4] USA	RCT	Community	Alzheimer's disease (CDR)	Moderate	341 (7%)
Knopman et al 1996 [6] USA	Observational study	Community	Alzheimer's disease (NINCDS)	Mild-moderate	663 (10%)
Ott et al 2002 [8] USA	Observational study	Nursing home	Clinical	Mild-moderate-severe	1 449+6 119
Rogers et al 1998 [11] USA	RCT	Community	Alzheimer's disease (NINCDS, DSM-III-R)	Mild-moderate	162+154+157 (20%, 15%, 32%)
Burns et al 1999 [12] United Kingdom	RCT	Community	Alzheimer's disease (NINCDS, DSM-III-R)	Mild-moderate	274+271+273 (20%, 22%, 26%)
Feldman et al 2001 [13] Canada	RCT	Community	Alzheimer's disease (NINCDS)	Moderate-severe	144+146 (16%, 14%)

Age-groups Mean/ Range (SD) (treatment(s), placebo)	Study period	Drug	Primary out-come*	Effects (end)	Remarks from reviewer	Quality of study
72.7–73.9 (7.1–8.9)	2 years	Selege-line (S), Vita-mine E, S + E	Mortality	NS in all com-binations ** (41 deaths)	Significant effects only after baseline adjustments. Vitamin E dose high	2
71.5–73.9 (7.5–8.2)	≥2 years	Tacrine high dose vs low dose	Mortality	NS (p = 0.06 for increased survival with high dose tacrine vs low dose) 81 deaths	Initial RCT not main-tained	1
82 (7.2), 84 (7.6)	3 years	Tacrine	Mortality	Tacrine users, particularly high dose users, have longer survival (HRR 0.76, 95% CI 0.70–0.83)	Not an RCT. Retrospective. Only nursing home residents. Validity of diagnoses questionable	1
72.6 (56–88), 72.9 (51–86), 74.6 (53–94)	6 months	Done-pezil	Mortality	NS (2 deaths in total)	Placebo, 5, 10 mg donepezil. Rather high attrition in 10 mg group. Short duration	2
71 (50–90), 72 (51–91), 72 (53–93)	6 months	Done-pezil	Mortality	NS (5 deaths in total)	Placebo, 5, 10 mg donepezil. Rather high attrition	2
73.3 (52–92), 74.0 (48–92)	6 months	Done-pezil	Mortality	NS (1 death)	Rather low power	2

The table continues on the next page

Table 29.1 *continued*

Author Year, reference Country	**Type of study**	**Setting**	**Dementia/ diagnosis**	**Severity of dementia**	**Patients (n) included (attrition). Active treatment first (treatment(s), placebo)**
Mohs et al 2001 [14] USA	RCT	Community	Alzheimer's disease (NINCDS, DSM-IV)	Moderate	217+214 (28%, 26%)
Winblad et al 2001 [15] Europe	RCT	Community	Alzheimer's disease (NINCDS, DSM-IV)	Mild-moderate	142+144 (33%, 33%)
Geldmacher et al 2003 [7] USA	Observational study	Community	Alzheimer's disease (NINCDS, DSM-IV)	Mild-moderate	1 115 (40%)
Corey-Bloom et al 1998 [16] USA	RCT	Community	Alzheimer's disease (NINCDS, DSM-IV)	Mild-moderate	233+231+235 (15%, 35%, 16%)
Rösler et al 1999 [17] Germany	RCT	Community	Alzheimer's disease (NINCDS, DSM-IV)	Mild-moderate	243+243+239 (13%, 33%, 14%)

Age-groups Mean/ Range (SD) (treatment(s), placebo)	Study period	Drug	Primary out-come*	Effects (end)	Remarks from reviewer	Quality of study
75.3 (49–94), 75.4 (50–91)	12 months	Done-pezil	Mortality	NS (7 deaths)	External validity questionable due to exclusion criteria	2
72.1 (49–86), 72.9 (51–88)	12 months	Done-pezil	Mortality	NS (7 deaths)	High attrition, rather low power	1
73.3	Max 96 months	Done-pezil	Mortality	266 deaths. Delayed start group lower mortality than minimum use ($p = 0.013$)	High attrition, initial RCT not maintained, pooled data from several studies, four groups (minimum use to maximal use of donepezil)	1
74.8 (45–89), 74.9 (45–89), 73.8 (50–89)	6 months	Rivastig-mine	Mortality	NS (1 death)	1–4 mg, 6–12 mg, placebo. High attrition in 6–12 mg group	2
72 (45–95)	6 months	Rivastig-mine	Mortality	NS (1 death)	1–4 mg, 6–12 mg, placebo. High attrition in 6–12 mg group	2

The table continues on the next page

Table 29.1 *continued*

Author Year, reference Country	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition). Active treatment first (treatment(s), placebo)
Farlow et al 2000 [18] USA	RCT	Community	Alzheimer's disease (NINCDS, DSM-IV)	Mild-moderate	233+231+235 (35%, 46%, 39%)***
Wilcock et al 2000 [19] United Kingdom	RCT	Community	Alzheimer's disease (NINCDS)	Mild-moderate	220+218+215 (20%, 25%, 13%)
Raskind et al 2000 [20] USA	RCT	Community?	Alzheimer's disease (NINCDS)	Mild-moderate	212 (32% 6 months, 55% 12 months, 211 (42% 6 months, 59% 12 months), 213 (19% 6 months, 60% 12 months)
Erkinjuntti et al 2002 [21]	RCT	?	AD with CVD-disease and VaD (NINDS-AIREN, NINCDS-ADRDA)	Mild-moderate	396 (26%), 196 (17%)
Bullock et al 2004 [22] United Kingdom	RCT	?	AD with CVD-disease and VaD (NINDS-AIREN, NINCDS-ADRDA)	Mild-moderate	188 (19% 6 months, 35% 12 months), 97 (11% 6 months, 44% 12 months)

Age-groups Mean/ Range (SD) (treatment(s), placebo)	Study period	Drug	Primary out-come*	Effects (end)	Remarks from reviewer	Quality of study
74.8 (45–89), 74.9 (45–89), 73.8 (50–89)	12 months	Rivastig-mine	Mortality	NS (5 deaths)	Extension of Corey-Bloom [16]. High attrition in 6–12 mg group	2
71.9 (8.3), 72.1 (8.6), 72.7 (7.6)	6 months	Galan-tamine (24 mg, 32 mg)	Mortality	NS (no deaths)	External validity questionable due to exclusion criteria	2–3
75.3, 75.9, 75.0	6 months (+ 6 months open label)	Galan-tamine (24 mg, 32 mg)	Mortality	NS (2 deaths)	Rather high attrition, particularly in 12 months	2
75.0 (6.8), 75.2 (7.3)	6 months	Galan-tamine 24 mg	Mortality	NS (9 deaths)**	Higher attrition in galantamine group ($p<0.05$)**	2
77.6, 75.8	6 months (+6 months open label)	Galan-tamine 24 mg	Mortality	NS? (1.6%, group differences not specified)	Rather low power, high attrition in 12 months	2

The table continues on the next page

Table 29.1 *continued*

Author Year, reference Country	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition). Active treatment first (treatment(s), placebo)
Lopez 2002 [9] USA	Observational	Community	Clinical	Mild-moderate (?)	135+135
Reisberg et al 2003 [23] USA	RCT	Community	DSM-IV, Alzheimer's disease (NINCDS), 283	Moderate-severe	126 (23%), 126 (33%)
Tariot et al 2004 [24] USA	RCT	Community	Alzheimer's disease (NINCDS)	Moderate-severe	203 (15%), 201 (25%)
Courtney et al "AD 2000" 2004 [3] United Kingdom	RCT	Community	DSM IV-AD	Mild-moderate	282 (32% withdrawn), 283 (31% withdrawn)
Aisen et al 2003 [5] USA	RCT	Community	Alzheimer's disease (NINCDS, DSM-III-R)	Mild-moderate	118+122+111 (24%, 27%, 21%)

* From the perspective of this analysis, these outcomes may be secondary in original trials.
** Chi2 test own calculations.
*** Based on study population in original publication [16].
Study quality: 1 = Limited study quality; 2 = Moderately high study quality; 3 = High study quality.

Age-groups Mean/ Range (SD) (treatment(s), placebo)	Study period	Drug	Primary out-come*	Effects (end)	Remarks from reviewer	Quality of study
72.7 (7.2), 72.8 (8.4)	3 years (aver-age)	CHEIs	Mortality	Endpoint mortality significantly lower in CHEI-group (p <0.001), but survival analysis NS (RR 0.38, 95% CI 0.14–1.08). 69 deaths	Not a RCT, diagnose accurancy not clear. Odd under-inter-preta-tion of mortality figures	1
75.5 (8.2), 75.8 (7.3)	6 months	Meman-tine	Mortality	NS (7 deaths)	High attrition, rather low power	2
75.5 (8.5), 75.5 (8.7)	6 months	Done-pezil, meman-tine	Mortality	NS (no deaths)	No placebo group	2
76 (54–93), 75 (46–90)	3 years	Done-pezil	Mortality	NS (22 in each group)	High attrition, unusual inclusion criteria	1
73.7 (7.2), 74.1 (7.8), 73.8 (8.0)	12 months	Napro-xen, rofe-coxib, placebo	Mortality	NS (4 deaths)	Well conduc-ted study	3

AD = Alzheimer's disease; CHEIs = cholinesterase inhibitor; CI = Confidence interval; CVD = Cerebrovascular disease; DSM = Diagnostic and statistical manual; NINCDS = National institute of neurological and communicable diseases; ns = not stated; p = points; RCT = Randomised controlled trial; SD = Standard deviation; VaD = Vascular dementia

Table 29.2 *Studies focusing on "programs" effects on mortality.*

Author Year, reference Country	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition)
Engedal 1989 [25] Norway	RCT	Community, Norway	DSM-III	–	38+39 (0%)
Lawton et al 1989 [26] USA	RCT	Community, USA	Clinical AD?, MSQ***	?	315+317
Mohide et al 1990 [27] Canada	RCT	Community, Canada	Clinical, DRS****, GDS	87.90% moderate, moderate-severe	30+30 (0% for inst follow-up)
Brodaty et al 1991 [28] Australia	Quasi-experimental	Community, Australia	DSM-III, CDR	Mild-moderate	100 (4%)
O´Connor et al 1991 [29] United Kingdom	Quasi-experimental	Community, United Kingdom	MMSE, Camdex	Mild-moderate-severe	86+73 (44%, 42%) (0% for mortality analysis)
Wimo et al 1993 [30] Sweden	Quasi-experimental	Institution	Clinical	Severe	43+40
Mittelman 1993 [31] USA	RCT	Community, USA	Clinical AD, GDS	Mild-moderate-severe	103+103 (0.5%)
Wimo et al 1993 [32] Sweden	Quasi-experimental	Community, Sweden	Clinical (Geriatrician)	Moderate	55+44 (0%)

Age-groups (patients) Mean (range or SD)	Study period	Intervention (end)	Out-come*	Effects (end)	Remarks from reviewer	Quality of study
79 (75–88), 80 (75–89)	1 year	Day care	Mortality	NS** (10 deaths)	Low power	1
76.7, 76.1	1 year	Respite care	Mortality	NS** (126 deaths)	Patient description limited	2
77.8 (9.2), 75.9 (7.7)	6 months	CGS	Mortality	NS** (no deaths)	Low power	1
70.2 (49–79)	39 months	Caregiver support (CGS), memory training (MT), waiting list (WL)	Mortality	NS** (between CGS and other groups) 22 deaths	Non randomized, low power	1
83.7, 83.7	2 years	CGS/Social support	Mortality	NS (69 deaths)	Rather low power, non randomised, 69% in the action group received the intervention	1
82 (62–96), 83 (63–92)	10 months	Multifaceted	Mortality	NS** (20 deaths)	Rather low power, non-randomised	0–1
(age class proportions)	1 year	CGS/Social support	Mortality	NS** (18 deaths)	Diagnose clinical	2
77.9 (76.0–77.9), 78.6 (77.1–80.5)	1 year	Day care	Mortality	NS** (21 deaths)	Non randomized, low power	1

The table continues on the next page

***Table 29.2** continued*

Author Year, reference Country	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition)
Volicer et al 1994 [10] USA	Quasi-experimental	LTC/SCU	DSM-III-R	Severe	113+50 (17% + 14%)
Rovner et al 1996 [33] USA	RCT	LTC (nursing home)	DSM-III-R	Severe (?)	42+39 (89 randomised)
Eloniemi-Sulkava et al 2001 [34] Finland	RCT	Community, USA	DSM-III-R, MMSE	Mild-moderate-severe	53+47 (0%)
Challis et al 2002 [35] United Kingdom	Quasi-experimental	Community, United Kingdom	OBS score	70% severe	43+43 (0%)
Teri et al 2003 [36] USA	RCT	Community, USA	Alzheimer's disease (NINCDS)	Moderate-severe	76+77 (41%, 43%) (0% for mortality analysis)
Keller et al 2003 [37] USA	Quasi-experimental	Nursing home/SCU	Clinical	Severe (?)	33+49
Huusko et al 2000 [38] Finland	RCT	Community	MMSE, clinical?	Mild-moderate-severe	130+130 (8%, 5%)

Age-groups (patients) Mean (range or SD)	Study period	Intervention (end)	Out-come*	Effects (end)	Remarks from reviewer	Quality of study
71.5 (6.7), 74.1 (10.9)	2 years	SCU-care	Mortality	Higher mortality in SCU-group. $p<0.05$** (65 deaths)	Groups not similar	1
82.0 (8.0), 81.2 (7.2)	6 months	AGE (Activiti-es, guidelines, education)	Mortality	NS** (2 deaths)	Rather low power	1
78.8 (65–97), 80.1 (67–91)	2 years	CGS	Mortaliy	NS** (17 deaths)	Rather low power	2
79.8–80.4	2 years	Case management	Mortality	NS**	Low power	1
78 (6), 78 (8)	2 years	BPSD + training	Mortality	NS** (4 deaths)	Rather low power	2
80 (7), 80 (7)	9 months	Nutritional program	Mortality	NS (10 deaths)	Diagnostics unclear, low power	1
80 (67–92), 80 (66–97)	1 year	Geriatric rehabilitation	Mortality	NS (35 deaths)	Dementia diagnostics unclear, diffe-rence in MMSE between groups	1

The table continues on the next page

Table 29.2 *continued*

Author Year, reference Country	Type of study	Setting	Dementia/ diagnosis	Severity of dementia	Patients (n) included (attrition)
Shaw et al 2003 [39] United Kingdom	RCT	Mixed	MMSE, clinical?	Moderate-severe	150+158 (31%, 28%)
Reimer et al 2004 [40] USA	Quasi-experimental	Institution	GDS	Moderate-severe (GDS 5–7)	62+64+59 (31%, 27%, 20%)
Mcdonald et al 2004 [41] United Kingdom	Quasi-experimental	Intermediate care, home for rest of life	Geriatric mental scale	"Significant dementia"	24+37

* From the viewpoint of this analysis, it may be secondary in original trials.
** Chi2 test own calculations.
*** Mental State Questionnaire.
**** Dementia Rating Scale.
Study quality: 1 = Limited study quality; 2 = Moderately high study quality; 3 = High study quality.

AD = Alzheimer's disease; AGE = Activities, guidelines, education; BPSD = Behavioral and psychological symptoms in dementia; CDR = Clinical Dementia Rating Scale; CGS = Caregiver support; DRS = Dementia rating scale; DSM = Diagnostic and statistical manual; GDS = Global deterioration scale; LTC = Long-term care; MMSE = Mini-mental state examination; NINCDS = National institute of neurological and communicable diseases; ns = not stated; RCT = Random controlled trial; SCU = Special care unit; SD = Standard deviation

Age-groups (patients) Mean (range or SD)	Study period	Intervention (end)	Out-come*	Effects (end)	Remarks from reviewer	Quality of study
84 (71–97) 84 (71–97)	1 year	Fall prevention program	Mortality	NS (56 deaths)	Dementia diagnostics unclear, MMSE based, not all study patients demented	1
80.2(7.2), 83.2 (7.2), 81.7 (8.0)	1 year	Special Care Facility	Mortality	NS (44 deaths)	Non rando-mised	1
–	1 year	Relocation	Mortality	NS (17 deaths)	Differences founding sub-groups. Small study, non-randomised	1

Appendix 29.1 *Search strategy.*

Database	Search term 1	Search term 2	Search term 3	Results
PubMed	Dementia or Alzheimer´s Disease (MeSH)	Mortality (MeSH)		548 (only titles reviewed)
	Dementia or Alzheimer´s Disease (MeSH)	Mortality (MeSH)	Controlled clinical trial (MeSH)	1
	Dementia	Mortality	Controlled trial	12
	Alzheimer´s disease	Mortality	Controlled trial	1
PsycInfo	Dementia	Mortality	Controlled trial	4
	Dementia	Mortality	Treatment	35
	Alzheimer('s) (Disease)	Mortality	Treatment	3
CRD: NHSEED/ HTA	Dementia	Mortality		20
	Alzheimer('s) (Disease)	Mortality		10
Sociological abstracts/ social services abstract/ERIC	Dementia or Alzheimer('s) (Disease)	Mortality		28
Ingenta	Dementia	Mortality		106
	Alzheimer('s) (Disease)	Mortality		32
Cochrane	Dementia	Mortality		25
	Alzheimer('s) (Disease)	Mortality		9

References

1. Post SG. Slowing the progression of Alzheimer disease: ethical issues. Alzheimer Dis Assoc Disord 1997;11 Suppl 5: S34-6; discussion S37-9.

2. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomised placebo-controlled trials. JAMA 2005;294:1934-43.

3. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004;363:2105-15.

4. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997; 336:1216-22.

5. Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomised controlled trial. JAMA 2003;289:2819-26.

6. Knopman D, Schneider L, Davis K, Talwalker S, Smith F, Hoover T, et al. Long-term tacrine (Cognex) treatment: effects on nursing home placement and mortality, Tacrine Study Group. Neurology 1996;47:166-77.

7. Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc 2003;51:937-44.

8. Ott BR, Lapane KL. Tacrine therapy is associated with reduced mortality in nursing home residents with dementia. J Am Geriatr Soc 2002;50:35-40.

9. Lopez OL, Becker JT, Wisniewski S, Saxton J, Kaufer DI, DeKosky ST. Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002;72:310-4.

10. Volicer L, Collard A, Hurley A, Bishop C, Kern D, Karon S. Impact of special care unit for patients with advanced Alzheimer's disease on patients' discomfort and costs. J Am Geriatr Soc 1994;42: 597-603.

11. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 1998;50:136-45.

12. Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Moller HJ, et al. The effects of donepezil in Alzheimer's disease – results from a multinational trial. Dement Geriatr Cogn Disord 1999;10:237-44.

13. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. A 24-week, randomised, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001;57:613-20.

14. Mohs RC, Doody RS, Morris JC, Ieni JR, Rogers SL, Perdomo CA, et al.

A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001;57:481-8.

15. Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, et al. A 1-year, randomised, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001;57:489-95.

16. Corey-Bloom J, Anand R, Veach J. A randomised trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholineesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. International Journal of Geriatric Psychopharmacology 1998;1:55-65.

17. Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999;318:633-8.

18. Farlow M, Anand R, Messina J, Jr, Hartman R, Veach J. A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe Alzheimer's disease. Eur Neurol 2000;44:236-41.

19. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ 2000;321:1445-9.

20. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomised, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology 2000;54:2261-8.

21. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet 2002;359:1283-90.

22. Bullock R, Erkinjuntti T, Lilienfeld S. Management of patients with Alzheimer's disease plus cerebrovascular disease: 12-month treatment with galantamine. Dement Geriatr Cogn Disord 2004;17:29-34.

23. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333-41.

24. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomised controlled trial. JAMA 2004;291:317-24.

25. Engedal K. Day care for demented patients in general nursing homes. Effects on admissions to institutions and mental capacity. Scand J Prim Health Care 1989;7:161-6.

26. Lawton MP, Brody EM, Saperstein AR. A controlled study of respite service for caregivers of Alzheimer's patients. Gerontologist 1989;29:8-16.

27. Mohide EA, Pringle DM, Streiner DL, Gilbert JR, Muir G, Tew M. A randomised trial of family caregiver support in the home management of dementia. J Am Geriatr Soc 1990;38:446-54.

28. Brodaty H, Peters KE. Cost effectiveness of a training program for dementia caregivers. Int Psychogeriatr 1991;3:11-22.

29. O'Connor DW, Pollitt PA, Brook CP, Reiss BB, Roth M. Does early intervention reduce the number of elderly people with dementia admitted to institutions for long term care? BMJ 1991;302:871-5.

30. Wimo A, Nelvig A, Nelvig J, Adolfsson R, Mattsson B, Sandman PO. Can changes in ward routines affect the severity of dementia? A controlled prospective study. Int Psychogeriatr 1993;5:169-80.

31. Mittelman MS, Ferris SH, Steinberg G, Shulman E, Mackell JA, Ambinder A, et al. An intervention that delays institutionalization of Alzheimer's disease patients: treatment of spouse-caregivers. Gerontologist 1993;33:730-40.

32. Wimo A, Mattsson B, Adolfsson R, Eriksson T, Nelvig A. Dementia day care and its effects on symptoms and institutionalization – a controlled Swedish study. Scand J Prim Health Care 1993;11:117-23.

33. Rovner BW, Steele CD, Shmuely Y, Folstein MF. A randomised trial of dementia care in nursing homes. J Am Geriatr Soc 1996;44:7-13.

34. Eloniemi-Sulkava U, Notkola IL, Hentinen M, Kivela SL, Sivenius J, Sulkava R. Effects of supporting community-living demented patients and their caregivers: a randomised trial. J Am Geriatr Soc 2001;49:1282-7.

35. Challis D, von Abendorff R, Brown P, Chesterman J, Hughes J. Care management, dementia care and specialist mental health services: an evaluation. Int J Geriatr Psychiatry 2002;17:315-25.

36. Teri L, Gibbons LE, McCurry SM, Logsdon RG, Buchner DM, Barlow WE, et al. Exercise plus behavioral management in patients with Alzheimer disease: a randomised controlled trial. JAMA 2003;290:2015-22.

37. Keller HH, Gibbs AJ, Boudreau LD, Goy RE, Pattillo MS, Brown HM. Prevention of weight loss in dementia with comprehensive nutritional treatment. J Am Geriatr Soc 2003;51:945-52.

38. Huusko TM, Karppi P, Avikainen V, Kautiainen H, Sulkava R. Randomised, clinically controlled trial of intensive geriatric rehabilitation in patients with hip fracture: subgroup analysis of patients with dementia. BMJ 2000;321:1107-11.

39. Shaw FE, Bond J, Richardson DA, Dawson P, Steen IN, McKeith IG, et al. Multifactorial intervention after a fall in older people with cognitive impairment and dementia presenting to the accident and emergency department: randomised controlled trial. BMJ 2003;326:73.

40. Reimer MA, Slaughter S, Donaldson C, Currie G, Eliasziw M. Special care facility compared with traditional environments for dementia care: a longitudinal study of quality of life. J Am Geriatr Soc 2004;52:1085-92.

41. Macdonald A, Philpot M, Briggs C. An attempt to determine the benefits of a 'home-for-life' principle in residential care for people with dementia and behavioral problems: a comparative cohort study. Dement Geriatr Cogn Disord 2004; 18:6-14.

Reports *published by SBU*

SBU Reports in English

Dementia (2008), three volumes, no 172E/1+2+3
Obstructive Sleep Apnoea Syndrome (2007), no 184E
Interventions to Prevent Obesity (2005), no 173E
Moderately Elevated Blood Pressure (2004), Volume 2, no 172/2
Sickness Absence – Causes, Consequences, and Physicians' Certification Practice, Scandinavian Journal of Public Health, supp 63 (2004), 167/suppl
Radiotherapy for Cancer (2003), Volume 2, no 162/2
Treating and Preventing Obesity (2003), no 160E
Treating Alcohol and Drug Abuse (2003), no 156E
Evidence Based Nursing: Caring for Persons with Schizophrenia (1999/2001), no 4E
Chemotherapy for Cancer (2001), Volume 2, no 155/2
CABG/PTCA or Medical Therapy in Anginal Pain (1998), no 141E
Bone Density Measurement, Journal of Internal Medicine, Volume 241 Suppl 739 (1997), no 127/suppl
Critical Issues in Radiotherapy (1996), no 130E
Radiotherapy for Cancer, Volume 1, Acta Oncologica, Suppl 6 (1996), no 129/1/suppl
Radiotherapy for Cancer, Volume 2, Acta Oncologica, Suppl 7 (1996), no 129/2/suppl
Mass Screening for Prostate Cancer, International Journal of Cancer, Suppl 9 (1996), no 126/suppl
Hysterectomy – Ratings of Appropriateness... (1995), no 125E
Moderately Elevated Blood Pressure, Journal of Internal Medicine, Volume 238 Suppl 737 (1995), no 121/suppl
CABG and PTCA. A Literature Review and Ratings... (1994), no 120E
Literature Searching and Evidence Interpretation (1993), no 119E
Stroke (1992), no 116E
The Role of PTCA (1992), no 115E
The Problem of Back Pain – Conference Report (1989), no 107E
Preoperative Routines (1989), no 101E

SBU Summaries in English

Caries – Diagnosis, Risk Assessment and Non-Invasive Treatment (2008), no 501-39
Methods of Prenatal Diagnosis (2007), no 510-38
Light Therapy for Depression, and Other Treatment of Seasonal Affective Disorder (2007), no 510-37
Dyspepsia and Gastro-oesophageal Reflux (2007), no 510-36

Obstructive Sleep Apnoea Syndrome (2007), 510-35

Benefits and Risks of Fortifying Flour with Folic Acid to Reduce the Risk of Neural Tube Defects (2007), no 510-34

Methods of Promoting Physical Activity (2007), no 510-33

Mild Head Injury – In-hospital Observation or Computed Tomography? (2007), no 510-32

Methods of Treating Chronic Pain (2006), no 510-31

Malocclusions and Orthodontic Treatment in a Health Perspective (2006), no 510-30

Psychiatric Risk Assessment Methods – Are Violent Acts Predictable? (2006), no 510-29

Treatment of Anxiety Disorders (2006), no 510-28

Interventions to Prevent Obesity (2005), no 510-27

Chronic Periodontitis – Prevention, Diagnosis and Treatment (2004), no 510-26

Moderately Elevated Blood Pressure (2004), no 510-25

Treatment of Depression (2004), no 510-24

Prescribed Sick Leave – Causes, Consequences, and Practices (2004), no 510-23

Osteoporosis – Prevention, Diagnosis and Treatment (2003), no 510-22

Radiotherapy for Cancer (2003), no 510-21

Hearing Aids for Adults (2003), no 510-20

Prevention of Dental Caries (2002), no 510-19

Prevention, Diagnosis & Treatment of Venous Thromboembolism (2002), no 510-18

Obesity – Problems and Interventions (2002), no 510-17

Hormone Replacement Therapy (2002), no 510-16 Treatment of Alcohol and Drug Abuse (2001), no 510-15

Chemotherapy for Cancer (2001), no 510-14

Treatment of Asthma and COPD (2000), no 510-13

Dyspepsia – Methods of Diagnosis and Treatment (2000), no 510-12

Back Pain, Neck Pain (2000), no 510-11

Urinary Incontinence (2000), no 510-9

The Patient – Doctor Relationship (2000), no 510-8

Prognostic Methods for Acute Coronary Artery Disease (1999), no 510-10

Smoking Cessation Methods (1998), no 510-7

Routine Ultrasound Examination During Pregnancy (1998), no 510-6

Smoking Cessation Methods (1998), no 510-5

Surgical Treatment of Rheumatic Diseases (1998), no 510-2

Preventing Disease with Antioxidants (1997), no 510-4

Community Intervention – Cardiovascular Disease (1997), no 510-3

The Use of Neuroleptics (1997), no 510-1

SBU Reports in Swedish

Yellow reports (1996–2008)

Rörbehandling vid inflammation i mellanörat (2008), nr 189
Karies – diagnostik, riskbedömning och icke-invasiv behandling (2007), nr 188
Benartärsjukdom – diagnostik och behandling (2007), nr 187
Ljusterapi vid depression samt övrig behandling av årstidsbunden depression (Uppdatering av Kapitel 9 i SBU-rapport 166/2 från 2004) (2007), nr 186. *Publicerad endast i elektronisk version på www.sbu.se*
Dyspepsi och reflux (2007), nr 185
Nyttan av att berika mjöl med folsyra i syfte att minska risken för euralrörsdefekter (2007), nr 183
Metoder för att främja fysisk aktivitet (2007), nr 181
Måttligt förhöjt blodtryck (Uppdatering av SBU-rapporten 2004 170/1) (2007), nr 170/1u
Metoder för tidig fosterdiagnostik (2006), nr 182
Hjärnskakning – övervakning på sjukhus eller datortomografi och hemgång? (Uppdatering av rapport från 2000) (2006), nr 180
Metoder för behandling av långvarig smärta (2006), nr 177/1+2
Demenssjukdomar (2006), nr 172
Bettavvikelser och tandreglering i ett hälsoperspektiv (2005), nr 176
Riskbedömningar inom psykiatrin – kan våld i samhället förutsägas? (2005), nr 175
Behandling av ångestsyndrom (2005), nr 171/1+2
Förebyggande åtgärder mot fetma (2004), nr 173
Måttligt förhöjt blodtryck (2004), två volymer, nr 170/1+2
Kronisk parodontit – prevention, diagnostik och behandling (2004), nr 169
Behandling av depressionssjukdomar (2004), tre volymer, nr 166/1+2+3
Sjukskrivning – orsaker, konsekvenser och praxis (2003), nr 167
Osteoporos – prevention, diagnostik och behandling (2003), två volymer, nr 165/1+2
Hörapparat för vuxna – nytta och kostnader (2003), nr 164
Strålbehandling vid cancer (2003), två volymer, nr 162/1+2
Att förebygga karies (2002), nr 161
Fetma – problem och åtgärder (2002), nr 160
Behandling med östrogen (2002), nr 159
Blodpropp – förebyggande, diagnostik och behandling av venös tromboembolism (2002), tre volymer, nr 158/1+2+3
Behandling av alkohol- och narkotikaproblem (2001), två volymer, nr 156/1+2
Cytostatikabehandling vid cancer/Chemotherapy for cancer (2001), två volymer, nr 155/1+2

Behandling av astma och KOL (2000), nr 151

Ont i magen – metoder för diagnos och behandling av dyspepsi (2000), nr 150

Ont i ryggen, ont i nacken (2000), två volymer, nr 145/1+2

Behandling av urininkontinens (2000), nr 143

Avancerad hemsjukvård och hemrehabilitering (1999), nr 146

Prognostiska metoder vid akut kranskärlssjukdom (1999), nr 142

Rutinmässig ultraljudsundersökning under graviditet (1998), nr 139

Metoder för rökavvänjning (1998), nr 138

Reumatiska sjukdomar, Volym 1, Analys av området (1998), nr 136/1

Reumatiska sjukdomar, Volym 2, Litteraturgranskning (1998), nr 136/2

Att förebygga sjukdom – med antioxidanter, Volym 1 (1997), nr 135/1

Antioxidanter, Cancersjukdomar (1997), två volymer, nr 135/2:1+2:2

Att förebygga sjukdom i hjärta och kärl (1997), nr 134

Behandling med neuroleptika (1997), två volymer, nr 133/1+2

Behandling med östrogen (1996), nr 131

Strålbehandling vid cancer, Volym 1 (1996), nr 129/1

Strålbehandling vid cancer, Volym 2, Litteraturgranskning (1996), 129/2

Mätning av bentäthet (1995), nr 127

White Reports (1998–2008)

Behandling med vitamin D och kalcium (2006), nr 178

Volym och kvalitet (2005), nr 179

ADHD hos flickor (2005), nr 174

Evidensbaserad äldrevård (2003), nr 163

Rökning och ohälsa i munnen (2002), nr 157

Placebo (2000), Ges ut av Liber, nr 154

Behov av utvärdering i tandvården (2000), nr 152

Sveriges ekonomi och sjukvårdens III, Konferensrapport (2000), nr 149

Alert – Nya medicinska metoder (2000), nr 148

Barn födda efter konstgjord befruktning (IVF) (2000), nr 147

Patient–läkarrelationen (1999), Ges ut av Natur och Kultur, nr 144

Evidensbaserad omvårdnad: Behandling av patienter med schizofreni (1999), nr 4

Evidensbaserad omvårdnad: Patienter med depressionssjukdomar (1999), nr 3

Evidensbaserad omvårdnad: Patienter med måttligt förhöjt blodtryck (1998), nr 2

Evidensbaserad omvårdnad: Strålbehandling av patienter med cancer (1998), nr 1

Evidensbaserad sjukgymnastik: Patienter med ländryggsbesvär (1999), nr 102
Evidensbaserad sjukgymnastik: Patienter med nackbesvär (1999), nr 101
Smärtor i bröstet: Operation, ballongvidgning, medicinsk behandling (1998), nr 140
Sveriges ekonomi och sjukvårdens II, Konferensrapport (1998), nr 137

SBU Alert Reports

Early assessment of new health technologies. Find them at www.sbu.se/alert in PDF format.