Pharmaceutical and non-pharmaceutical interventions for Alzheimer's Disease, a rapid assessment

KCE reports 111C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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Pharmaceutical and non-pharmaceutical interventions in Alzheimer's Disease, a rapid assessment.

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Executive summary

INTRODUCTION

No hard data exist, but experts estimate that in 2008 around 75 000 patients were suffering from Alzheimer's disease (AD) in Belgium. This is more than half of all patients with dementia. Two-thirds of the AD patients are women and about 45% are institutionalized. Clinical AD is preceded by a slowly progressing accumulation in the brain of amyloid plaques and neurofibrillary tangles with hyperphosphorylated tau protein. In many cases AD is present in combination with some degree of cerebrovascular damage (mixed dementia). With the exception of some genetically well-defined forms of AD, at present a definitive diagnosis of AD still requires histopathological confirmation of a probabilistic clinical diagnosis.

Memory impairment is usually one of the first symptoms of AD. As the disease progresses cognitive deficits start to interfere with activities of daily living (ADL) and behavioural problems may appear. These behavioural and psychological signs and symptoms in dementia (BPSD) commonly include depression, apathy, agitation, disinhibition, psychosis, wandering, aggression, incontinence and altered eating habits. They contribute significantly to caregiver burden, institutionalization (placement in an elderly home), and decreased quality of life for patients with dementia.

The most frequently used cognitive test to assess the severity of AD is the 30 points Mini Mental State Exam (MMSE). Severe AD is defined as a MMSE less than 10 points. The life expectancy of AD patients is about half that of a person with the same age but without AD. The overall goals of current interventions and care are to improve the patient (and caregiver) quality of life and if needed, to "attenuate" the behavioural disorder of the patient. It is expected that earlier intervention with disease-modifying therapies will be more effective than current symptomatic therapies. If such disease-modifying therapies become available, an early accurate diagnosis will be more important than it is now, even at the pre-dementia phase referred to as mild cognitive impairment (MCI).

SCOPE AND METHODS

We studied the effectiveness and cost-effectiveness of the currently available pharmaceutical and non-pharmaceutical interventions targeting AD patients. We limited our search to HTA reports and systematic reviews that minimally covered the literature published until 2003 for non-pharmacological interventions and mid 2004 for pharmacological interventions. We did not perform any formal scoring of the quality of the reviews, which can be considered a limitation of the study. With regard to cost-effectiveness analyses also original full economic evaluations were included if published after 2004. Finally, we analysed Belgian drug prescription data for the 2002-2006 period.

The aim of this rapid assessment of interventions for AD was not to repeat the numerous systematic reviews and health technology assessment reports which have been published over the last years. The objective of this report was to summarize the conclusions of these reviews and to focus on findings of relevance for the Belgian decision makers. We have therefore tried to be complementary to other Belgian research reports on AD.

RESULTS

THE DIAGNOSTIC PROCESS

Targeted screening

At present, no single diagnostic instrument is good enough for use as a tool for population screening. Many methods (scales and indices) are used to measure the severity of various symptoms of dementia, such as cognitive deterioration, functional decline and behavioural changes. The insufficient evaluation of most screening and diagnostic methods makes it even more difficult to assess the efficacy of specific care and treatment approaches. Also the lack of biomarkers which reliably predict progression reduces the ability to assess response to treatment.

An initial selection or screening of patients for possible further diagnosis can be made by general practitioners and can be based on standardised interviews with collateral sources, such as informal or family caregivers, as well as on simple tests such as the MMSE, the clock drawing test and other simple tests. Such initial selection by general practitioners is to be distinguished from a diagnostic work-up.

Diagnosis

Neuropsychological testing has been recommended following the baseline assessment in all patients but is particularly useful in patients with MCI and mild AD.

The reference standards for the diagnosis of AD are given in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR) and by the National Institute of Neurological and Communicative Disorders and Stroke – the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) working group. Based on an analysis of all available evidence, a revision of these latter criteria for clinical diagnosis has been proposed in 2007. The revised criteria reflect the increasing importance of new markers, in addition to the core diagnostic criterion of early episodic memory impairment (episodic memory is memory for events that the patient experienced and should be able to recall, more specifically for recent events). These new supportive features are now being used in clinical trials and in expert centres. They require further standardisation and demonstration of incremental diagnostic benefit over and above that of episodic memory impairment benefit before they can enter routine care. These four supportive tests are 1. the presence of medial temporal lobe atrophy on magnetic resonance imaging (MRI), 2. abnormal cerebrospinal fluid (CSF) biomarker values (amyloid beta1-42, total tau, and phospho-tau), 3. a specific pattern on functional neuroimaging with 18F-FDG positron-emission tomography (PET), or 4. a proven AD autosomal dominant mutation within the immediate family. Other promising tests such as the visualisation of amyloid plaques using specific PET exams are still in the early research phase.

Health-economic studies that have combined different types of testing are lacking. As a consequence, it is not known with certainty which approaches are most cost-effective.

NON-PHARMACOLOGICAL INTERVENTIONS

Many methodological difficulties were encountered when non-pharmacological interventions were reviewed. Most of the studies have a small sample size. Compared with pharmacological treatments there is a relative lack of large randomized controlled trials (RCTs). The patient study population are often 'dementia' patients without a well-documented clinical diagnosis, a reason for study exclusion for some authors of systematic reviews. Often there is also no involvement of physicians in the studies. In addition, there is often a lack of standardization of the specific non-pharmacological interventions and validation of the scales used as study endpoint. As a result different authors tend to group studies differently. We grouped interventions into four categories.

1. Patient interventions, analysis by type of intervention

A first group of reviews focused on specific interventions and their effects on the patient. These interventions target patient cognition (reality orientation, cognitive stimulation, training or rehabilitation), patient emotion (reminiscence therapy, validation therapy, self-maintenance therapy, individualized special instruction), sensory stimulation ("snoezelen" or multisensory stimulation, massage and touch, aromatherapy, simulated presence therapy, music therapy), structured or physical activities, ADL rehabilitative care, interventions targeting communication or interventions on the patient environment (bright light, broad intensive care programs in dementia units, redirect attention away from the exit).

We could not find any high quality evidence to support or reject these interventions. Sometimes a single study was positive, but in this field of research repeating a study using the same intervention and the same endpoint is exceptional. When studied, effects were often transient. For some interventions two or more RCTs reported positive outcomes. However, intervention modalities and outcome measures differed between these trials. Such interventions are considered promising and include cognitive stimulation (alone or add-on to therapy with inhibitors of acetylcholinesterase), ADL-rehabilitative care, music therapy, massage/touch, and physical activity.

2. Patient interventions, analysed for effect on patient behaviour and wandering

A second group of reviews focused on specific patient signs and symptoms, and especially on the effect of interventions on patient behaviour and wandering. Again, high quality evidence is lacking.

3. Technological support interventions

Thirdly, a single review discussed technological support interventions (eg communication tools). These have mainly been developed for younger persons with physical disabilities. No good quality studies on the use of such tools for dementia patients are available.

4. Interventions targeting caregivers

Last but not least, one of the promising area's of dementia research concerns the interventions to prevent the negative consequences of caring for a person with dementia. Care at home for as long as possible is often preferred over institutionalisation both by the patient and the family-caregiver. Caring for a person with dementia at home is however intensive and burdensome. Caregivers are at high risk of psychosocial morbidity and associated breakdown in care. Some moderate level evidence was found for a positive effect of several forms of psychosocial interventions and psychoeducation on informal caregiver depression and stress. However, reviews draw different conclusions on the benefit of individual sessions versus group based sessions. Education and training of staff were found to be promising interventions.

Because of conflicting conclusions between systematic reviews, SBU concluded that there was no evidence of benefit for caregivers from respite care, nor for placing the elderly relative in a nursing home or special care unit.

Support measures preventing caregivers from becoming overburdened and depressed result in a delay of institutionalisation, as shown in a meta-analysis of 13 support programs. For example, the large randomized controlled trial (RCT) by Mittelman et al. studied over a 9.5-year period 406 spouse caregivers of community dwelling AD patients in New York City. Enhanced counseling and support consisted of six sessions of individual and family counseling, support group participation, and continuous availability of ad-hoc telephone counseling. This intervention was associated with a delay in median time to placement of 557 days. In addition, self-rated health in intervention group caregivers was significantly better than control group caregivers. This compares very favorably with the results for this endpoint based on pharmacological treatments (as discussed in the next section). However, not all support studies targeting both caregiver and patient had such a positive result, and a critical analysis of the predictors of response may be of use to optimize the benefit of the intervention in other settings.

PHARMACOLOGICAL TREATMENT

Inhibitors of acetylcholinesterase (ChEIs) (Aricept/donepezil, Reminyl/galantamine, and Exelon/rivastigmine) and Ebixa/memantine (in monotherapy) were evaluated in AD using large placebo-controlled randomized trials, mainly involving specialist care centres. The primary endpoints in most studies were cognitive tests performed by the patient, eg the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog) and measurements of global function, eg the Clinician's Interview-based Impression of Change with caregiver support (CIBIC+). The CIBIC+ integrates the treatment result as judged by the patient, the caregiver and the physician. Activities of daily living (ADL) and behavioural disturbances, as reported by the caregiver, were secondary outcomes. In Belgium, Ginkgo biloba is also reimbursed for the symptomatic treatment of mild to moderately severe AD (MMSE > 11).

Inhibitors of acetylcholinesterase (ChEIs)

Based on 10 randomized, double blind, placebo-controlled trials of 6 months duration, the change (improvement) in cognitive function with ChEIs was on average -2.7 points (95%CI -3.0 to -2.3, $p<0.00001$), in the midrange of the 70 point ADAS-Cog Scale (greater ADAS-Cog scores indicate greater cognitive impairment). This mean change is smaller than the minimum change of 4 points or even 7 points which was arbitrarily defined by experts as clinically relevant. Such small average improvement is statistically significant but only marginal from a clinical point of view. This average effect of ChEIs corresponds to a 1 to 1.5 points improvement on the 30 points MMSE scale.

A cut-off for (minimal) improvement consisting of at least a 4 point improvement on the ADAS-cog plus no worsening on the CIBIC+ or another functioning scale has been proposed. Using this cut-off and based on the phase 3 clinical trial populations a number needed to treat (NNT) of about 10 was calculated for the ChEIs. This means that for each 10 patients treated one patient will show this improvement. No factors could be identified predicting response to ChEIs. The improvement attributable to the ChEIs is no longer apparent 6 weeks after the medication is stopped. Both effects and adverse event rates (mainly anorexia, nausea, vomiting and diarrhoea) are dose-dependent, limiting dose increases of ChEIs. These gastrointestinal adverse events are common but can be partly avoided by means of a slower dose titration rate. Also cardiac side-effects (bradycardia, AV-block) have been reported but these are less frequent.

For all 3 ChEIs, there are indications of a minor benefit in activities of daily living. In the AD2000 trial, the risk of institutionalisation in persons taking donepezil was not found to be different from the risk of institutionalisation in persons taking placebo over a 3-year follow-up period. The 2008 preliminary report by IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) concludes that no interpretable data are available for the other ChEIs for prevention of institutionalisation.

Memantine

The effect of memantine on cognitive function is small. Based on data published, reviewers conclude there is "some improvement in mild to severe AD" (SBU, 2008), "a small beneficial effect in moderate to severe AD" (Cochrane review, 2006), or "consistent evidence of improvement but the effect size for the ADAS-cog is not clinically significant" (Raina, 2008). It was striking that data of 7 studies could not be included in the preliminary report of the systematic review by IQWiQ because the study results or the specific subgroup analyses were not made public by the sponsor of study. HTA agencies have no access to dossiers submitted to the national and European medicines agencies. There is no standard way to obtain and handle study data that are not made public. Different authors may include/exclude studies differently. All these factors may explain why authors arrive at slightly different conclusions. IQWiG concluded that in the analysis of moderate and severe AD patients, there was "no significant effect on cognition" of memantine monotherapy.

According to IQWiG the improvements in clinician's global impression, ADL and for psychopathology are minor. The clinical relevance of these findings is questionable. The data collected for memantine on reduction in degree of care by caregivers or institutions were not made public, nor were data made public for the endpoint prevention of institutionalisation.

Two RCTs in which memantine was combined for 6 months with ChEIs in AD patients with a MMSE 3-14 reported positive results for cognitive function and CIBIC+ versus ChEI monotherapy, but this was not confirmed in a similar trial in AD patients with a MMSE 10-22. None of these three RCTs included a placebo-only arm.

Ginkgo biloba

Recent systematic reviews conclude the evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia is inconsistent and unreliable. Also in MCI no indications of efficacy were found.

Antipsychotics and antidepressants

It is now well established that the use of both typical and atypical antipsychotics in patients with dementia is associated with an increased mortality rate and that their use should be restricted, eg to hostile, aggressive patients. The optimal diagnosis and management of depression in AD patients is not well-defined.

COST-EFFECTIVENESS OF INTERVENTIONS

Cost-effectiveness analyses for decision making require the presence of effectiveness as denominator. The efficacy of many of the pharmaceutical and non-pharmaceutical interventions currently in use for AD is however questionable. With the possible exception of support for carers, there are no interventions of big effect size. The results for cost-effectiveness of AD medications reported in the literature are heterogeneous and often unreliable. They are very variable and dependent on the underlying assumptions used in the models.

Cost-effectiveness models for pharmaceutical interventions extrapolate (without validation) the short term (6 or maximum 12 months) improvement in cognition for ChEIs into long term improvement, such as a delay of institutionalisation. There are however also other determinants of institutionalisation, such as the functional ability, age, psychosis,... and the presence of a caregiver. Only a few models defined disease progression according to both cognitive and non-cognitive criteria. Another common problem across all reported cost-effectiveness modelling studies is the lack of good quality input data, e.g. health state utilities, transition probabilities... Numerous sources of data had thus to be combined from disparate studies to feed the models and many assumptions had to be made to palliate this paucity of data.

Assuming drug therapy causes a delay in institutionalisation, as most models do, is however contradictory with the available evidence as discussed above. The many AD cost-effectiveness models based on this assumption (and which may have been used to justify drug reimbursement) are therefore unreliable.

In general, model-based economic evaluations of non-pharmaceutical interventions suffered from the same limitations as those described above for the evaluations of pharmaceutical interventions in the treatment of AD. The short-term outcomes used in those evaluations were changes in the scale score between AD interventions and usual care, for which significant differences were reported in the trial. The limitation with this approach is that such change in scale score do not translate easily into clinically meaningful final outcomes. Therefore the results of such economic evaluations are difficult to interpret. Despite these shortcomings there are indications from a single UK trial that group-based cognitive stimulation sessions in patients with mild to moderate dementia in day-care or care homes is promising and might be cost-effective.

Studies with longer term follow-up are needed to feed cost-effectiveness models. One step in this direction is the study of Mittelman et al. demonstrating a significant reduction in the rate of institutionalisation with enhanced counseling and support of AD patients' caregivers. Economic studies based on these results would be highly informative.

ANALYSIS OF BELGIAN DRUG PRESCRIPTION DATA

In Belgium the three ChEIs are reimbursed by the RIZIV/INAMI for mild to moderately severe AD (MMSE > 11) since mid 2002. Ebixa/memantine is reimbursed in moderate to severe AD (MMSE >3, <15) starting from 2004. Reimbursement of these medications for AD requires confirmation of the diagnosis (based on DSM-IV criteria) by a psychiatrist, a neurologist, or a geriatrician specialist in internal medicine. The care and support team should include the specialist and the patient general practitioner. Exclusion of other pathology (eg brain infarction) is done using a brain CT or MRI scan. The functional evaluation should include the 6 points ADL Katz scale, the instrumental ADL Lawton scale (9 points), as well as the NPI (Neuro-Psychiatric Inventory) for behaviour. A RIZIV/INAMI registry was planned for AD medication but has not been implemented up till now.

We explored the use of new diagnostic tests and medications in AD patients based on a selection from the "permanente steekproef / échantillon permanent" (PS/EP) database, containing reimbursed activities and demographic data of a population of 300 000 patients, and representative of the Belgian population. We selected patients who had at least one reimbursed prescription for a ChEI or Ebixa/memantine in the 2002-2006 period.

It was not surprising to see that the recently proposed diagnostic markers for AD (based on MRI, CSF, PET or genetic analyses) were not used routinely in this period (using codes of reimbursed activities as a proxy). Based on our data we estimate that each year over 10 000 patients start ChEI therapy. For 2008 we estimated that over 40 000 of the estimated 75 000 AD patients received a ChEI: one in three of the estimated 34 000 AD patients in elderly homes versus about 70% of the estimated 41 000 AD patients cared for at home. With regard to Ebixa/memantine we estimate that about 5000 AD patients were treated with this drug in Belgium in 2008.

The mean patient age at the start of ChEI therapy was 79 years (on average more than 5 years older compared with patients enrolled in AD phase 3 trials). Two in three patients were female. When started in patients cared for at home ChEIs were given for over 3 years (median). Patients on ChEI therapy received concomitant therapy with an antipsychotic (30%) or an antidepressant (34%) at some point in time. Concomitant antipsychotic use was especially high (42%) during the year of institutionalisation.

Analysis of overall survival of patients after starting ChEI therapy using a Cox proportional hazard model showed age, male sex, concomitant antipsychotic use, ChEI first prescription in a hospital or an elderly home, as well as institutionalisation itself were all highly significant predictors of mortality in this model (which did not include a direct measure of behaviour or disease severity). There were no significant differences between ChEIs. Concomitant use of an antidepressant was not a significant predictor of mortality. In hospitalized patients who started ChEI therapy a slightly increased early mortality was observed during the first 6 months following ChEI therapy initiation. Although the cause of the excess mortality was not studied, most probably the excess mortality can be attributed to severe comorbidity.

RECOMMENDATIONS

Clinical Practice

- Physicians should limit the use of antipsychotics in AD patients to situations where their use is absolutely necessary. Our data analysis confirmed previous studies demonstrating that the use of antipsychotics is associated with a significant increase in mortality.
- Initiation of ChEI treatment in hospitalised medically instable AD patients should be judged carefully given the slightly increased early mortality in such patients.

Reimbursement

- As robust clinical efficacy and cost-effectiveness data are lacking, reimbursement of Ginkgo biloba cannot be justified.
- Awaiting further data on the combination treatment of ChEI plus memantine, the reimbursement of memantine in monotherapy should be questioned given the very weak (to absent) clinical efficacy of memantine monotherapy and the lack of robust cost-effectiveness data.
- Based on their well documented low level of clinical efficacy reimbursement of ChEIs can be continued but should be the subject of a revision of the reimbursement criteria as foreseen under article 38 of the law of December 21, 2001. It should be noted that robust cost-effectiveness of ChEIs has not been demonstrated as the assumptions on clinical effectiveness used in the models were not confirmed by clinical trials.
- As medicines for Alzheimer's Disease are being prescribed mainly to geriatric patients is seems appropriate to take into account during the revision procedures the possible benefits on behavioural disturbances in these patients.
- The non-pharmaceutical intervention which has shown to delay institutionalisation while maintaining quality of life of the caregiver and the patient (based on the Mittelman study), should be implemented in Belgium, ideally as a large randomized trial sponsored by government. The cost-effectiveness of such intervention should also be studied.

Methodological Recommendations in the Context of Reimbursement Policies

- Health technology assessments should include as much as possible all sources of evidence and not only trials published. Exchange of information with national and European medicines agencies is required as they have access to a more complete set of trial data.

- In addition to the reimbursed medicines, coding of non-reimbursed prescription medicines eg benzodiazepines, is necessary for analysing their use.

Research Agenda

- The cost-effectiveness of performing MRI and neuropsychological testing in all patients who screened positive for dementia is not known and deserves further investigation.
- Comparative analyses of incremental diagnostic benefit and cost-effectiveness of the new supportive diagnostic tests for AD (medial temporal lobe atrophy on MRI, CSF biomarkers, FDG-PET scan, genetic tests) would be instructive to guide future reimbursement decisions for these tests.
- The field of non-pharmaceutical intervention would greatly benefit from standardization initiatives of interventions. Repeating positive studies using the same intervention and the same validated endpoint should become the rule rather then the exception, as it is now.
- The fact that in many patients ChEIs are first started after institutionalisation (often during the preceding hospitalisation) suggests the diagnosis of AD is made rather late and this requires further study.
- A more accurate assessment of the prevalence of dementia is needed. As the number of patients with dementia is expected to increase, the required supply of appropriate elderly homes and other services should be estimated.

Scientific summary

Table of content

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale, cognitive subscale
ADCS/ADL	AD Cooperative Study Activities of Daily Living inventory
ADL	Activities of daily living
AE	Adverse event
BPSD	Behavioral and psychological signs and symptoms in dementia
CBT	Cognitive behaviour therapy
CDR	Clinical Dementia Rating scale
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CST	Cognitive Stimulation Therapy
CGIC	Clinical Global Impression of Change
ChEI	Acetylcholinesterase inhibitor
CI	Confidence interval
CIBIC	Clinician's Interview-based Impression of Change
CT	Computed tomography
DAD	Disability Assessment for Dementia
DLB	Dementia with Lewy bodies
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders fourth edition text revision
EPS	Extrapyramidal symptoms
FLD	Frontal lobe dementia
FTC	Full-time care
GBS	Gottfries–Bråne–Steen
GDS	Global Deterioration Scale
HADS	Hospital Anxiety and Depression Scale
HTA	Health Technology Assessment
IADL	Instrumental Activities of Daily Living
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
LOCF	Last observation carried forward
MMSE	Mini-mental state examination
MR	Maison de Repos
MRI	Magnetic resonance imaging
MRS	Maison de Repos et de Soins
NICE	National Institute for Health and Clinical Excellence
NINCDS- ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NMDA	N-methyl-D-aspartate
NNT	Number-needed-to-treat
NOSGER	Nurses' Observation Scale for Geriatric Patients
NPI	Neuropsychiatric Inventory
NPI-D	Neuropsychiatric Inventory, distress subscale
PDS	Progressive Deterioration Scale
PLST	Progressively Lowered Stress Threshold
QALY	Quality adjusted life-year
QoL	Quality of life
RCT	Randomised controlled trial
ROB	Rustoord voor Bejaarden
RVT	Rust- en Verzorgingstehuis
SBU	Swedish Council on Technology Assessment in Health Care
SD	Standard deviation
SIB	Severe Impairment Battery
TENS	Transcutaneous Electrical Nerve Stimulation
VaD	Vascular dementia
WMD	Weighted mean difference

1 INTRODUCTION AND RESEARCH QUESTIONS

1.1 INTRODUCTION

1.1.1 Project scope

Many studies have been published over the last two decades on the subject of Alzheimer's disease or Alzheimer's dementia (AD). They have been summarized and analyzed as systematic reviews and health technology assessment (HTA) reports. Our ambition with this short HTA was not to repeat these enormous tasks but to list the conclusions drawn of the most recently published reviews and to focus on findings that might be of relevance for the Belgian decision makers. We included original research studies only for the health-economic chapter.

Alzheimer's disease or Alzheimer's dementia (AD) accounts for more than half of the cases of dementia (around 60%).[1] In many cases AD is present together with some degree of cerebrovascular damage (mixed dementia). The prevalence of dementia and AD increases with age, and the most common form of AD is Senile Dementia of the Alzheimer Type (SDAT). With the exception of some genetically well-defined forms of AD, a definitive diagnosis of AD still requires histopathological confirmation of a probabilistic clinical diagnosis.

Interventions targeting AD and dementia care in general constitute a vast domain of research. Especially the manpower needed to care for a growing number of AD patients poses a challenge for societies with increasing proportions of elderly people. In this report we limited the research questions to an evaluation of the effectiveness and cost-effectiveness of the pharmaceutical and non-pharmaceutical interventions targeting AD patients. For the topics organisation of care, including care for the (presenile) smaller patient groups with AD, patient rights and legal aspects, obtaining patient consent, we refer to a project concerning these topics conducted in parallel to the KCE project by the Koning Boudewijnstichting and mentioned below under the local initiatives section.

The overall goals of interventions and care are to improve the patient quality of life (and that of the caregiver) and to to "attenuate" the behaviourial disorder of the patient. We do not cover in this report the financing of care, and the appropriateness of funding based on functions lost by the patient rather than the efforts needed to maintain or stimulate the remaining functions. We also briefly look into advances in technology which are aimed at expanding the possibilities to maintain independency or facilitate care giving.

Care for AD patients at home or in an elderly home requires the input of a dedicated "coordinator" (can be a family member) to assess the needs for care to schedule the care interventions, as well as a dedicated "caregiver" (can be the same family member), who "fills the gaps" and assures continuity of care. Patient care is provided in various forms, often on a volunteer basis.

AD patients are mainly elderly, and may be suffering from a large number of concomitant diseases for which they may receive medication or other forms of treatment. Avoiding drug interactions in elderly patients is another challenge. Avoiding toxicity and adverse outcomes may even prove impossible when multiple drugs all have to be metabolized using competing systems in an ageing body. The study of drug interactions is not within the project scope, but we analyse the medication prescribed for AD patients in Belgium.

1.1.2 Some epidemiological data

In 2005, the proportion of people with dementia in the European Union was estimated at 1.14% to 1.27% of the population. For Belgium the estimate was 1.22% to 1.35%, corresponding to 127 174 and 140 639 subjects.(www.dementia-in-europe.eu, consulted May 14, 2008). The number of AD patients in Belgium is not well documented but can be estimated at about 75 000 patients in 2008 (presentation Prof Patrick Santens, Ghent, 2008). This corresponds to about 55% of all dementia patients.

The published prevalence of dementia ranges from 6.3% to 9.3% for subjects 65 years of age and older. About one in three persons aged 90 years and older has dementia. A Belgian study based on GP consultations reported a prevalence of 11% in subjects 65 and older, living at home.[2] The prevalence varies strongly with the study context: from a prevalence of dementia diagnosed by a GP of 2% in subjects 60 years and older, to 44.1% to 47% for institutionalized subjects over 60 years of age.[3] About two thirds of the dementia patients in Belgium are women, mainly because the life expectancy is higher for women than men, but also because of a somewhat higher incidence in elderly women. The average life expectancy after diagnosis of AD is 5 to 6 years, or 8 years after the first symptoms. Life expectancy depends on the age at the moment of the diagnosis: as high as 10.7 years for the youngest patients (65-69 years) to a low of 3.8 years for the oldest (90 or older at diagnosis). Roughly, this is about half of the life expectancy of a person with the same age but without AD. In the Walloon region, it is estimated that 60% of patients diagnosed with dementia are cared for at home and 40% in institutions.(Dementia in Europe, Yearbook 2007, www.dementia-in-europe.eu). In Flanders 48% of the patients in institutions are scored as patient with dementia (KCE Report 47). In Belgium institutionalisation capacity is 127 365 beds (ROB, Rustoord voor Bejaarden, and RVT, Rust- en Verzorgingstehuis – MR, Maison de Repos and MRS, Maison de Repos et de Soins beds in 2008, RIZIV/INAMI) This would mean that of the 75 000 patients with AD in Belgium, about 34 000 AD patients are institutionalized and 41 000 AD patients are cared for at home.

1.1.3 Pathophysiology and symptoms

Clinical AD is preceded a by slowly progressing accumulation in the brain of amyloid plaques and neurofibrillary tangles with hyperphosporylated tau protein. Memory impairment is usually one of the first characteristics of AD. As the disease progresses cognitive deficits start to interfere with usual activities. The predemential phase of AD, characterized by relatively isolated memory impairment in patients that are still autonomous, was labelled as "mild cognitive impairment" (MCI). The proportion of MCI patients who evolve to overt AD varies by study setting and is about 5-10% per year.[4] This new entity became a major field of research in recent years, in an effort to establish the diagnosis of AD at an earlier stage. It is expected that earlier intervention with future disease-modifying therapies will be more effective than current symptomatic therapies, indicating that an early accurate diagnosis will become even more important. Clinically significant neuropsychiatric symptoms, named and grouped as BPSD (Behavioral and Psychological Signs and Symptoms of dementia), are found in about one-third of dementia patients with mild impairment and in two-thirds of those with more severe impairment.[5] These proportions are even higher in dementia patients in residential care. Neuropsychiatric symptoms contribute significantly to caregiver burden, institutionalization, and decreased quality of life for patients with dementia.

Several different methods are used to assess the severity of Alzheimer's disease but the most frequently used test for this purpose is the Mini Mental State Exam (MMSE). [6] The MMSE (a 30 point scale) denotes the severity of cognitive impairment as follows (cut-off values may differ slightly according to the source) :

- mild Alzheimer's disease: MMSE $\geq$ 20 (>= 21 for NICE)
- moderate Alzheimer's disease: MMSE 10 to 19, (10-20 for NICE)
- moderately severe Alzheimer's disease: MMSE 10 to 14,
- severe Alzheimer's disease: MMSE less than 10.

The MMSE is not sensitive enough to diagnose AD at the MCI stage.

Based on a European survey by the EFNS,[7] in most European countries about three quarters of the AD patients are diagnosed by a specialist in psychiatry, neurology, or geriatrics.

1.1.4 Local initiatives

Various initiatives exist and reports were made over the last years (or are in preparation) covering multiple aspects of AD for Belgium.

- A most relevant project has been conducted by the Koning Boudewijnstichting - Fondation Roi Baudouin (KBS-FRB) and concerns "Improvement of the quality of life of patients with dementia and their caregivers". The following topics were studied:
  - The "image" of dementia (Carbonelle, Klein, Cassini, ULB)
  - Daily living and interventions to improve quality of life in AD (E. Salmon, Memory Centre, University Hospital, Liège)
  - Education and training of all types of caregivers;
  - Available services and organization of the care for the various target groups and during the different stages of the disease (C. Van Audenhove, KULeuven and M. Ylieff, ULg), including end-of-life and advanced care planned (Deliens L, VUB), and starting from the patient needs;
  - Patient rights and legal aspects (Nys H, Defloor S, KULeuven).
  - The report is to be published in 2009. Rondia et al., a KBS-FRB report
- Qualidem studies I en II, conducted by teams at the Universities of Leuven and Liège, and sponsored by RIZIV/INAMI.[3] A book published in 2007 with recommendations based on the Qualidem project is available.[8]
- A consensus report concerning the good medical use of medicines for dementia, published by the RIZIV/INAMI,[9]
- A systematic literature review of AD therapy summarized as 'Transparantiefiche' published by the Belgian Centre for Pharmaceutical Information, updated September 2006, and July 2008.[10]
- Controverses in policy concerning AD, WHO Collaborating Centre, F Baro et al, 2005
- Development of clinical pathways for dementia care, 2005 and 2006 reports by the Federal public service, G. Haelterman, https://portal.health.fgov.be.
- BelRAI (http://www.kuleuven.be/lucas/RAI), a Federal public service sponsored project on the use of a computer-based Resident Assessment Instrument (RAI) in selected elderly homes, in collaboration with the Universities of Leuven and Liège. This measurement tool is being proposed to become a standard assessment tool across care settings.
- Expertise network for AD (http://www.dementie.be/#), 9 centres plus a coordination centre providing information and education on AD, targeting professionals, and funded by the Flemish government; associated with the Northsea Dementia Group, and eg involved in the development and evaluation of quality standards for residential care dementia.
- Local activities of Baluchon Alzheimer, mainly in the French speaking parts of Belgium. This concerns an international organization providing respite care for caregivers, and financially supported by the insurance organizations.
- Multiple patient organizations co-exist in Belgium:
  - Alzheimer Belgique – Mme Marguerite Mormal
  - Alzheimer Liga Vlaanderen (www.alzheimerliga.be)
  - Ligue Alzheimer Wallonia (www.alzheimer.be)
- INTERDEM: A multi – professional network of gerontological research-practitioners who focus on psychosocial (as opposed to neurobiological) approaches to the early recognition and intervention in dementia, throughout Europe (http://interdem.alzheimer-europe.org)

- Belgian Dementia Council: a group of Belgian neurologists and other dementia specialists, providing expert literature searches and expert advice for government and RIZIV. The group of experts is working to settle practice guidelines for Belgium. In contrast to the situation in The Netherlands where dementia practice guidelines for general practitioners and specialists have been published,[11, 12] no formal local practice guidelines were identified for Belgium.

1.1.5 Initiatives at the EU level

- A first interim report of the Alzheimer Europe, European Collaboration on Dementia (http://ec.europa.eu/health/ph_projects/2005/action1/docs/action1_2005_inter_10_en.pdf)
- The EFNS (European Federation of Neurological Societies) published practice recommendations based on a literature review and expert consensus.[13] (publications covered until January 2006).
- In the context of the EU sponsored EuroCoDE project (http://ec.europa.eu/health/ph_information/dissemination/diseases/alzheimer_en.htm#eurocode) guidelines are being prepared both for non-pharmacological interventions (by the end of 2008) and on the diagnosis and treatment of AD (draft in preparation by McShane, Alzheimer Europe).
- The European Alzheimer's Disease Consortium is an EU funded consortium, where several task forces gather European experience on diagnosis, evolution and treatment of AD.

1.2 RESEARCH QUESTIONS

This short HTA briefly covers diagnostic, therapeutic and caregiving aspects of Alzheimer's disease, mainly from a clinical and cost-effectiveness perspective.

1. How is the diagnosis made of Alzheimer disease, and what is the clinical evidence for the use of non-pharmacologic and pharmacologic treatment of Alzheimer disease?
2. What is the cost-effectiveness of the selected interventions?
3. What essential patient/caregiver and organisational aspects are to be considered in the context of the above research questions?

For the purpose of this project the search will be limited to Alzheimer's disease and will not include all forms of dementia. Of course, some conclusions may apply to dementia in general.

2 SCREENING, DIAGNOSIS AND STAGING

2.1 SEARCH

First, relevant HTA reports were searched in the HTA database of the Centre for Reviews and Dissemination (CRD). Second, a search was done for systematic reviews (using the Cochrane Database, DARE, and Medline) focusing on Alzheimer disease. HTA reports and systematic reviews were identified June 5, 2008 using "Alzheimer" as keyword for searching the databases HTA at CRD and DARE at CRD, and searching PubMed (Medline) using ("Alzheimer Disease/diagnosis"[Mesh] OR "Alzheimer Disease/drug therapy"[Mesh] OR "Alzheimer Disease/therapy"[Mesh]) AND systematic[sb]

We selected HTA reports and systematic reviews which minimally covered the literature published up to mid 2004 or which were found to be of particular relevance. The identified studies were selected based on title and abstract. We did not perform any formal scoring of the quality of the reviews, which can be considered a limitation of the study.

2.2 THE DIAGNOSTIC PROCESS

Compared with AD therapy, fewer systematic reviews were identified covering the diagnostic process. SBU performed a systematic review on this subject[14] (publications covered until June 2004) and also an EFNS task force reviewed the literature[13] (publications covered until January 2006). Also the dementia practice guidelines by NICE-SCIE[1] were considered.

SBU[14] classified evidence into evidence grade 1 or strong evidence, evidence grade 2 or moderately strong evidence, evidence grade 3 or limited evidence, and no evidence. The classification also took into account whether all or most of the studies met the general criteria (sensitivity >80%, specificity > 80% and a likelihood ratio (LR+) >=5 for tests used to diagnose dementia). The EFNS task force also graded the recommendations according to decreasing strength of evidence into grade A, B, or C.[13]

SBU concluded there are no diagnostic instruments sufficiently developed to be used for dementia screening.[14] A gold standard is lacking for identifying dementia and ruling out other syndromes. Many methods (scales and indices) are used to measure the severity of various symptoms of dementia, such as cognitive deterioration, functional decline and behavioural changes. The insufficient evaluation to which most methods have been subjected makes it more difficult to assess the efficacy of specific care and treatment approaches.[14]

An initial selection or screening of patients for possible further diagnosis can be made by general practitioners and be based on standardised interviews with collateral sources, such as informal or family caregivers (Evidence Grade 2), as well as simple tests such as the MMSE, the clock drawing test and other simple tests (Evidence Grade 2).[14] Such initial selection by GPs is to be distinguished from diagnosis and is considered more difficult in mild AD and in MCI compared with more advanced disease. Potential limitations, particularly of the MMSE, include associations with education level and sensitivity to depression.[1] In patients for whom the MMSE is not an appropriate tool, an assessment tool sensitive to their level of competence should be used.[1]

SBU concludes that after a baseline assessment, detection of atrophy of the medial temporal lobe by computer tomography (CT scan) and magnetic resonance imaging (MRI scan), respectively can identify people who have Alzheimer's disease with a high degree of certainty (Evidence Grade 1).[14] Experts agree with this statement at group level but consider the sensitivity may be too low at the individual level. Recently, based on structural MRI, medial temporal lobe atrophy was also found to distinquish probable AD from mild cognitive impairment.[15] Volumetric MR techniques are however very time consuming to apply in clinical practice.[1]

EFNS recommends non-contrast CT to identify treatable lesions and vascular disease (evidence Level A). In specific situations of differential diagnosis MRI is a more appropriate technique (evidence Level A).[13]

SBU concludes that after a baseline assessment, in cases where the diagnosis could not be established by classical methods, biochemical diagnostic markers such as cerebrospinal fluid analysis (Evidence Grade 1) effectively identify (> 80% sensitivity and > 80% specificity) people with Alzheimer's disease.

According to EFNS CSF total tau, phospho-tau and amyloid-beta1-42 can be used as an adjunct in cases of diagnostic doubt (Level B). According to NICE more standardization of CSF tests is required.[1]

EFNS recommends cognitive assessment is performed in all patients (level A). SBU concludes that after a baseline assessment, neuropsychological testing (Evidence Grade 1) effectively identifies people with Alzheimer's disease. A more comprehensive standardised cognitive assessments is particularly useful in patients with with mild or questionable impairment, and in other selected cases to assist with specific subtype diagnosis and differential diagnosis.[1]

According to SBU, functional diagnosis – positron emission tomography (PET scan) and single photon emission computed tomography (SPECT scan) – has moderate value (Evidence Grade 2), while neurophysiological testing – EEG brain mapping and quantitative EEG – has limited value (Evidence Grade 3) for identifying dementia disorders. According to EFNS SPECT and PET may be useful in those cases where diagnostic uncertainty remains after clinical and structural imaging work up, and should not be used as the only imaging measure (Level B).[14] FDG PET may show some superiority over perfusion SPECT in detecting AD but remains an expensive and invasive investigation.[1] PET scan tests demonstrating brain amyloid deposits are promising tools and are being used in clinical research studies.[16] These tests were however not yet included in the HTA reports.

The Apolipoprotein E (ApoE) e4 allele is known to increase the risk for AD (Evidence Grade 1) but it is a poor marker for identifying Alzheimer's disease or for differential diagnosis.[14]

Definitive diagnosis of AD requires histopathological confirmation of the clinical diagnosis. For research purposes, the diagnosis of AD is given in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR)[17] and the National Institute of Neurological Disorders and Stroke – Alzheimer Disease and Related Disorders (NINCDS-ADRDA) working group.[18] The NINCDS-ADRDA criteria for the clinical diagnosis of probable Alzheimer's disease have been the reference standard for clinical research studies since 1984.

<u>The DSM-IV criteria</u>[17]

A. The development of multiple cognitive deficits manifested by both:

(1) memory impairment (impaired ability to learn new information or to recall previously learned information)

(2) one (or more) of the following cognitive disturbances:

(a) aphasia (language disturbance)

(b) apraxia (impaired ability to carry out motor activities despite intact motor function)

(c) agnosia (failure to recognize or identify objects despite intact sensory function)

(d) disturbance in executive functioning (ie, planning, organizing, sequencing, abstracting).

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

(1) other central nervous system conditions that cause progressive deficits in memory and cognition (eg, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)

(2) systemic conditions that are known to cause dementia (eg, hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)

(3) substance-induced conditions.

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (eg, Major Depressive Disorder, Schizophrenia).

The NINCDS-ADRDA criteria[18]

I. Criteria for the clinical diagnosis of PROBABLE Alzheimer's disease:

- dementia established by clinical examination and documented by the Mini-Mental Test; Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests
- deficits in two or more areas of cognition
- progressive worsening of memory and other cognitive functions
- no disturbance of consciousness
- onset between ages 40 and 90, most often after age 65
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perceptions (agnosia)
- impaired activities of daily living and altered patterns of behavior
- family history of similar disorders, particularly if confirmed neuropathologically
- laboratory results of:
  - normal lumbar puncture as evaluated by standard techniques
  - normal pattern or non-specific changes in EEG, such as increased slow-wave activity
  - evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

- plateaus in the course of progression of the illness
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder
- seizures in advanced disease
- CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

- sudden, apoplectic onset

- focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and
- incoordination early in the course of the illness
- seizures or gait disturbances at the onset or very early in the course of the illness.

The sensitivity and specificity of a probable AD diagnosis made according to the NINCDS-ADRDA criteria with postmortem pathology as reference standard are 0.65 and 0.75.[19] Sensitivity and specificity are generally above 80% when the diagnosis is made in expert centres and when healthy subjects are used as controls, but are much lower when patients with other forms of dementia are used as controls. Recently a revision of these criteria for clinical diagnosis has been proposed,[20] reflecting the increasing importance of new markers. The criteria were based on a literature review, followed by an expert meeting in June 2005.

The new proposed criteria for the diagnosis of probable AD consist of the core diagnostic criterion of early episodic memory impairment (episodic memory is memory for events that the patient experienced and should be able to recall, more specifically for recent events) plus one or more of the following supportive features:

- presence of medial temporal lobe (MTL) atrophy on MRI
- abnormal cerebrospinal fluid biomarkers (amyloid beta1-42, total tau, and phospho-tau)
- a specific pattern on functional neuroimaging with 18F-FDG PET (SPECT technique did not meet criteria for diagnostic accuracy)
- a proven AD autosomal dominant mutation within the immediate family

The Dubois criteria are very specific and they are currently mainly used in clinical research studies in order to get validated. Further standardization of these new tests is needed before their routine use can be considered.[1]

In Belgium, reimbursement of medication for AD requires confirmation of the diagnosis (based on DSM-IV criteria) by a psychiatrist, a neurologist, or a geriatrician specialist in internal medicine. The care and support team should include the specialist and the patient general practitioner. Exclusion of other pathology (infarction) is required using a brain CT or MRI scan. The MMSE score should be in agreement with the indication approved for the medication class. The functional evaluation should include the 6 points ADL Katz scale, the instrumental ADL Lawton scale (9 points), as well as the NPI (Neuro-Psychiatric Inventory) for behaviour. A re-evaluation of the patient after 6 months is required before reimbursement can be prolonged.

Conclusions

There are no diagnostic instruments sufficiently developed to be used for dementia screening. Many methods (scales and indices) are used to measure the severity of various symptoms of dementia, such as cognitive deterioration, functional decline and behavioural changes. The insufficient evaluation to which most methods have been subjected makes it more difficult to assess the efficacy of specific care and treatment approaches.

An initial selection or screening of patients for possible further diagnosis can be made by general practitioners and be based on standardised interviews with collateral sources, such as informal or family caregivers, as well as simple tests such as the MMSE, the clock drawing test and other simple exercises. Such initial selection by GPs is to be distinguished from diagnosis and is considered more difficult in mild AD and in MCI compared with more advanced disease. Neuropsychological testing is recommended after a baseline assessment in all patients and is particularly useful in patients with MCI and mild AD.

The reference standards for the diagnosis of AD are given in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR) and the National Institute of Neurological Disorders and Stroke – Alzheimer Disease and Related Disorders (NINCDS-ADRDA) working group.

Recently a revision of these latter criteria for clinical diagnosis has been proposed by Dubois et al, reflecting the increasing importance of new markers, in addition to the core diagnostic criterion of early episodic memory impairment (episodic memory is memory for events that the patient experienced and should be able to recall, more specifically for recent events). These new supportive features are the presence of medial temporal lobe (MTL) atrophy on MRI, abnormal cerebrospinal fluid biomarkers (amyloid beta1-42, total tau, and phospho-tau),a specific pattern on functional neuroimaging with 18F-FDG PET, or a proven AD autosomal dominant mutation within the immediate family.

2.3 HEALTH-ECONOMICS

Studies are lacking that have combined different types of testing. As a result, it is not known with certainty which approaches are most cost-effective.[14]

2.4 ASSESSING THE IMPACT OF INTERVENTIONS IN AD

The most relevant endpoints may be quality of life of the patient and the caregiver and delay in institutionalization. However, assessment of interventions is often focused on other endpoints, such as scales for cognitive functioning. In this section we briefly list the most commonly used scales. For details, we refer the interested reader to full HTA reports.[14] The MMSE, Katz-scale (ADL), Lawton-scale (IADL), and NPI are used in Belgium in the context of reimbursement of drugs for AD.

According to the SBU, there is strong evidence that neuropsychological testing including at least 4 of 6 cognitive domains (spatial, verbal, executive, attention, memory, general) contributes substantially to the diagnosis of dementia.[21] From a scientific point-of-view, outcome scales have to be thoroughly evaluated on their psychometric properties, including reliability as well as validity and ability to measure change. This subject was beyond the scope of the current study, but the HTA report by the SBU deals with it.[21] These authors conclude from an evidence-based literature review (up to July 2004), that only for the Clock test and the CAMCOG (the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly) moderate evidence exists in their ability to discriminate dementia patients from normal controls, if the administration of the tests is standardized. For the MMSE or other tests, not enough evidence is available to discriminate AD from age-matched controls without dementia. In the Belgian context, the Qualidem-study[3] also comments on the value of several outcome scales, but unfortunately without providing documentation on quality appraisal of the included publications. Despite their frequent use in daily practice and in scientific publications, the psychometric quality of many dementia scales remains questionable and a thorough evaluation of their diagnostic value is still to be performed.

2.4.1 Frequently used global function rating scales

The **CIBIC+** (Clinician's Interview-Based Impression of Change scale) provides a global rating of function in four areas: general, cognitive, behaviour and ADL. All participants are scored on a scale of 1 to 7 relative to baseline, with 1 showing marked improvement and 7 marked worsening. Information is ideally obtained from the caregiver and the patient by a blinded independent clinician. Any change in score is considered clinically relevant. Older studies used the less detailed CGI-C (The Clinical Global Impression of Change), also a seven point global rating of change.

The **GDS** (Global Deterioration Scale) reflects the assessment of the severity of the dementia by the physician, from 1 (normal) to 7 (very severe dementia).

2.4.2 Frequently used cognitive assessments

The most widely used test, certainly in clinical research studies, is the **ADAS-cog**, the cognitive part of the Alzheimer's Disease Assessment Scale. It comprises 11 individual tests, spoken language ability (0 to 5), comprehension of spoken language (0 to 5), recall of test instructions (0 to 5), word finding difficulty (0 to 5), following commands (0 to 5), naming object (0 to 5), construction drawing (0 to 5), ideational praxis (0 to 5), orientation (0 to 8), word recall (0 to 10) and word recognition (0 to 12). The total score ranges from 0 to 70, the high score indicating greater impairment.

A 4 point improvement has been reported as a clinically relevant improvement in mild to moderate AD. Other authors considered only a 7 point change as clinically relevant.[10] Some of the experts consulted find ADAS-cog too rigid, not enough sensitive to change in the early stages and not appropriate for the differential diagnosis with other forms of dementia. Recently, an alternative neuropsychological test battery (NTB) to the cognitive subscale of the ADAS has been proposed for measuring drug efficacy in AD trials, especially for trials involving mild AD patients.[22]

The **MMSE** (Mini-mental state examination) is frequently used for screening and to help define study populations. MMSE scores range from 0 (severe impairment) to 30 (normal). Mild to moderate AD is usually defined as a MMSE above 10 or 11. A 2 point change on the ADAS-cog roughly corresponds to a one point change on the MMSE. The main interest of the MMSE is that it is an universal tool at hand, feasible by specialists but also by generalists and even by trained nurses, and it is not too lengthy. It allows the professionals in the field to "communicate" the patient's state in a common language.

The **SIB** (Severe Impairment Battery) evaluates cognitive performance in more advanced Alzheimer's Disease and assesses social interaction, memory, language, visuospatial ability, attention, praxis and construction. The scores range from 0 (greatest impairment) to 100.

According to the experts involved in this study, in the French speaking part of Belgium neuropsychologists use currently an ad-hoc battery that can be adapted to the dementia level. It includes tests of:

- episodic memory (verbal and visual)
- working memory
- language & conceptual and semantics
- visio-spatial abilities & praxis
- attention
- executive functions

Other tests and questionnaires may be required depending on the clinical situation (ex. driving competency assessment) and the differential diagnosis to be made.

2.4.3 Activities of daily living and function

The **ADCS-ADL** (Alzheimer's Disease Cooperative Study-Activities of Daily Living) was specifically designed to assess functional capacity over a broad range of severity in patients with Alzheimer's disease. The 19 item ADCS-ADLsev19 has 54 points and is used for patients with moderate to severe AD, and assesses mainly basic functions. The 23 item ADCS-ADL23 has 78 points and is used for patients with mild to moderate AD.

Many other scales are being used, including the ADL-scale of Katz (Activities of Daily Living), the IADL-scale of Lawton and Brody (Instrumental Activities of Daily Living), the PDS (Progressive Deterioration Scale) and the DAD (Disability Assessment in Dementia).

In Belgium, frequently used scales are the **Katz** scale for basic ADL (washing, dressing, eating) and the **Lawton**-scale for instrumental ADL (shopping, use of telephone).[10]

2.4.4 Behavioural disturbances

The **NPI** (Neuropsychiatric Inventory) assesses the frequency and the severity of behavioral and neuropsychiatric symptoms in patients with dementia based on an interview with the caregiver. There are 12 items with a total score ranging from 0 to 144 (severe). Caregiver quality of life is assessed as part of the NPI, the NPI Caregiver Distress Scale (NPI-D).

The European Alzheimer's Disease Consortium Behavioural group, an EU funded consortium,[23, 24] has argued against the idea of BPSD (Behavioral and Psychological Symptoms in Dementia) associated with AD as a unitary concept and distinguishes symptom clusters: apathy, depression, psychotic symptoms, aggressiveness & agitation, and sleep disorders.

Key points

- **At present, no single diagnostic instrument is good enough for use as a tool for population screening.**
- **The insufficient evaluation of most screening and diagnostic methods makes it even more difficult to assess the efficacy of specific care and treatment approaches. Also the lack of biomarkers which reliably predict progression reduces the ability to assess response to treatment.**
- **An initial selection or screening of patients for possible further diagnosis can be made by general practitioners and can be based on standardised interviews with collateral sources, such as informal or family caregivers, as well as on simple tests.**
- **Neuropsychological testing has been recommended following the baseline assessment in all patients but is particularly useful in patients with MCI and mild AD. No data on its cost-effectiveness is available.**
- **Revised research criteria for AD diagnosis specify supportive features in addition to the core diagnostic criterion of early episodic memory impairment. These four supportive tests are 1. the presence of medial temporal lobe atrophy on magnetic resonance imaging (MRI), 2. abnormal cerebrospinal fluid (CSF) biomarker values (amyloid beta1-42, total tau, and phospho-tau), 3. a specific pattern on functional neuroimaging with 18F-FDG positron-emission tomography (PET), or 4. a proven AD autosomal dominant mutation within the immediate family. Other promising tests such as the visualisation of amyloid plaques using specific PET exams are still in the early research phase.**
- **These new supportive features require further standardisation and demonstration of incremental diagnostic benefit over and above that of episodic memory impairment benefit before they can enter routine care.**
- **Health-economic studies that have combined different types of testing are lacking. As a consequence, it is not known with certainty which approaches are most cost-effective.**
- **Many scales exist for patient cognitive function, global function, activities of daily living, and behavioural disturbances, but only few have been fully validated, hampering the interpretation of trial results based on these scales.**

3 NON-PHARMACOLOGICAL INTERVENTIONS

3.1 BACKGROUND AND SEARCH

Non-pharmaceutical interventions used in the treatment of dementia form a heterogeneous group. Some authors prefer to use the term care interventions. Also the term psychosocial intervention has been used. Most studies of such interventions are not restricted to a given type of dementia, or the patient diagnosis is not well documented, hampering the comparison with pharmaceutical trials. The multiple types of non-drug interventions have been reviewed in the literature.[5, 25, 26]

Based on the intervention target, non-drug therapies for AD can be grouped into categories. Interventions can directly target the patient's cognition, behaviour, emotion, or level of activation, or target the patient indirectly through the material and social environment (milieu), the formal or informal caregiver. Interventions may be unimodal (eg movement therapy), multimodal (eg a combination of reality orientation, validation therapy and self maintenance therapy) or involve general procedures (eg milieu therapy).

One aim of the therapy is to positively influence the emotions and behaviour of the patient (agitation, the tendency to wander, day-night rhythm, depression, apathy or aggression), thereby lessening the burden for the carers. Another aim is to enhance the remaining skills and reduce emerging deficiencies. The systematic reviews on these topics have highlighted the poor quality of many published studies. The lack of randomized controlled trials, has been suggested to be related to poor funding of the studies, compared with drug trials.[25]

Outcome parameters vary a lot between studies, and as already discussed before, measurement instruments are not always validated. Moreover, some outcome parameters which are regularly addressed in pharmacological studies, such as mortality or adverse effects, are only rarely addressed in this type of interventions. This makes a scientific comparison of both types of interventions (pharmacological- non pharmacological) even more complicated. Efforts to improve the reporting of adverse events in social behavioral intervention trials have started.[27]

As already pointed out, most studies on non-pharmacological interventions are not restricted to a given type of dementia; therefore the search for this part of our study was broadened to all forms of dementia (provided that a valid clinical diagnosis of dementia had been given to the patients included in the studies).

For this review, only meta-analyses or systematic reviews published or updated after 2004 and including an original literature search as well as a formal appraisal of the included primary studies, were taken into consideration. Also reviews not providing a clear search strategy, or narrative reviews were excluded. Another criterion was that the primary studies included in the review should have provided a formal definition of dementia, and should have applied this definition to the included patients.

We did however not perform any formal scoring of the quality of the reviews, which can be considered a limitation of the study.

In June 2008 websites of HTA agencies (SBU, NICE, HAS, DIMDI, CADTH, Nivel, AHRQ) and of the National Guideline Clearinghouse were searched for relevant information. During the course of the project, DIMDI published a report[28] on this subject (2009); their results were also included. Other HTA reports and systematic reviews were identified June 16, 2008 using "Alzheimer" or "dementia" as keyword for searching the databases HTA at CRD and DARE at CRD; and searching PubMed (Medline) using ("Alzheimer Disease"[Mesh] OR "Dementia"[Mesh]) AND systematic [sb].

PEDro was searched on December 22, 2008 using the search term ("dementia" or "Alzheimer*") yielding 117 results. Only publications from 1/1/2005 onwards and quoted as systematic review or meta-analysis on the website, were screened for inclusion. After discarding duplicates, and after evaluation of title and abstract on their relevance, 2 publications on non-pharmacological treatment were retained. After evaluation of the full text, one of these two could be rejected, because of inadequate details on the definition of dementia.

PsycInfo was searched on December 22, 2008, using the search term ("dementia"), and limited to publications from 2005 onwards and to (reviews, high specificity). A total of 319 results were found. After discarding duplicates and screening of title/abstract, 8 results on non-pharmacological treatment were retained. After full text evaluation, 3 of those 8 results were rejected because no systematic appraisal of the included publications had been performed. One more systematic review was not included because the general review considered older people in general and for the subgroup of dementia, only two Cochrane reviews were retained that were already dealt with in our study. Another review was also excluded because of uncertainty concerning the diagnosis of dementia in the included studies.

All results identified for full evaluation, are listed in Table 1.

Table 1. Reviews of non-pharmacological interventions (full evaluation)

Reference	Final search date in review
Forbes D, Forbes S, Morgan DG, Markle-Reid M, Wood J, Culum I. Physical activity programs for persons with dementia. Cochrane Database Syst Rev. 2008(3):CD006489.	September 2007
Rieckmann N, Schwarzbach C, Nocon M, Roll S, Vauth C, Willich SN, Greiner W. Concepts of care for people with dementia. HTA report. DIMDI, DAHTA, Köln, Germany, 2009.	March 2007
Peng WN, Zhao H, Liu ZS, Wang S. Acupuncture for vascular dementia. Cochrane Database Syst Rev. 2007(2):CD004987.	February 2007
NICE-SCIE. Dementia: supporting people with dementia and their carers in health and social care. Care guideline. National Institute for Health and Clinical Excellence (NICE); 2006. Clinical Guideline 42.	2006
Robinson L, Hutchings D, Dickinson HO, Corner L, Beyer F, Finch T, et al. Effectiveness and acceptability of non-pharmacological interventions to reduce wandering in dementia: a systematic review. Int J Geriatr Psychiatry. 2007;22(1):9-22.	May 2006
Spijker A, Vernooij-Dassen M, Vasse E, Adang E, Wollersheim H, Grol R, et al. Effectiveness of Nonpharmacological Interventions in Delaying the Institutionalization of Patients with Dementia: A Meta-Analysis. J Am Geriatr Soc. 2008.	March 2006
Hermans DG, Htay UH, McShane R. Non-pharmacological interventions for wandering of people with dementia in the domestic setting. Cochrane Database Syst Rev. 2007(1):CD005994.	March 2006
Logsdon RG, McCurry SM, Teri L. Evidence-based psychological treatments for disruptive behaviors in individuals with dementia. Psychol Aging. 2007;22(1):28-36.	January 2006
Parker D, Mills S, Abbey J. Effectiveness of interventions that assist caregivers to support people with dementia. International journal of evidence-based healthcare 2008;6(2):137-72.	End 2005
Ayalon L, Gum AM, Feliciano L, Arean PA. Effectiveness of nonpharmacological interventions for the management of neuropsychiatric symptoms in patients with dementia: a systematic review. Arch Intern Med. 2006;166(20):2182-8.	December 2005
Gallagher-Thompson D, Coon DW. Evidence-based psychological treatments for distress in family caregivers of older adults. Psychol Aging. 2007;22(1):37-51.	December 2005

Thompson CA, Spilsbury K, Hall J, Birks Y, Barnes C, Adamson J. Systematic review of information and support interventions for caregivers of people with dementia. BMC Geriatr. 2007;7:18.	October 2005
Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, et al. A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use. Health Technol Assess. 2006;10(26):iii, ix-108.	Not included, as more recent SR available
Viggo Hansen N, Jorgensen T, Ortenblad L. Massage and touch for dementia. Cochrane Database Syst Rev. 2006(4):CD004989.	July 2005
Smits CH, de Lange J, Droes RM, Meiland F, Vernooij-Dassen M, Pot AM. Effects of combined intervention programmes for people with dementia living at home and their caregivers: a systematic review. Int J Geriatr Psychiatry. 2007;22(12):1181-93.	February 2005
SBU. Dementia – Caring, Ethics, Ethnical and Economical Aspects. A systematic review. Volume 3. June 2008.	2005
Sitzer DI, Twamley EW, Jeste DV. Cognitive training in Alzheimer's disease: a meta-analysis of the literature. Acta Psychiatr Scand. 2006;114(2):75-90.	December 2004
Kuske B, Hanns S, Luck T, Angermeyer MC, Behrens J, Riedel-Heller SG. Nursing home staff training in dementia care: a systematic review of evaluated programs. Int Psychogeriatr. 2007;19(5):818-41.	December 2004
Selwood A, Johnston K, Katona C, Lyketsos C, Livingston G. Systematic review of the effect of psychological interventions on family caregivers of people with dementia. J Affect Disord. 2007;101(1-3):75-89.	July 2003
McGonigal-Kenny ML, Schutte DL. Nonpharmacologic management of agitated behaviors in persons with Alzheimer disease and other chronic dementing conditions. J Gerontol Nurs. 2006;32(2):9-14.	No systematic review (excluded)
Woods B, Spector A, Jones C, Orrell M, Davies S. Reminiscence therapy for dementia. Cochrane Database Syst Rev. 2005(2):CD001120.	May 2004
Livingston G, Johnston K, Katona C, Paton J, Lyketsos CG, Old Age Task Force of the World Federation of Biological P. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. Am J Psychiatry. 2005;162(11):1996-2021.	July 2003
Verkaik R, van Weert JC, Francke AL. The effects of psychosocial methods on depressed, aggressive and apathetic behaviors of people with dementia: a systematic review. Int J Geriatr Psychiatry. 2005;20(4):301-14.	February 2003
Frank W, Konta B. Congitive training in dementia and other disorders with cognitive deficits. Köln: DAHTA-DIMDI; 2005. HTA Berichte (26) Available from: www.dimdi.de	2004?
Sung H-C, Chang AM. Use of preferred music to decrease agitated behaviours in older people with dementia: a review of the literature. J Clin Nurs. 2005;14(9):1133-40.	?
Cameron M, Lonergan E, Lee H. Transcutaneous electrical nerve stimulation (TENS) for dementia. Cochrane Database Syst Rev. 2003(3):CD004032.	December 2002
Bharucha A, Anand V, Forlizzi J, Dew M, Reynolds Cr, Stevens S, et al. Intelligent Assistive Technology Applications to Dementia Care: Current Capabilities, Limitations, and Future Challenges. Am J Geriatr Psychiatry. 2008	2007?
Cooper C, Balamurali TBS, Selwood A, Livingston G. A systematic review of intervention studies about anxiety in caregivers of people with dementia. Int J Geriatr Psychiatry. 2007;22(3):181-8.	June 2005
Watson R, Green SM. Feeding and dementia: a systematic literature review. J Adv	December 2003

Nurs. 2006;54(1):86-93.	
Nguyen Q-A, Paton C. The use of aromatherapy to treat behavioural problems in dementia. Int J Geriatr Psychiatry. 2008;23(4):337-46.	March 2007

3.2 REVIEWS OF NON-PHARMACOLOGICAL INTERVENTIONS

3.2.1 Introduction

A systematic review of a very broad range of psychological approaches to the management of neuropsychiatric symptoms of dementia was published by the Old Age Task Force of the World Federation of Biological Psychiatry.[5] The SBU health technology assessment report covering various aspects of dementia, also includes a systematic review of care interventions.[21] Many studies reviewed in this HTA were rejected because of lack of adequate diagnoses.[21] The reason suggested could be the lack of involvement of a physician in many studies. Other important large reviews are the NICE[1] and the DIMDI report[28], and several Cochrane reviews.

These main reviews, as well as others will be discussed below, and the level of evidence supporting the various interventions will be mentioned.

Interventions may target the patient, the caregiver or both. Likewise outcomes of these interventions may be assessed in patients, caregivers or both. Outcome parameters vary a lot between studies.

Whereas some reviews focus specifically on the type of interventions, other reviews focus on a specific symptom or cluster of symptoms (mostly behavioral problems e.g. agitation, aggression, wandering) and consider the different interventions to improve it.

Further, different authors tend to group the studies in different ways, illustrating the lack of standardization of interventions in this research area and also illustrating the many variations and combinations of interventions that are evaluated in the studies. The fact that few studies addressed the same issues in comparable ways is a major methodological problem, limiting the level of evidence which can be associated with such unique interventions.

In the next paragraphs, we will describe:

- Interventions addressing the patient
  - studies focusing on specific interventions : interventions addressing patient cognition, patient emotion, patient sensory enhancement; physical activity interventions; communication/interaction/relationship interventions; environmental adaptations
  - studies focusing on signs and symptoms: non-pharmacological interventions for challenging behavior, neuropsychiatric symptoms and wandering
  - studies focusing on technological support
- Interventions that include the caregiver
  - Staff education: effects on patients or caregivers
  - Psychoeducation/psychosocial interventions for informal caregivers: effects on patients or caregivers
  - Respite care and special care units: effects on informal caregiver depression and stress
  - Interventions to delay institutionalization
  - Miscellaneous

3.2.2 Interventions addressing the patient

3.2.2.1 Studies focussing on specific interventions

In the following table we have mentioned the level of evidence supporting the various interventions targeting the person with dementia, describing studies focussing on the intervention itself. Included are interventions addressing patient cognition, patient emotion, patient sensory enhancement; physical activity interventions; functional performance interventions; communication/interaction/relationship interventions; environmental interventions.

Table 2. Non-pharmaceutical interventions targeting the person with dementia (specific interventions)

Intervention	**Method and aims**	**Number of studies (mainly RCTs; if other type accepted in the review listed it is mentioned below) and level of evidence or effect size as given in the reference**
Patient cognition		
Reality Orientation (RO)	Multimodal intervention, contains formal RO in small groups; 24-hour RO at each contact; attitude RO for all interacting partners.	Livingston: 2 Studies, low level of evidence[5] Frank: 14 Studies (also including cognitive stimulation, reminiscence therapy, validation therapy): low level of evidence as 8 Studies were negative[29] 1 Cochrane review (2000) but no studies accepted by SBU, mostly because of doubt on the diagnosis dementia: no evidence DIMDI: 2 partly positive studies[28] NICE-SCIE: 3 studies, no effect on behaviour.[1]
Cognitive stimulation or training	Unimodal specific exercises directly aimed at memory improvement in mild AD, avoiding frustration. Two types of strategies: restorative (trying to improve functioning in specific domains to premorbid levels) and compensatory strategies ('working around' cognitive deficits). Cognitive training: guided practice on memory, attention, problem-solving (executive functions). Cognitive stimulation: repetition of orientation information (e.g. month, famous faces) Cognitive rehabilitation: individualised approach, identification of goals and strategies to improve functioning in everyday context, this can include various forms of cognitive therapy. Note: definitions not used consistently in all publications	Livingston: 4 RCTs (2 also included by Cochrane), studying cognitive training or stimulation: moderate level of evidence (evidence not consistent), effect lasting months[5] Sitzer: 14 RCTs (including 8 of the 9 Cochrane review studies; 2 other RCTs only 5 participants), and 5 non-RCTs. All 19 studies: medium effect size for learning and memory, restorative strategies may result in larger effect size. Five studies with highest quality: overall effect size below 0.2 (very low) [30] 1 Cochrane review (2003), including 9 studies on cognitive training only (of which 5 studies excluded by SBU); concluding that no significant positive nor negative effects were found; no evidence is available. No studies found on cognitive rehabilitation. SBU: 1 study on cognitive stimulation (also included in Livingston): significant improvement in cognition was seen, but only in a single study; hence no evidence [21] NICE: 4 studies on cognitive stimulation on a background of ChEI therapy: 3 positive trials (including an RCT with n=13), 1 negative trial.[1]
Patient emotion		
Reminiscence therapy	Contemplation of experiences from a life (old newspapers and	Livingston: 2 very small RCTs (5 resp. 9 subjects) with positive effect, low level of evidence[5]

	household items) and sharing these with others (group may include relatives). Aims to promote social interaction and self-esteem.	1 Cochrane review including 4 small RCTs (of which only 1 accepted by SBU) with significant effect on cognition, mood and behavior low level of evidence[31]. SBU:1 RCT without positive effect: no scientific evidence [21] DIMDI: two negative studies[28] NICE-SCIE: 4 studies, no effect on behaviour.[1]
Validation therapy	Offers security to the patients using verbal and non-verbal communication, leaving them in their own emotional state. Aims to reduce anxiety. Based on Rogerian humanistic psychology.	Livingston: 1 study, evidence level: low.[5] 1 Cochrane review (2003): no evidence, theory has been called into question[21] DIMDI: 3 studies, no difference vs usual care in two studies[28] NICE-SCIE: 4 studies, no effect on behaviour.[1]
Self-maintenance therapy	Multimodal training of self-related knowledge and activities of daily living, and ensuring that communication is validating.	Livingston: 0 studies, hence no evidence[5]
Individualized special instruction	Sessions with focused individual attention and participation in an appropriate activity.	Livingston: 1 study, low level of evidence[5]
Patient sensory enhancement		
"Snoezelen", multisensory stimulation	Individualized program including changing distressing situations, lighting, sensory stimulation, aromatherapy, and education of care providers on how to best assist residents in activities of daily living	Livingston: 3 RCTs (one with N=5; 2 others by the same author and included by Cochrane but both replaced by a larger update study from the same author), moderate level of evidence, but no lasting effect[5] 1 Cochrane review (2002), 2 studies (both interventions differed): no evidence, one study showed effects for some outcomes; result confirmed by SBU[21] DIMDI: 4 studies on snoezelen (3 by the same author); same results as Cochrane and SBU review [28] NICE-SCIE: 2 studies on multisensory stimulation vs active control, no effect on behaviour.[1]
Other sensory stimulation[a]	White noise: low intensity, monotonous sound (eg whirling fan) as an auditory stimulation intervention. Slow stroke massage, hand massage and therapeutic touch, aromatherapy, smell, or taste. TENS (transcutaneous electrical nerve stimulation). Acupuncture for vascular dementia.	Livingston: 1 RCT (8 subjects) on white noise: no effect (no evidence) Livingston: 3 RCTs on massage or combined forms of sensory stimulations, showed diverging results on behavior [5] Cochrane review: 1 Study of massage to improve behavior and 1 study of touch to improve eating : both positive effect but evidence insufficient[32] 1 Cochrane review (2003) for aromatherapy but no studies accepted by SBU for aromatherapy or massage: no evidence[21]. One systematic review on aromatherapy[33], reporting conflicting results, hence no evidence 1 Cochrane review: meta-analysis of 3 trials on TENS, applied to the patient's back to improve cognition and behavior in early and mid-stage AD

[a] One review on art therapy, and one review on animal therapy (including Pets to improve behavior) were retrieved but discarded because of methodological problems.

		(by altering activity of neurotransmitters):[34] some temporary improvements but too limited data (small studies) to allow definite conclusions 1 Cochrane review on acupunture for vascular dementia:[35] no RCTs, no conclusion. NICE-SCIE: 2 RCTs showing aromatherapy reduced agitation and BPSD in severe dementia.[1] However, both studies had been excluded by SBU. DIMDI: 1 negative study on therapeutic touch; 1 negative study on progressive muscle relaxation[28]
Simulated presence therapy	SimPres is a technique in which a family member, or established caregiver, makes an audiotape about positive events in the life of the individual with dementia that is played to simulate their presence. It is a patented intervention of SimPres Inc., Boston, Massachusetts, US	Livingston: 1 RCT, low level of evidence[5]
Music therapy	Listening (individualized music), singing or musical activity	Livingston: 6 Studies (4 also presented in Cochrane), moderate level of evidence, but not lasting[5] Sung: 0 Studies on agitation and preferred music[36] 1 Cochrane review (2004) including 5 RCTs but all concerned different types of interventions; only 2 studies accepted by SBU showing reduced agitation and increased wellbeing during the intervention. SBU included another 3 RCTs showing the same results; however 2 were excluded in Cochrane[21] NICE-SCIE: 1 RCT, no effect on behaviour.[1]
Structured activity interventions, including Physical activity		
Activity therapy	Structured activity consisting of sporting activities or games used to stimulate cognitive and psychosocial functions.	Livingston: 5 studies, all different interventions, inconsistent results and low level of evidence[5]
Exercise therapy	Exercise, movement, walking as an intervention for neuropsychiatric symptoms.	Livingston: 2 studies, low level of evidence[5] SBU: 1 meta-analysis and 5 studies (of which one excluded by Cochrane): some significant positive outcomes (physical fitness and mood in one RCT, cognition, and behavior in another RCT) but no scientific evidence: studies used different inputs and outputs; many drop-outs[21] Cochrane review: 2 studies (not included by SBU) and 1 meta-analysis: insufficient evidence and many differences in study parameters between studies[37]
Functional performance interventions		
ADL rehabilitative care / ergotherapy	Eating, dressing, bathing.	SBU: one study "dressing" intervention: positive effect on participation and behavioral problems during ADL; caregiver time doubled[21] SBU: one study on nutritional supplements and staff teaching on nutrition: increased weight but not improved cognitive function or ADL; one study on informal caregiver instruction about

		nutrition and behavioral (eating-related) interventions, no significant weight gain after one year[21] Watson et al[38]: systematic review on interventions for feeding difficulties: one RCT (not accepted by SBU) and 12 non-randomised studies: not enough good quality studies to conclude and more research needed. DIMDI: 5 studies on ergotherapy, no differences vs usual care in two studies[28] The studies by Gitlin et al.[39-41] are grouped under caregiver support by other authors. The study by Graff et al. reports improvement for ADL performance as well as for caregiver's sense of competence.[42, 43]
Communication, interaction and relationship interventions		
SBU: 6 studies on communication, interaction and relationship interventions[21]	Various designs and outcome measures.	Various positive effects. As effects were not confirmed in a second trial, SBU concluded that no evidence could be stated.[21]
Environmental manipulation		
Milieu therapy category I	The shaping of the material environment, eg collective living unit versus classic nursing home, wandering areas, bright light therapy during meals or daytime to re-establish circadian rhythms	Livingston: Low level of evidence for group living (1 study).[5] 1 Cochrane review and 1 study for bright light: no evidence as only 1 study[21] NICE-SCIE: 5 RCTs on light therapy, no effect on behaviour.[1]
Category II	Broad, care program interventions, includes sensory stimulation (see also above).	Livingston: Low level of evidence for special care "dementia units" (6 controlled non- randomized studies (none included by SBU), conflicting results) SBU: 1 controlled study of "intensive" care program interventions: progression of dementia not delayed - 2 controlled studies on Special dementia care units: one positive outcomes and less health care use, one no clear outcomes, no scientific evidence. One controlled study (12 months, N=54, Controls=44) on day care vs. classical home care: less stress in caregivers, delayed institutionalisation[21]
Category III	'gentle' subjective barriers to obscure the exit or to avoid agited patients will wander (see also paragraph 3.2.2.2 on behavioral problems)	Livingston: Weak level of evidence for changing the environment to obscure the exit (consistent evidence of 9 small non-randomised studies)[5] Low level of evidence for mirrors, signposting, unlocking doors (all non randomized studies).[5]

In conclusion, for the therapies described and discussed above, insufficient high quality evidence is available to support or reject ***reality orientation, self-maintenance therapy, individualized special instruction*** or ***validation therapy***. The results for ***reminiscence therapy*** are positive (4 studies) according to the Cochrane authors, but need to be confirmed because of the variation in types of reminiscence exercises and the limited number and relative low quality of studies. However, in the SBU study only one RCT of these 4 RCTs is retained, mainly because of inclusion criteria for dementia. This study showed no improvement.

Therapies aiming at ***enhancing cognitive functions*** can be subdivided by the type of stimulation. For cognitive training, insufficient high quality evidence is available to decide on efficacy or effectiveness, since different authors (Cochrane review and SBU review) judge the studies in a different way, mostly because of inclusion criteria for dementia.

For cognitive stimulation, 1 good-quality RCT shows positive results, but more evidence was found necessary by SBU. NICE-SCIE identified 4 studies on cognitive stimulation (also referred to as reality-orientation, cognitive rehabilitation or memory training in the studies) as add-on therapy to ChEIs. Three trials gave positive results (Chapman et al 2004;[44] Onder et al, 2005;[45] and an RCT in 13 patients by Bottino et al, 2005[46]). The RCT by Cahn-Weiner et al, 2003[47] was negative.[1] In the RCT by Chapman et al. [44] cognitive stimulation improved cognition, discourse and functional abilities at month 12 in AD patients on donepezil.

Concerning therapy based on sensory stimulation, ***snoezelen therapy*** might have an effect on some behavioral outcomes (1 RCT). It is concluded that snoezelen failed to demonstrate short-term or long-term effect but more evidence is needed because of the limited number of studies (2 RCTs) with a different format of implementation (session-based, 24h integrated).

Music therapy seems promising, showing reduced agitation and increased wellbeing during the intervention, but the effect is not lasting. However, the two RCTs concerned different types of interventions, so these results are to be confirmed. Another 6 RCTs had to be discarded because of inconsistent appraisal of quality (no agreement between SBU study and Cochrane review, mostly on inclusion criteria for dementia).

Promising seems also ***massage and touch***, since 2 RCTs demonstrated positive effects, one on eating behaviour and one on general behavior measures. However, more research has to confirm these results.

For other sensory stimulation techniques (***white noise, aromatherapy, art therapy, TENS, acupuncture for vascular dementia, simulated presence therapy***) insufficient high quality evidence is available to conclude on the value of these therapies in dementia.

Structured activity therapy consisting of sporting activities or games used to stimulate cognitive and psychosocial functions, was only described in 1 review. No evidence was found because of inconsistent results and a high degree of diversity among the interventions.

Physical activity (exercise therapy like moving, walking) seems promising as well: it seems to influence positively some domains like physical fitness and mood in one RCT, cognition and behavior in another RCT. However, these results still need to be confirmed, because of the small number of studies and because all studies included different patient populations and outcome measures. Also, many drop-outs were described.

Interventions addressing ADL rehabilitative care including functional performance like ***feeding difficulties or difficulties during dressing*** are considered promising.

Six studies aiming at ***improving communication and interaction*** with dementia patients were evaluated by SBU. Although some positive results were found, no conclusion on evidence level could be made, because of the large differences in study design and outcome measures.

Not enough evidence is available to conclude about effects in dementia patients caused by environmental changes like ***group living, intensified care programs*** or ***special dementia care units***.

Conclusion

Some promising evidence exists for cognitive stimulation (alone or as add-on therapy to ChEIs), music therapy, physical activity, massage/touch, ADL rehabilitative care and maybe interventions aiming at improving communication and interaction. For these interventions, positive results were reported in at least 2 RCTs respecting clear diagnostic criteria for dementia.

However, for all of these interventions, additional high-quality research is necessary, because of the diverging intervention strategies and outcome measures. Further, several small, non-randomized studies suggest a decrease in escaping behavior by patients with severe dementia if the exit is obscured. However, the Cochrane review on management of wandering behavior in dementia (see further), did not confirm these results.

3.2.2.2 Studies focusing on signs and symptoms: challenging behavior, neuropsychiatric symptoms and wandering

Behavioral training, including competence training of the caregivers, is addressed in the SBU-review[21], the Livingstone review[5], a review by Logsdon et al.[48] and another review by Ayalon et al.[49] The psychological methods used are very diverse, based on experimental psychology (operant methods or model learning) aimed at reducing eg agitation/ apathy. This requires functioning memory of the patient and trained staff.

The SBU review mentions 1 RCT of behavioral therapy (also included by Livingston et al., Logsdon et al. and Ayalon et al.); they note a positive effect on patient behavior and on depression in caregivers. They conclude that there is no evidence as there is only 1 study[21].

Livingston et al. mention 4 studies, two of which are also accepted by the SBU reviewers (however, one is mentioned under ADL training). The level of evidence Livingston assigns to standard behavioral management techniques applied to patients with dementia is moderate, effects are lasting months. [5] However, it is notable that the best evidence for the effects of behavioural approaches comes from studies targeting comorbid depression and anxiety in dementia.

The Logsdon review also discusses behavioral therapy and finds two additional RCTs with a significant positive effect on care recipients' behavior. They conclude that behavioral therapy is an evidence based treatment for behavioral problems in dementia. However, one RCT is discarded by the SBU because of uncertainty about the dementia diagnosis; and one RCT is very small including only 9 patients. This review also found significant evidence to support therapy based on the PLST model (Progressively lowered stress threshold). The PLST model implies environmental changes to support the care recipient's cognitive limitations, as well as pleasant activities in a structured daily routine. However, the included RCT (1 RCT) that studies effects of PLST on care recipients is discarded by the SBU review because of uncertainty about the dementia diagnosis in participants.

Ayalon et al.[49] focused in their systematic review on studies reporting neuropsychiatric symptoms (NPS) in patients with dementia. Most published studies were rejected because of low quality. The most promising interventions based on an RCT-design, were individually tailored behavioral interventions that include caregivers. Three RCTs for caregiving interventions were identified, of which two RCTs were by the same author as the study accepted by the SBU review. Such interventions were considered possibly efficacious pending replication. The authors comment that in absence of obtaining a significant reduction in NPS, the goal of studies may need to be modified.

Although behavior itself may not change, perceived management of the behavior may change and potentially result in reduced caregiver distress, disability, staff turnover, and overall cost of care.

Verkaik et al.[50] reviewed 19 studies on the effects of **13 types of psychosocial interventions on depressed, aggressive and apathic behaviors** of people with dementia. The conclusions are given below.

Table 3. Effects of psychosocial interventions on depressed, aggressive and apathic behaviours of people with dementia

Technique	Apathy improvement	Depression improvement	Agression improvement
Reality orientation	no	no	no
Skills training	no	no	no
Reminiscence therapy	no	no	no
Validation therapy	no	no	no
Behavior training of patients and caregivers (pleasant activities for patients; problem-solving for caregivers)	no	1 RCT (also accepted by SBU): limited improvement[50]	no
Snoezelen	2 RCTs (also accepted by Cochrane & SBU): some improvement[50]	no	no
Other sensory stimulation, gentle care, art therapy	no	no	no
Stimulated presence therapy	no	no	no
Psychomotor therapy	no	no	1 RCT (not accepted by Cochrane or SBU): limited improvement[50]
Activity therapy	no	no	no

NICE-SCIE concludes there is no evidence that standardised approaches, such as validation, cognitive stimulation and reminiscence, reduce behaviour that challenges in people with dementia. In general, this is not the major objective of such approaches, although some improvements in mood have been noted. Little research is yet available regarding music-based approaches, multi-sensory stimulation and bright light therapy. Aromatherapy in severe dementia has been evaluated in two controlled trials with some evidence of benefit in terms of reduced agitation and general neuropsychiatric symptoms.[1] However, these two trials were excluded by SBU because of inclusion criteria.

NICE-SCIE also concludes there is limited evidence from one RCT, albeit with relatively small numbers, that a cognitive behavioural therapy (CBT)-based approach may be helpful in treating depressive symptoms in people with AD, and this may also benefit carers who are actively involved in the treatment.[1]

Wandering occurs in 15-60% of people with dementia. It represents a diverse range of behaviours which occur for different reasons, thus necessitating a variety of therapeutic approaches. A Cochrane review focussed on non-pharmacological interventions for wandering of people with dementia in the domestic setting. Interventions considered include

- exercise and walking therapies,
- environmental modification interventions,
- behavioural modification interventions,
- occupational therapy,
- complementary and psycho-social therapies,
- Safe Return registration and identification program,
- electronic tagging used to restrain a person within a limited area or to locate a person

In the Cochrane review of 2007 on wandering in the domestic setting, no RCTs were identified.[51] A second systematic review also concluded that there was no robust evidence to recommend the use of non-pharmacological intervention to reduce wandering in dementia.[52] Note that several small, non-randomized studies (mostly in institutional settings) all suggest a decrease in escaping behavior by patients with severe dementia if the exit is obscured[5] (see Table 2, environmental manipulation).

Conclusion

Behavioral training of patients (or training of caregivers in behavioral management) might reduce challenging behavior in patients (and/or depression in caregivers). However, due to the limited amount of studies, replication of these results is necessary before efficacy can be considered to be proven.

No high-quality evidence is available on methods to reduce wandering in dementia.

3.2.2.3 Studies focusing on technological support

Many innovative applications of telecommunications have emerged in health care but the evidence is limited.[21] Two studies supported the effects of (computer) technological support, but no evidence could be stated given their differing outcomes (absence of confirmation in a second trial). NICE concluded initial findings support the use of assistive technology (telecare) in aiding people to stay in the community longer, thereby delaying moves to higher dependency care, but further research is needed before any firm conclusions can be drawn.[1] Qualitative evidence on the experience of people with dementia and carers points to the contribution that assistive technology can make by reducing risks and promoting independence.[1]

In a comprehensive review of intelligent assistive technology applications[53], the available tools are grouped as cognitive aids, physiological sensors, environmental sensors, advanced integrated sensor systems, wearable radiofrequency transmitters and the Proactive Activity Toolkit. Most of the tools and research studies focus on the physical disability of younger persons with typically non-progressive brain injury. Unfortunately, no good quality studies have yet been published using such tools in persons with dementia.[53]

3.2.3 Interventions that include the caregiver

One of the new area's of dementia research concerns the interventions to prevent the negative consequences of caring for a person with dementia. Care at home for as long as possible is often preferred over institutionalization both by the patient and the family-caregiver. Caring for a person with dementia at home is however intensive and burdensome. Caregivers are at high risk of psychosocial morbidity and associated breakdown in care. Support measures preventing caregivers from becoming overburdened and depressed may theoretically result in a delay of institutionalization.

3.2.3.1 Staff education: effects on patients or caregivers

Livingston et al. describe 3 RCTs (as well as 6 other studies), evaluating staff education in managing behavioral problems. It is concluded by the authors that a moderate level of evidence exists to support staff education in improving behavioral problems in dementia.

The **SBU review** also discusses the effect of formal caregiver interventions on caregiver knowledge and attitude. Because only few studies were identified as having sufficient quality, it was concluded that insufficient evidence is available to show that formal caregiver education or training has any effect on their attitude or knowledge.

Kuske et al.[54] evaluated nursing home staff training in dementia care (several aspects); they found 3 RCTs of good methodological quality, demonstrating positive effects on the level of caregiver (knowledge and attitude) and care recipient (behavioral disturbances). The authors conclude that the evidence level is low.[54] Two of these 3 studies were also included by Livingston; one study was included by SBU under "communication enhancement" and another study was excluded by SBU.

It can be concluded that insufficient evidence is available to conclude on the effect of formal caregiver education or training; more studies are necessary. Based on the multiple positive studies, however using different interventions, the approach can be considered promising. According to **NICE**, training programmes that teach specific skills in the workplace, and which build in managerial support, do seem to be associated with positive outcomes.[1]

3.2.3.2 Psychoeducation and psychosocial interventions for informal caregivers: effects on patients or caregivers

Patient behavior: effects of teaching and psychoeducation of informal caregivers.

Livingston describes 6 RCTs on teaching caregivers principles of behavior therapy, but one RCT is excluded by SBU; and one RCT involves a double intervention (also exercise therapy). Because of inconsistent findings it is concluded by the authors that no evidence exists for teaching caregivers principles of behavior therapy to improve behavioral problems in dementia[5].

Livingston also includes 7 RCTs involving psychoeducation to teach (mostly informal) caregivers how to change their interactions with dementia patients. One of these studies was excluded by SBU. Livingston concludes that a high level of evidence supports that psychoeducation of caregivers improves behavior disturbances in dementia patients. In two of the included RCTs this postponed institutionalization (one during the first 3 months, one during 329 days); these two studies were also included by SBU and by Spijker et al.(see further).

Informal caregiver depression and stress: effects of psychosocial interventions and psychoeducation.

In the **SBU review**, the positive effect on informal caregivers (improvement in distress, depression; feelings of well-being) of several forms of psychosocial interventions and psychoeducation is described; this conclusion of moderately strong evidence is based on 3 systematic reviews, 3 high-quality RCTs (one also included by Logsdon et al. and using PLST) and several medium quality studies. Concerning skill-training and cognitive-behavioral programs, the SBU review concludes that limited scientific evidence is available from several medium quality studies that this reduces caregiver depression and perceived stress.

Positive effects on informal caregivers (improvement in feelings of depression and burden, well-being) of several forms of psychological support and psychoeducation were also reported in the meta-analysis by **Parker et al**.[55] including 34 RCTs, 3 systematic reviews and 3 meta-analyses. Case management and computer aided support yielded mixed results. In the Parker review, two of the three meta-analyses mentioned by the EFNS taskforce are also included. The EFNS taskforce[13] did not conduct a new meta-analysis nor include any additional RCTs. They conclude that psychosocial and psychoeducational interventions have positive effects on caregivers.

The study by Graff et al.[42, 43] (included in the review by **DIMDI**[28]) reports a positive effect of occupational therapy on the sense of competence of caregivers.

Cooper et al.[56] reviewed studies reporting anxiety level in caregivers. This was the primary outcome measure in only one study. There was little evidence of efficacy for any intervention.

The only RCT to report significantly reduced anxiety involved cognitive behavioral therapy (CBT) and relaxation-based intervention specifically devised to treat anxiety, and there was preliminary evidence (no randomised controlled trials) that caregiver groups involving yoga and relaxation without CBT were effective. The authors concluded that there was moderate ("grade B") evidence that behavioural management, exercise therapies and respite care were not effective.

Based on 6 moderate quality RCTs (3 of which were also mentioned in the SBU study) and 10 other papers **Selwood et al,**[57] found no evidence of benefit for providing only education to caregivers or for dementia specific therapies targeted at the patient.

Selwood et al. grouped educational programmes into training programmes based on stress and coping theory versus training in behavioral management techniques. For each programme category thus defined, an individual or a group educational approach was studied, with a varying number of sessions (under 6 or minimum 6 sessions).

Group training programmes (six or more sessions) for caregivers based on stress and coping theory were studied in five RCTs (one of high quality). There is moderate level of evidence that these programmes result in less depression for the caregivers lasting up to 3 months after the intervention. The effect on caregiver burden was less consistent.[57]

Individual coping strategies lasting at least 6 sessions were studied in four RCTs (one of high quality). There is moderate level of evidence that such interventions lead to less depression in caregivers, and lasting up to 3 months after the intervention.[57]

Group behavioral management techniques (behavioral management theory and how to manage problem behavior) have been studied in RCTs, often combined with caregiver coping strategies. There is moderate level of evidence that group behavioral management is not an effective intervention, either immediately or for up to 8 months. Similarly, there is moderate level of evidence that less than 6 sessions of individual behavioral management is not an effective intervention, either immediately or for up to 6 months. However, when 6 or more individual sessions are given there is high level evidence from RCTs for a benefit on depression in caregivers (but no effect on caregiver burden) immediately and up to 32 months.

Finally, for support programs (mainly by telephone, self-help group, or nurses) there is moderate level of evidence of no effect on CG depression, anxiety, or burden.

Selwood et al. concludes there is evidence that the psychosocial health of the caregiver can be improved after 6 or more individual behavioral management training sessions focusing on the patient's behavior, or by teaching coping strategies for caregivers, taught either individually or in a group. It should be noted that Selwood did not mention which databases were searched; studies were included until July 2003.

In their systematic review (RCTs only) of information and support interventions for caregivers of people with dementia, **Thompson et al**. [58] used yet another way of classification. Interventions were grouped into technology-based (3 RCTs), group-based (13 RCTs) and individual-based (27 RCTs). Only 4 of these studies were also discussed in Selwood et al. Two of the 3 high quality papers included in the SBU study are included by Thompson, as well as 13 other SBU papers. A statistically significant positive impact of group-based supportive interventions was found, but not for technology-based interventions or individual-based interventions for caregivers. A statistically significant effect of group psycho-educational approaches on depression in caregivers was seen but the evidence was very limited and the clinical significance of these benefits remained unclear. The authors also reported difficulties pooling the reported outcomes of mostly poor quality studies. Thompson et al. based their search on the Cochrane Register for Dementia and included studies until October 2005.

Logsdon et al. [48] reviewed 14 studies, of which 6 studies demonstrated a trend but no statistical significance. They found some evidence (1 RCT, also accepted by SBU) that a standard protocol based on PLST (Progressively lowered stress threshold) significantly lowers caregiver distress over behavior problems. They also mentioned 1 RCT of behavioral therapy (also included by the SBU review, Livingston et al., and Ayalon et al.) describing a positive effect on depression in caregivers. Mainly individuals with depressive or anxious behaviors seemed to benefit.

Their conclusions for care recipients concerning PLST or behavioral/ social learning theory have been mentioned before (see paragraph 4.2.2.2).

Gallagher-Thompson et al.[59] categorized studies into psychoeducational-skill building programs, psychotherapy-counselling studies and multicomponent interventions. However, the focus was on caregivers of older adults, not necessarily persons with dementia, which strongly limits the conclusions of this review.

Conclusion

There is evidence that several forms of psychosocial interventions and psychoeducation diminish caregiver burden and distress and increase their feelings of well-being. However, evidence is inconclusive as to the specific content of these interventions, and whether these interventions should be given individually or in group.

3.2.3.3 Respite care and special care units: effects on informal caregiver depression and stress

Because of conflicting conclusions between systematic reviews, SBU concluded that was no evidence of benefit for caregivers from respite care (**SBU review**: based on Cochrane review; one additional systematic review showing conflicting results). [21] No significant differences in health and well-being were seen between family caregivers who placed elderly relatives in a nursing home and those who kept them at home or in the community (3 original studies). Neither did caregivers seem to benefit from placement in special care units.[21] Effects of special care units on outcomes in patients has been discussed in paragraph 3.2.2.1.

3.2.3.4 Interventions to delay institutionalization

A recent meta-analysis was conducted by **Spijker et al.**[60] investigating the effectiveness of nonpharmaceutical interventions in delaying the institutionalization of patients with dementia. A total of thirteen support programs were selected, ten of which were studied using randomized trials. Most of the interventions were multicomponent and individualized and intensive, and includes dementia patients from the mild to the severe spectrum. The meta-analysis, according to a random-effects model, showed a lower odds of institutionalization in the intervention groups (OR 0.66; 95%CI: 0.43-0.99), as well as a significant increase in time to institutionalization (mean difference ~5 months).

The most effective interventions were characterized by a multicomponent program, including supportive care-giving interventions, and individually tailored to the needs of the caregiver and care recipient. The authors concluded that the active involvement of caregivers in making choices about treatments, including counseling and personal assistance with problem solving, seemed to be the crucial intervention characteristic distinguishing effective and non-effective interventions. Being able to choose one of several interventions might lead to satisfactory involvement. The results of this meta-analysis were confirmed when the analysis was restricted to the studies with the best methodological quality.

We briefly discuss the two larger RCTs included in the meta-analysis. In particular, the RCT by Mittelman et al. included in this meta-analysis deserves our attention. In two later publications by the same author, the initial sample was extended to 406 spouse caregivers of community dwelling patients in New York City with Alzheimer disease enrolled over a 9.5-year period, which is the largest follow-up period described so far.[61, 62] Enhanced counseling and support consisted of six sessions of individual and family counseling, support group participation, and continuous availability of ad-hoc telephone counseling. The study arm with these counseling and support interventions for spouse caregivers was associated with a delay in model-predicted median time to placement of 557 days. In addition, self-rated health in intervention group caregivers was significantly better than control group caregivers. Similar benefits of intervention were found for number of illnesses.

Another very large study included in the review of Spijker et al. is the study of Miller et al.[63] describing usual care (N= 3944) in the USA Medicare system, and case management (N=4151) with a case load from 30 to 100 cases/manager, including a follow-up of 3 years. This study failed to show a shorter time to institutionalization for the intervention group (OR 1.05 (0.96-1.15). The difference with the previous study might be caused by the different concept of the intervention.

The **SBU review** describes 13 studies (one also included by Livingston[5]) analyzing the impact of the intervention on institutionalization. Three studies including caregiver support led to postponed institutionalization but studies were not comparable (two also included in Spijker et al.), and four studies (two also included in Spijker et al.) did not[21].

The authors conclude that results are inconsistent and hence that no evidence exists. Two programs focused on day care, and one on respite care; four programs focused on case management, but one of these programs also included caregiver support. (One small case management study was also included in Spijker et al.) It was concluded that insufficient evidence was available for day care, respite care and case management concerning postponing of institutionalization.

It can be concluded that promising evidence is available concerning the effect of caregiver counseling and support to postpone institutionalization by a period that is comparable to (or longer than) specific pharmacological interventions. However, these results need to be confirmed by further well-constructed studies.

3.2.3.5 Miscellaneous

In a systematic review **Smits et al.**,[64] describe 25 studies using combined programmes involving both care recipient and caregiver. The interventions concerning the care recipients were diverse: music groups, memory training, participation in a social club, art therapy, behavioral therapy, medication by geriatrician, etc. The interventions for the caregivers included mainly counseling, support (individual or group) and psychoeducation, but also case management, respite care, skills training, psychotherapy, art therapy, etc. Some of the included studies were also reported in the Livingston review[5] or the SBU review, [21] and 7 were included in the Thompson review on information and support to informal caregivers. Smits et al. concluded that interventions targeting both the patient and the caregiver are often effective in delaying admittance to long stay care, and have a positive effect on general health of the caregiver and the mental health of the person with dementia. No conclusion could be drawn for other mental health outcomes for caregivers, such as depressive symptoms, well-being, burden and competence. Effects on cognitive functioning and behavioural problems of the person with dementia were also inconclusive.

The value of this review probably lies in the fact that positive effects on both caregiver and care recipient are underlined, whereas many other reviews study and emphasize outcomes in one of the two. The results on institutionalization confirm the results of Spijker et al.[60]

3.2.4 General conclusion on non-pharmacological interventions in dementia

Many methodological difficulties are encountered when evidence on non-pharmacological interventions are summarized. Inclusion criteria on dementia are often not well-defined, and even more common is the lack of information on the content of the intervention. Even when the intervention is well-described, it is often difficult to repeat it exactly, because of specific local circumstances and contextual influences which impact on the results. However, this might be inevitable in the kind of interventions that belong to this category. Further, many studies include only a limited number of participants. Last but not least, many different outcome measurements exist, and many of them are not fully validated.

The study limitations illustrate the lack of organization and standardization in this field. This can be viewed as a direct result from the lack of intellectual property protection and company - regulatory authority interactions which have advanced the standards for the development of pharmaceuticals. This is however no excuse for our society not to implement high quality government-sponsored multicentre RCTs for non-pharmaceutical interventions that have shown promising results in preliminary studies.

Some of the interventions discussed in this chapter are indeed supported by sufficient evidence justifying cost-effectiveness studies and eventually implementation in routine care. For some other interventions there are promising results that need further confirmation using randomized trials.

Given the potential impact of this knowledge for the growing number of dementia patients, their caregivers and our society, support should be found to conduct such studies nothwithstanding the inheritant methodological difficulties.

Key Points

- **Most of the non-pharmacological studies have a small sample size. The patient study population are often 'dementia' patients without a well-documented clinical diagnosis. In addition, there is often a lack of standardization of the specific non-pharmacological interventions and validation of the scales used as study endpoint.**
- **These limitations seriously hamper firm conclusions from the available literature. Only for non-pharmacological interventions including caregivers, enough good-quality evidence could be found to consider the intervention as evidence-based (see further).**
- **However, interventions were considered to be "promising" if at least 2 well-conducted RCTs on a certain therapeutic principle (e.g. music therapy) showed positive results, but implemented different intervention standards and/or used different endpoints.**

<u>Patient targeted interventions</u>

- **Patient targeted interventions can be divided into:**

-patient cognition (reality orientation, cognitive stimulation-training-rehabilitation)

-patient emotion (reminiscence therapy, validation therapy, self-maintenance therapy, individualized special instruction),

-sensory stimulation ("snoezelen" or multisensory stimulation, massage and touch, white noise therapy, aromatherapy, TENS, acupuncture, simulated presence therapy, music therapy),

-structured or physical activities,

-ADL rehabilitative care,

-interventions targeting communication-or interventions on the patient environment (bright light to re-establish circadian rythms, broad intensive care programs in dementia units, obscuring the exit to prevent wandering).

- **Among these interventions, promising are cognitive stimulation (alone or add-on to therapy with inhibitors of acetylcholinesterase), ADL-rehabilitative care, music therapy, massage/touch, physical activity, and maybe interventions aiming at improving communication/interaction.**
- **For all the other interventions, insufficient high quality evidence is available to support or reject the therapy; including environmental changes like group living, intensified care programs or special dementia care units.**

<u>Interventions targeting specific signs and symptoms</u>

- **Another category of interventions target specific signs and symptoms, mostly patient behaviour and wandering. Again, insufficient high quality evidence is available to support or reject these therapies.**

<u>Interventions including technological support</u>

- **This third type of interventions has mainly been developed for younger persons with physical disabilities. No good quality studies on the use of such tools for dementia patients are available.**

Interventions involving formal or informal caregiver(s)

- **The last category of interventions involves the formal or informal caregiver(s), studying effects in patients and/or caregivers.**
- **Some moderate level evidence was found for a positive effect of several forms of psychosocial interventions and psychoeducation on informal caregiver depression and stress. However, reviews draw different conclusions on the benefit of individual sessions versus group based sessions.**
- **Education and training of staff were found to be promising interventions.**
- **Because of conflicting conclusions between systematic reviews, SBU concluded that there was no evidence of benefit for caregivers from respite care, nor for placing the elderly relative in a nursing home or special care unit.**
- **Support measures preventing caregivers from becoming overburdened and depressed result in a delay of institutionalisation, as shown in a meta-analysis of 13 support programs.**
- **One example from this meta-analysis is the study by Mittelman et al., for which the longest follow-up period is available. This large randomized controlled trial (RCT) studied over a 9.5-year period 406 spouse caregivers of community dwelling AD patients in New York City. Enhanced counseling and support consisted of six sessions of individual and family counseling, support group participation, and continuous availability of ad-hoc telephone counseling. This intervention was associated with a delay in median time to placement of 557 days. In addition, self-rated health in intervention group caregivers was significantly better than control group caregivers.**

4 PHARMACOLOGICAL TREATMENT

4.1 SEARCH

First, relevant HTA reports were searched in the HTA database of the Centre for Reviews and Dissemination (CRD). Second, a search was done for systematic reviews (using the Cochrane Database, DARE, and Medline) focusing on Alzheimer disease. HTA reports and systematic reviews were identified June 5, 2008 using "Alzheimer" as keyword for searching the databases HTA at CRD and DARE at CRD, and searching PubMed (Medline) using ("Alzheimer Disease/drug therapy"[Mesh] OR "Alzheimer Disease/therapy"[Mesh]) AND systematic[sb]

We selected HTA reports and systematic reviews which minimally covered the literature published up to mid 2004 or which were found to be of particular relevance. The identified studies were selected based on title and abstract. Reviews that included meta-analyses and/or used quality criteria to include primary studies were considered in detail. We excluded reviews which did not provide a qualitative evaluation of studies included. We did not perform any formal scoring of the quality of the reviews, which can be considered a limitation of the study.

Also transcripts of FDA discussions in the context of the drug approval process were checked (www.fda.gov). We also want to mention the RIZIV/INAMI consensus report on the use of medication, including antipsychotics, for the treatment of dementia in the elderly, and the 2008 update by BCFI.[9, 10] These documents provide a clear and detailed overview of the literature and evidence published, as well as the medications available in Belgium.

4.2 INTRODUCTION

In a first part of this section we briefly cover the efficacy and safety of the agents developed for the indication AD. We have not searched individual studies as recent systematic reviews were available. In the second part we summarize the use of these and other drugs for the treatment of depression and BPSD in AD patients.

In contrast to agents historically used for the treatment of dementia, such as co-dergocrine and piracetam, the ChEIs (donepezil, galantamine, and rivastigmine) and memantine were evaluated using large randomized placebo-controlled trials, mainly involving specialist care centres.[10]

Symptomatic improvement has been demonstrated for the ChEIs (donepezil, galantamine, and rivastigmine) in mild to moderately severe AD (MMSE > 11) and for memantine in moderately severe to severe AD (MMSE >3, <15). In Belgium, these drugs are reimbursed as monotherapy and the conditions for reimbursement require a collaboration of a GP and a specialist physician. A RIZIV/INAMI registry was planned for AD medication but was never implemented.

ChEIs also include tacrine, but tacrine is no longer used because of hepatotoxicity. ChEIs increase the concentration of acetylcholine at sites of neurotransmission. Donepezil (Aricept, Eisai/Pfizer) is a specific and reversible inhibitor of AChE, licensed at a dosage of 5 mg/day and 10 mg/day. Galantamine (Reminyl, Shire/J&J) is a selective, competitive and reversible inhibitor of AChE. In addition, galantamine enhances the intrinsic action of acetylcholine on nicotinic receptors, probably through binding to an allosteric site of the receptor. The maintenance dosage is 16–24 mg daily. Rivastigmine (Exelon, Novartis) is an acetylcholinesterase and butyrylcholinesterase inhibitor. The usual maintenance dosage is 3–6 mg twice daily, or once daily using a transdermal patch.

Memantine (Ebixa, Lundbeck) is a voltage-dependent, moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA)-receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. The recommended maintenance dosage is 10 mg twice daily.

Ginkgo biloba

Ginkgo biloba leaf extract is one of the most widely sold phytomedicines in Europe. First, we had planned not to discuss Ginkgo biloba in this report as not robust data were available. However, as a few reports covering Ginkgo were identified during the course of this project we provide a brief summary here. The trials are weak from a methodological point of view (patient population not well characterized, lack of power, assessment of efficacy) and do not allow to make any firm conclusion.[10] Extract of Ginkgo biloba can provide some relief of cognitive and Activities of Daily Living (ADL) impairment (Evidence Grade 3).[14] Knowledge about long-term effects is limited to therapy for six months. The recent IQWiG report (http://www.iqwig.de/ginkgo-biloba-in-alzheimer-s-disease-evidence.818.en.html) concludes that for the therapy goal "activities of daily living", there is evidence of a benefit of high-dose (240 mg daily) Ginkgo extract EGb 761 in AD patients (but not for a lower dose or other extracts). IQWiG reported the evidence was primarily based on 2 recent Ukrainian studies.[65]

As results across studies are very heterogeneous; no summarizing conclusion can be made on the potential effect size. In addition, there is an indication that this benefit is only present in patients with accompanying psychopathological symptoms.[65] A recent Cochrane review[66] concluded that the evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable. In addition, a recently published study did not show efficacy for this drug in MCI patients.[67]

In Belgium, Ginkgo biloba is reimbursed for the symptomatic treatment of mild to moderately severe AD (MMSE > 11).

Other agents

Co-dergocrine or piracetam are not included in this evaluation because robust trial data are lacking.

It must be stated that a number of molecules have shown promising results when studied in AD patients. Some of the novel approaches to treating AD offer the potential for disease modification. In addition to the approaches aiming to modify the amyloid cascade or the protein aggregation, some molecules target the intraneuronal accumulation of neurofibrillary tangles. Active or passive immunization trials, aiming at various antigens, are also underway.

Guidance for the clinical development of medicinal products in Europe in the treatment of Alzheimer's Disease is available in a CPMP Note for Guidance (http://www.emea.europa.eu/pdfs/human/ewp/055395en.pdf). Symptomatic improvement after at least 6 months of treatment is to be demonstrated for the cognition domain and either for activities of daily living or overall clinical response. An update is in preparation for the development of possible disease modifying treatments.

Using the search strategy described above, we identified the following recent systematic reviews of the published clinical trials.

Table 4. Systematic Reviews by Search Date

Reference	Search date
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Memantin bei Alzheimer Demenz. Vorbericht A05-19C. Köln: IQWiG; 2008.	December 2007
Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D, Levine M, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. 2008;148(5):379-97.	November 2006
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Cholinesterase inhibitors in Alzheimer's disease. Final report A05-19A. Köln: IQWiG; 2007.	June 2006
NICE-SCIE. Dementia: supporting people with dementia and their carers in health and social care. Care guideline. National Institute for Health and Clinical	May 2006

Excellence (NICE); 2006. Clinical Guideline 42.	
Hansen RA, Gartlehner G, Lohr KN, Kaufer DI. Functional outcomes of drug treatment in Alzheimer's disease: A systematic review and meta-analysis. Drugs Aging. 2007;24(2):155-67.	December 2005
McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev. 2006(2):CD003154.	July 2005
Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006(1):CD005593.	June 2005
A. P. A. Work Group on Alzheimer's Disease and other Dementias, Rabins PV, Blacker D, Rovner BW, Rummans T, Schneider LS, et al. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. Am J Psychiatry. 2007;164(12 Suppl):5-56.	2004
SBU. Dementia – Diagnostic and Therapeutic Interventions. A systematic review. Volume 2. June 2008.	July 2004
Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, et al. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. Health Technol Assess. 2006;10(1):iii-iv, ix-xi, 1-160. NICE, 2006.	July 2004
Kirby J, Green C, Loveman E, Clegg A, Picot J, Takeda A, et al. A systematic review of the clinical and cost-effectiveness of memantine in patients with moderately severe to severe Alzheimer's disease. Drugs Aging. 2006;23(3):227-40.	July 2004

4.3 REVIEWS OF ALZHEIMER DISEASE MEDICATION

For the medicines considered, large randomized, double-blind, placebo-controlled phase 3 trials were conducted resulting in regulatory approval. Most of these studies were funded by the pharmaceutical industry. In a few studies the comparator was another ChEI. No trials were identified comparing ChEIs versus other medications or non-pharmaceutical interventions. With the exception of three donepezil trials and a small size Exelon trial, the treatment duration did not exceed 6 months.[68]

The patients were diagnosed as AD according to at least one of the following criteria: NINCDS-ADRDA, ICD-10 and DSM-III, DSM-III-R or DSM-IV. In the more recent trials on mild to moderate dementia the criteria also stated that CT or MRI should be consistent with the diagnosis of AD, and a modified Hachinski ischemic score <5 (the scale uses patient history and exams to quantify the presence of vascular type of dementia) was commonly used to further differentiate AD from VaD.[14] The collaboration of a caregiver was required in most study protocols.

The primary endpoints in most studies were measurements of global function and cognitive tests performed by the patient. ADL and behavioural disturbances, as reported by the caregiver, were secondary outcomes.

4.3.1 Results overview

The results overview below shows the difference with the placebo group in change from baseline. They are mainly based on ITT or ITT-LOCF (last observation carried forward) analyses and are given for studies that lasted 6 months or longer and used the doses that are recommended for clinical practice in Europe.

Table 5. Difference with the placebo group for AD medications

	Donepezil 5 - 10 mg/d	Galantamine 16 – 24 mg/d	Rivastigmine 6 – 12 mg/d	Memantine 20 mg/d in moderately severe to severe AD (monotherapy)
Indication in Belgium	Mild to moderately severe dementia	Mild to moderately severe dementia	Mild to moderately severe dementia	Moderate to severe dementia
Institutionalization prevention	No interpretable data[69]	No interpretable data[69]	No interpretable data[69]	No interpretable data; indications that data were collected but not made public[19]
Global clinical impression	7 point CIBIC+ Significant improvement[69] Improved: 21-26% vs 11-14% on placebo; improved or stable: 57-75% vs 49-55%[14] mean change -0.45 (-0.54 to -0.36)[70]	7 point CIBIC+ Significant improvement[69] improved: not significant; % patients stable or improved (66% vs 52%): significant in the three studies[14] RR improved or stable 1.22 (1.12 to 1.33)[70]	7 point CIBIC+ Significant improvement[69] improved: significant (37% vs 20%) in one of the four studies; endpoint stable or improved not stated[14] mean change -0.36 (-0.45 to -0.27)[70]	7 point CIBIC+ No indications for improvement based on available data[19] Mean change of borderline significance[14] -0.28 (-0.41 to -0.15)[71] -0.27 (-0.43 to -0.10)[70]
Cognition improvement at 6 months	70 point ADAS-cog: about 2 points improvement[69] - 2.02 (-2.77 to -1.26) for 5 mg; -2.92 (-3.74 to –2.10) for 10 mg[14] -2.83 (-3.29 to -2.37)[70]	70 point ADAS-cog: about 3 points improvement[69] -3.1 (-4.1 to -2.1) for 16 mg; -3.3 (-3.9 to -2.7) for 24 mg[14] - 2.46 (-3.47 to -1.44)*[70]	70 point ADAS-cog: about 3 point improvement[69] -2.09 (-2.65 to -1.54) for 6 to 12 mg[14] -3.91 (-5.48 to -2.34)*[70]	100 point SIB Results not clear, not robust, heterogeneous[19] 7 points on SIB but not significant for MMSE[14] 4.46 (1.87 to 7.04)*[70] 2.97 (1.68 to 4.26)[71]
ADL improvement	No interpretable data, effect (minor) can be assumed[69]	About 3 points on DAD (minor effect)[69]	About 3 points on PDS (minor effect)[69]	ADCS-ADL 1.39 (0.39 to 2.39)**[70] 1.27 (0.44 to 2.09)[71]
Patient QoL	No effect[69]	No data[69]	No data[69]	No data[19]
Caregiver QoL	No effect can be inferred from	Indications for a minor positive effect	No relevant data found[69]	No effect can be inferred from available

	available data[69]	(0.1 SD)[69]		data, indications that data were collected but not made public[19]
Reduction in degree of care by caregivers or institutions	Data insufficiently robust for methodological reasons[69]	One study showing indications of a positive effect[69]	Indications that data were collected but not published[69]	No effect can be inferred from available data; indications that data were collected but not published[19]
Psychopathology improvement	Unconvincing data[69]	144 point NPI Indications for a minor effect of 1-2 points[69]	No data[69]	144 point NPI No effect can be inferred from available data[19] -3.19 (-5.09 to -1.29)[70] -2.76 (-4.63 to -0.88)[71]
Adverse events (% of patients affected)	5 to 10%[14]	5 to 20%[14]	10 to 40%[14]	Adverse events are not frequent[19]
Nausea	5 mg: no difference 10 mg: 11-17% vs 5-9%[14] RR 2.54 (1.97 to 3.29)[70]	16-37% vs 3-13%[14] RR 2.84 (1.76-4.61)[70]	47% vs 12%[14] RR 2.79 (1.26 to 6.19)[70]	
Vomiting	5 mg: no difference 10 mg: 12% vs 5% (all groups under 5% in Nordic study) [14] RR 2.25 (1.26 to 4.03)[70]	15-21% vs 4-7%[14] RR 3.27 (2.13 to 5.01)[70]	30% vs 6%[14] RR 6.06 (3.88 to 9.45)[70]	
Anorexia	RR 3.21 (CI, 1.94 to 5.33)[70]	RR 3.41 (2.36 to 4.93)[70]	RR 5.34 (2.30 to 12.42)[70]	

*high inconsistency
**all severity levels

4.3.2 Donepezil, rivastigmine, or galantamine in AD

The systematic reviews conclude that there is moderately strong evidence of limited effects on cognitive performance and global function in mild to moderate AD patients after 6 months of donepezil, rivastigmine, or galantamine treatment.[14, 69, 72] For donepezil symptomatic improvement was also demonstrated for 12 months of treatment. Based on 10 randomized, double blind, placebo controlled trials of 6 months duration, with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due to Alzheimer's disease, the improvement in cognitive function was on average -2.7 points (95%CI -3.0 to -2.3, p<0.00001), in the midrange of the 70 point ADAS-Cog Scale.[73]

The average effect of ChEIs corresponds to a 1 to 1.5 points improvement on the MMSE. Such improvement is statistically significant but only marginal from a clinical point of view.[70] For example, the average change for cognition is smaller than the minimum change which has (arbitrarily) been defined as clinically relevant (4 points or 7 points depending on the source).

A cut-off for improvement consisting of at least a 4 point improvement on the ADAS-cog plus no worsening on the CIBIC+ or functioning scale (ADL or PDS) has been proposed. Using this cut-off the number needed to treat (NNT) is about 10 for the ChEIs.[12] This means that 10 patients are to be treated to detect such response in one patient. No factors could be identified predicting response to ChEIs. Both effects and adverse event rates are dose-dependent, limiting dose increases of ChEIs.[69] All improvements disappeared after a wash-out of 6 weeks. Patients with AD and concomitant cerebrovascular dementia (VaD) respond similarly to treatment as patients with pure AD. The efficacy of acetylcholinesterase inhibitors in patients with pure VaD is very small.

According to IQWiQ all 3 ChEIs consistently improved the global clinical impression.[69] According to SBU,[14] there is moderately strong evidence for an effect on the CIBIC+ after 6-12 months of donepezil or 6 months of galantamine treatment. The CIBIC+ is improved or maintained in 57-75% of patients versus 42-56% of placebo patients.[14]

For all 3 ChEIs, there are indications of a minor benefit in respect of the therapy goal "improvement in or prevention of restriction in activities of daily living".[69] Based on data published for ChEIs or memantine a small pooled standardized effect size of 0.29 (0.22 to 0.36) was calculated.[32]

Whereas the direct comparison between rivastigmine and donepezil showed indications of an additional benefit of rivastigmine for activities of daily living, rivastigmine also had a higher potential to cause harm. No conclusions can be made on the other two comparisons (galantamine vs. donepezil or galantamine vs. rivastigmine).

For galantamine, there are indications of a minor benefit with regard to accompanying psychopathological symptoms. For donepezil, no corresponding benefit could be inferred from the available data, and for rivastigmine, no data were available.[69]

No data were available (galantamine and rivastigmine) for the therapy goal "improvement in or maintenance of health-related quality of life", or they provided no indication of a benefit (donepezil).[69]

An effect on mortality cannot be inferred from the available data; however, the studies were not designed to make conclusions in this regard.[69] One should note that the mean patient age in most phase 3 studies with ChEIs was in the 69 to 76 years range.[14]

No interpretable data were available on the therapy goal "prevention of placement in a nursing home" (institutionalization).[69]

All 3 drugs triggered therapy-related adverse events in a dose-dependent manner, mainly consisting of anorexia, nausea, vomiting and diarrhoea.[69] Adverse events are generally mild and transient. For all trials that compared rivastigmine with placebo, discontinuation due to adverse events was more common in patients who received active treatment. Adverse events can be partly avoided by means of a slower dose titration rate.

In addition, ChEIs have been associated infrequently with cardiac side-effects such as bradycardia and atrioventricular block.(Cardiale ongewenste effecten van cholinesterase-inhibitoren, Folia Pharmacotherapeutica 33, June 2006, www.bcfi.be). These side-effects may lead to syncope, pacemaker insertion and hip fracture.[74]

4.3.3 Memantine in AD

Results reported for cognition are summarized in Table 5 and vary from "not clear" to an average improvement of 7 points on the 100 points SIB scale. SBU concluded some cognitive improvement was seen in mild to severe AD (evidence grade 3), but that long-term data were lacking[14] A Cochrane review concluded that memantine had a small beneficial effect on cognition, ADL and behaviour in moderate to severe AD, and a barely detectable effect in mild to moderate AD.[71] Loveman et al. concludes that the results suggest that memantine is beneficial when assessed using functional and global measurements.[72]

For the evaluation of memantine for AD it was striking that data of 7 studies could not be included in the preliminary report of the systematic review by IQWiQ[19] because the study results or the specific subgroup analyses were not made public by the sponsor of study. HTA agencies have no access to dossiers submitted to the regulatory authorities. There is no standard way to obtain and handle study data that are not made public. Different authors may include/exclude studies differently. All these factors may explain why authors arrive at slightly different conclusions.

In their preliminary report, IQWiG considered three studies of memantine versus placebo (without ChEIs): Merz study 9605 in the US (MMSE 3-14), Forest study MD-01 in the US (MMSE 5-14), and study 10116 in China (MMSE 3-18). In the subgroup analysis of moderate to severe AD patients no significant effect on cognition or aspects of caregiver quality of life (NPI-D) were seen.[19] This was mainly due because of the inclusion of the results of study MD-01,[75] which were not available at the time the drug had been approved in the major markets.

The improvements for clinician's global impression, ADL (0.2 SD) and for psychopathology (< 0.5 SD) are minor. The improvement in ADL was restricted to patients with MMSE 10-14 (moderately severe) in the single study for which this subanalysis was provided (study 9605). The clinical relevance of the improvement is questionable.[19] Also Raina et al.[70] conclude there is consistent evidence that memantine improves cognition and global assessment, but the magnitude of the effect size for the ADAS-cog does not approximate those considered clinically significant.

According to a company-sponsored meta-analysis, an effect is seen mainly on the ADCS-ADL19/sev scale as this scale is more sensitive to change as compared with the ADCS-ADL23 scale, which is used in mild to moderate AD studies.[76]

The data collected for memantine on reduction in degree of care by caregivers or institutions, or on institutionalisation rates were not made public[19] No data were available for the endpoint mortality.

One study (MD-02) found a small beneficial effect (55% vs 45% unchanged or improved on CIBIC+, SIB 3.4 points improvement, NPI 3.8 points improvement) combining memantine and donepezil as opposed to donepezil monotherapy for 6 months in AD patients with MMSE 4-14.[14] The adverse event profile was similar to that of donepezil alone. The findings on cognition and global impression were confirmed in a second similar trial MD-50 in AD patients with a MMSE 3-14.(http://www.forestclinicaltrials.com) Another trial (MD-12) where memantine or placebo was added to a stable dose of ChEIs in patients with MMSE 10-22 did however not confirm these findings.[77]

4.4 TREATMENTS FOR DEPRESSION AND BEHAVIORAL PROBLEMS

Institutionalization of AD patients and caregiver distress are often the result of behavioural problems of the AD patient.[12, 78]

Table 6. Systematic Reviews of Pharmacologic management of depression and behavioral problems in dementia patients

Reference	Search date
BCFI. Transparantiefiche. Geneesmiddelen bij Dementie. July 2008 (http://www.bcfi.be/pdf/tft/TN_DEM.pdf)	January 2008
Maidment ID, Fox CG, Boustani M, Rodriguez J, Brown RC, Katona CL. Efficacy of memantine on behavioral and psychological symptoms related to dementia: a systematic meta-analysis. Ann Pharmacother. 2008;42(1):32-8.	July 2007
Herrmann N, Lanctot KL. Pharmacologic management of neuropsychiatric symptoms of Alzheimer disease. Can J Psychiatry. 2007;52(10):630-46.	March 2007
Katz I, de Deyn PP, Mintzer J, Greenspan A, Zhu Y, Brodaty H. The efficacy and safety of risperidone in the treatment of psychosis of Alzheimer's disease and mixed dementia: a meta-analysis of 4 placebo-controlled clinical trials. Int J Geriatr Psychiatry. 2007;22(5):475-84.	
Thompson S, Herrmann N, Rapoport MJ, Lanctot KL. Efficacy and safety of antidepressants for treatment of depression in Alzheimer's disease: a metaanalysis. Can J Psychiatry. 2007;52(4):248-55.	June 2006[79]
Yury CA, Fisher JE. Meta-analysis of the effectiveness of atypical antipsychotics for the treatment of behavioural problems in persons with dementia. Psychother Psychosom. 2007;76(4):213-8.	2006[80]
Zuidema SU, van Iersel MB, Koopmans RTCM, Verhey FRJ, Olde Rikkert MGM. [Efficacy and adverse reactions of antipsychotics for neuropsychiatric symptoms in dementia: a systematic review]. Ned Tijdschr Geneeskd. 2006;150(28):1565-73.	2005[81]
Grimmer T, Kurz A. Effects of cholinesterase inhibitors on behavioural disturbances in Alzheimer's disease: a systematic review. Drugs Aging. 2006;23(12):957-67.	End of 2004 ?
Daiello LA. Atypical antipsychotics for the treatment of dementia-related behaviors: an update. Med Health R I. 2007;90(6):191-4.	
Franco KN, Messinger-Rapport B. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. J Am Med Dir Assoc. 2006;7(3):201-2.	June 2004[82]
Carson S, McDonagh MS, Peterson K. A systematic review of the efficacy and safety of atypical antipsychotics in patients with psychological and behavioral symptoms of dementia. J Am Geriatr Soc. 2006;54(2):354-61.	
Ballard C, Waite J, Birks J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev. 2006(1):CD003476	December 2004[83]
Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006;14(3):191-210.	?
SBU. Dementia – Diagnostic and Therapeutic Interventions. A systematic review. Volume 2. June 2008.	July 2004
Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA. 2005;293(5):596-608.	July 2004
De Lepeleire J, Ylieff M, Buntinx F, Bouckaert F, Steeman E, Van Tichelt K, editors. Omgaan met dementerenden. Aanbevelingen van het Qualidem-project. : Garant; 2007	May 2003

4.4.1 Antidepressants

Depression, often including symptoms of anxiety, is common in dementia and may worsen cognitive impairment. The best approach to diagnosing depression in the contex of dementia is not yet clear.[68]

There is only limited evidence supporting the efficacy of antidepressants in dementia patients.[8] In a meta-analysis based on only 82 subjects treated in 5 studies (antidepressants were imipramine, clomipramine, sertraline, or fluoxetine), a NNT of 5 (95%CI, 3 to 59) was calculated.[79]

If antidepressive drugs are used, agents with an anticholinergic profile should be avoided, and the starting dose should be low.[8] SBU concludes the research on the treatment of depression in patients with severe dementia is inconclusive.[14] There is limited evidence that SSRIs are tolerated well and are effective for the treatment of depression in mild to moderate dementia.(Evidence Grade 3).[14, 78] Tricyclic antidepressants have shown conflicting results, and there is only limited evidence for an effect on depressive symptoms in dementia (Evidence Grade 3).[14]

Tricyclic antidepressants produce prominent side-effects, including reduced cognitive functions, in dementia (Evidence Grade 3).[14, 78]

There is limited evidence that serotonin-active antidepressants reduce behavioral symptoms in dementia (Evidence Grade 3).[14] According to Hermann and Lanctôt, more data are required to determine the efficacy of trazodone (a serotinine modulator) and the SSRIs for the treatment of agitation and other BPSD.[78] Negative results were obtained in studies evaluating the effect of antidepressive drugs on agitation in dementia patients.[10] With the possible exception of citalopram, antidepressant agents did not reduce agitation.[82]

4.4.2 Treatment of Behavioral and Psychological Signs and Symptoms of dementia

Psychotic symptoms are seen in 34% of dementia patients, but the use of antipsychotic drugs has been mainly to treat behavioral symptoms included in the concept of BPSD (Behavioral and Psychological Signs and Symptoms of dementia).[14] The majority of the studies did not differentiate dementia diagnoses. BPSD may account for up to 30% of the total cost of care of dementia patients.[78] A frequently used rather broad scale to evaluate BPSD is the 144 point NPI scale, rating the frequency and severity of 12 behaviors.

Before one considers a pharmacological intervention, one should rule out underlying disorders, conditions which could explain the psychosis (eg delirium) or reduce the triggers, and try non-pharmacological interventions, unless the patient or others are at risk of harm.[8, 78]

As a reminder, approval of a pharmaceutical intervention typically requires evidence based on a minimum of two high-quality RCTs. As discussed in the section on non-pharmaceutical interventions it is important to note that for none of the non-drug interventions this level of evidence has been demonstrated.[78]

The results obtained with ChEIs for the treatment of behavioral problems in AD patients are contradictory. Moreover, in the studies demonstrating a positive effect, the clinical relevance has been questioned. For memantine, the positive effect on neuropsychiatric symptoms remained limited to the subgroup of moderate and severe AD, and was not detected in AD patients with mild to moderate disease.[10] In a recent meta-analysis an improvement in NPI of nearly 2 points was found for memantine.[84] Hermann and Lanctôt conclude there is emerging evidence that ChEIs and memantine have beneficial effects on behaviour. They suggest that for untreated patients with mild to moderate BPSD, initial treatment with a ChEI and (or) memantine might be preferable to treatment with other psychotropic agents, given the efficacy of the former for cognition and function as well.[78]

In combination with donepezil, but not in monotherapy, memantine slightly improves BPSD in moderately severe (MMSE 10-14) AD patients (effect size < 0.5 SD).[19]

This was howver not confirmed in another trial in patients mild or moderate AD (MMSE 10-22) where memantine or placebo was added to ChEIs.[77]

Antipsychotics

The best-studied interventions for BPSD are the antipsychotics. Use of antipsychotics (including atypical antipsychotics) has however been associated with an increased incidence of stroke, especially in dementia patients,[85] as well as an increased mortality.[10] According to Zuidema et al, the adverse reactions were inadequately described in the published data, making it impossible to confirm the warning of an increased risk of mortality.[81]

FDA notified healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.(FDA alert June, 16 2008). Also EMEA confirmed this finding (http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional_%20Antipsychotics_Article5.3-Appendix1-CHMPAR.pdf). AD patients with severe non-cognitive symptoms (psychosis and/or agitated behaviour causing significant distress) may be offered treatment with an antipsychotic drug provided there has been a full discussion with the person with dementia and/or carers about the possible benefits and risks of treatment.[1]

The evidence of an increased risk of death following atypical antipsychotic drug treatment is strong (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. However, 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.

Especially dementia patients with Lewy-body pathology patients are highly sensitive to the extrapyramidal side-effects of antipsychotics. Because extrapyramidal side-effects are somewhat less frequent, atypical antipsychotics are to be preferred in dementia patients, using the start low, go slow principle.[8] However, Zuidema et al concludes the efficacy of typical and atypical antipsychotics is comparable, only low-dose risperidone seems to be associated with fewer (extrapyramidal) side effects.[81]

Trials studying antipsychotics for behavioral disturbances associated with dementia continue to show contradictory results.[10] Especially studies in outpatients, often with less severe BPSD, turned out negative.[78] 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).[14, 78] Two meta-analyses conclude that atypical antipsychotics are probably not very effective for the management of BPSD.[80, 86]

Evidence suggests that risperidone and olanzapine are useful in reducing aggression and risperidone reduces psychosis, but both are associated with serious adverse cerebrovascular events and extrapyramidal symptoms. Despite the modest efficacy, the significant increase in adverse events confirms that neither risperidone nor olanzapine should be used routinely to treat dementia patients with aggression or psychosis unless there is severe distress or risk of physical harm to those living and working with the patient.[83] The efficacy of risperidone was stronger in patients with severe symptoms, and the safety profile in AD did not differ from that in other forms of dementia.[87]

Other agents

Few RCTs have been published on BPSD with antiepileptic drugs. In a well-designed RCT carbamazepine had small but significant effects on behavioral symptoms, but its use in elderly is limited because of tolerability and drug-drug interaction issues.[78] Valproate and divalproex are better tolerated but were shown to have no clinical value.[14, 78]

The use of benzodiazepines in elderly in general has been associated with excessive sedation, falls and cognitive impairment.[14] Methodological problems limit the interpretation of the RCTs.[78]

Key Points

Ginkgo biloba

- **Recent systematic reviews conclude the evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia is inconsistent and unreliable. Also in MCI no indications of efficacy were found.**

Inhibitors of acetylcholinesterase (ChEIs)

- **ChEIs significantly improve cognitive function from a statistical point of view. Around 10 patients need to be treated for each clinically detectable improvement. The CIBIC+ is improved or maintained in 57-75% of patients versus 42-56% of placebo patients.**
- **For all 3 ChEIs, there are indications of a minor benefit in activities of daily living. No interpretable data were available (or no indication of benefit for donepezil) for prevention of placement in a nursing home (institutionalisation).**
- **Both effects and adverse event rates (mainly anorexia, nausea, vomiting and diarrhoea) are dose-dependent. After drug discontinuation both effects and side-effects disappear.**

Memantine

- **The effect of memantine monotherapy on cognitive function is small, or even not statistically significant.**
- **The improvements in clinician's global impression, ADL and for psychopathology are minor. The clinical relevance of these findings is questionable. The data collected for memantine on reduction in degree of care by caregivers or institutions were not made public, nor were data made public for the endpoint prevention of institutionalisation.**
- **Two RCTs in which memantine was combined for 6 months with ChEIs in AD patients with a MMSE 3-14 reported positive results for cognitive function and CIBIC+ versus ChEI monotherapy, but this was not confirmed in a similar trial in AD patients with a MMSE 10-22.**

Antipsychotics and antidepressants

- **It is now well established that the use of both typical and atypical antipsychotics in patients with dementia is associated with an increased mortality rate and that their use should be restricted, eg to hostile, aggressive patients.**
- **The optimal diagnosis and management of depression in AD patients is not well-defined.**

5 COST-EFFECTIVENESS OF ALZHEIMER'S DISEASE INTERVENTIONS: REVIEW OF THE LITERATURE.

5.1 REVIEW METHODS

5.1.1 Literature search strategies

The strategies for searching the literature were aimed at providing an answer to the following questions of interest:

- Is there scientific evidence to support the cost-effectiveness of pharmacologic treatments in Alzheimer's patients?
- Is there scientific evidence to support the cost-effectiveness of non-pharmacological treatments in Alzheimer or dementia's patients?

The searches for the published economic literature were performed by consulting various databases up to the end of August 2008.

5.1.1.1 Health technology assessment (HTA) reports

The CRD HTA database was consulted to retrieve HTA reports using the search terms "MeSH Alzheimer Disease EXPLODE 1 2 3" or "MeSH Dementia EXPLODE 1 2". The websites of the HTA institutes listed in the International Network of Agencies for Health Technology Assessment (INAHTA) website were also consulted to retrieve additional references. Seventy-nine (79) citations were returned from the CRD HTA database for both Alzheimer disease and Dementia. The search on the HTA websites allowed the identification of one additional citation.[21]

5.1.1.2 Economic evaluations and reviews of economic evaluations

The NHS EED(CRD), Medline(OVID), EMBASE and Econlit(OVID) databases were searched to identify full economic evaluations and reviews of full economic evaluations of non-pharmacologic and pharmacologic treatments for Alzheimer's disease patients, and of non-pharmacologic treatments for Dementia patients. The search was restricted to articles published after 2004, which corresponds to the time limit of the literature review performed by Loveman et al.,[72] an HTA report identified in the pre-assessment phase of this project. No restrictions on language were imposed. The details of the search strategies used in each database for each research question are provided in appendix. A brief description of the search results is provided here (Table 7):

Table 7: Summary of the results of the cost-effectiveness literature searches

Database	Date of database search	Number of citations identified
Pharmacologic and non-pharmacologic treatment in AD patients		
CRD EED	January 2004 – August 2008	50
OVID MEDLINE	January 2004 – August 2008	235
EMBASE	January 2004 – August 2008	333
OVID ECONLIT	January 2004 – August 2008	1
Total		*619*
Non-pharmacologic treatment in dementia patients		
CRD EED	January 2004 – September 2008	36
OVID MEDLINE	January 2004 – September 2008	41

EMBASE	January 2004 – September 2008	52
OVID ECONLIT	January 2004 – September 2008	2
Total		*131*

Total Research questions 1 and 2	750
Duplicates within Research question 1	152
Duplicates within Research question 2	22
Duplicates between Research questions 1 and 2	22
Unique citations for Research questions 1 and 2	**554**

5.1.2 Selection criteria

5.1.2.1 HTA reports

Only the most recent HTAs including a qualitative systematic review of the economic literature related to the above questions of interest were retained.

5.1.2.2 Economic evaluations and reviews of economic evaluations

All retrieved references were assessed against pre-defined selection criteria, in terms of population, intervention, and design (Table 8) in a two-step procedure: initial assessment of the title, abstract, and keywords, followed by a full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, consideration of the citation was directly made on the basis of full-text assessment. Reference lists of the selected studies were checked for additional relevant citations. The selected full economic evaluations, i.e. the studies comparing at least two alternative treatments in terms of costs and outcomes (see classification in appendix), were then summarised in in-house data extraction forms.

Table 8: Economic evaluations selection criteria

	Inclusion criteria	Exclusion criteria
Pharmacologic and non-pharmacologic treatment in AD patients		
Population	Patients suffering from AD	Other patient groups
Intervention	Pharmacologic and non-pharmacologic treatment	Other interventions, diagnostic tools
Design	Full economic evaluations (primary or secondary studies)	Partial economic evaluations, etc
Non-pharmacologic treatment in dementia patients		
Population	Patients suffering from dementia	Other patient groups
Intervention	Non-pharmacologic treatment	Other interventions, diagnostic tools
Design	Full economic evaluations (primary or secondary studies)	Partial economic evaluations, etc

5.1.3 Selection process

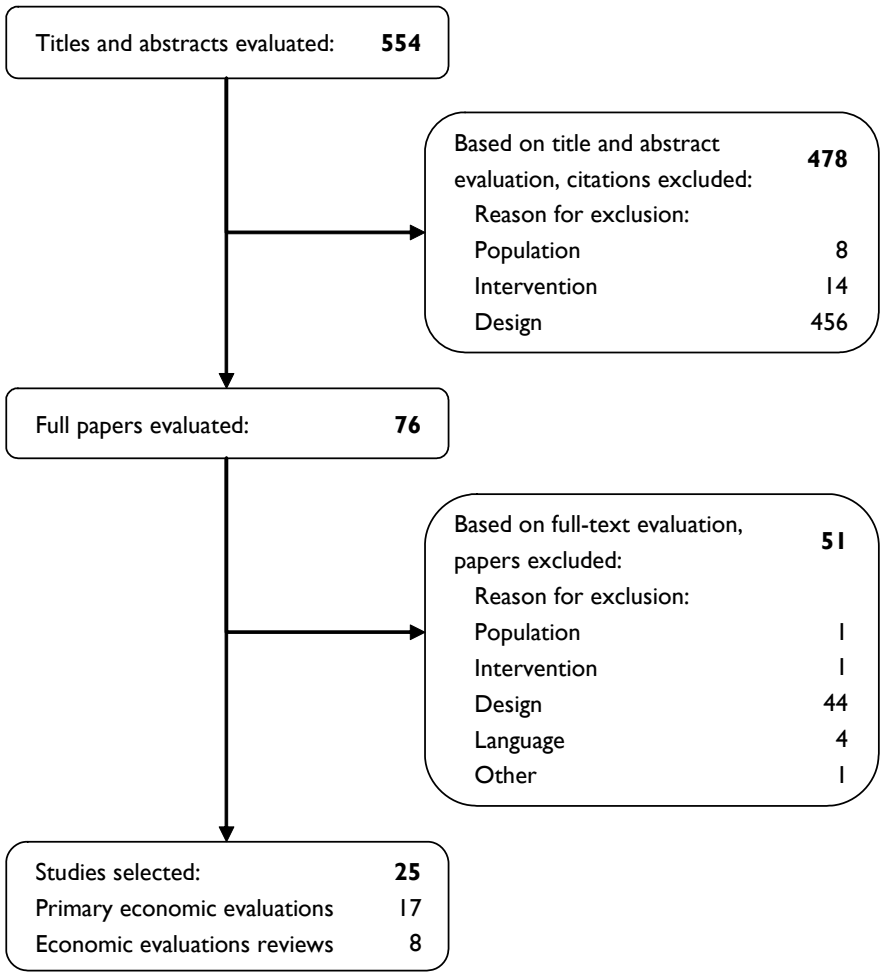
5.1.3.1 HTA reports

Of the 80 HTA citations identified, 5 HTA reports including a systematic review of the economic literature on Alzheimer disease or dementia treatments fulfilled the selection criteria.[1, 21, 72, 88, 89] Of those, the two eldest HTA reports[88, 89] were discarded since both reports were updated and included in most recent HTAs' reviews.[21, 72]

5.1.3.2 Economic evaluations and reviews of economic evaluations

Altogether, the searches on the NHS EED (CRD), Medline(OVID), EMBASE and Econlit(OVID) returned 554 unique citations which were assessed against our inclusion criteria (Table 8). Of these 554 references, 478 did not meet the inclusion criteria based on title and abstract evaluation. Of the 76 citations retained for full-text assessment, 51 were excluded: 44 studies had an inappropriate design, 1 did not meet the population criteria, 1 did not meet the intervention criteria, 4 were not published in English and 1 could not be obtained.[90] Twenty-five (25) studies were thus retained with our search strategies; 17 were primary economic evaluations[43, 72, 91-105] and 8 were reviews of economic evaluations.[106-113] The flow chart of this selection process is presented in Figure 1.

Figure 1: Identification and selection of the economic evaluations and reviews of economic evaluations of Alzheimer disease or dementia treatments



5.1.4 Brief presentation of the studies selected

5.1.4.1 Systematic reviews of economic evaluations

Table 9 lists the selected systematic reviews of the economic literature; either derived from the HTA reports retained (3) or as review articles separately published (8).

Table 9: Systematic reviews of the cost-effectiveness of Alzheimer disease or dementia treatments (search date: 2004 – August 2008)

Reference	Articles included	Search limit
Reviews of pharmacological treatments		
Oremus M. Systematic review of economic evaluations of Alzheimer's disease medications. Expert Review of Pharmacoeconomics and Outcomes Research. 2008;8(3):273-89.[109]	33	12/2007
Wimo A, Norlund A. Cost-effectiveness of treatments for Alzheimer's dementia. Expert Review of Pharmacoeconomics and Outcomes Research. 2007;7(1):83-90.[1121]	13	07/2004
Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, et al. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. Health Technol Assess. 2006;10(1).[72]	20	02/2004
Kirby J, Green C, Loveman E, Clegg A, Picot J, Takeda A, et al. A systematic review of the clinical and cost-effectiveness of memantine in patients with moderately severe to severe Alzheimer's disease. Drugs & Aging. 2006;23(3):227-40.[1082]	5	07/2004
Wimo A. Cost effectiveness of cholinesterase inhibitors in the treatment of Alzheimer's disease: a review with methodological considerations. Drugs & Aging. 2004;21(5):279-95.[110]	11	07/2003
Reviews of pharmacological and non-pharmacological treatments		
SBU. Dementia – Caring, Ethics, Ethnical and Economical Aspects. A systematic review. Volume 3. June 2008.[21]	19	07/2004
Wimo A, Norlund A. Commentary on "Health economics and the value of therapy in Alzheimer's disease." Cost-effectiveness studies. Alzheimer's and Dementia. 2007;3(3):157-61.[1131]	20	07/2004
Wimo A. Clinical and economic outcomes--friend or foe? Int Psychogeriatr. 2007;19(3):497-507.[1111]	19	07/2004
Reviews of non-pharmacological treatments		
NICE-SCIE. Dementia: supporting people with dementia and their carers in health and social care. Care guideline. National Institute for Health and Clinical Excellence (NICE); 2006. Clinical Guideline 42. [1]	6	2006
Reviews of simulation models		
Cohen JT, Neumann PJ. Decision analytic models for Alzheimer's disease: State of the art and future directions. Alzheimer's and Dementia. 2008;4(3):212-22.[106]	22	2005
Green C. Modelling disease progression in Alzheimer's disease: a review of modelling methods used for cost-effectiveness analysis. Pharmacoeconomics. 2007;25(9):735-50.[107]	22	12/2005

1. Derived from SBU.[21] 2. Derived from Loveman et al.[72]

The three reviews performed by Wimo et al.[111-113] in 2007 were all derived from the HTA report conducted by the Swedish Council on Technology Assessment in Health Care (SBU) and published in 2008.[21] Likewise, Kirby et al.'s review[108] reports the results of the HTA of Loveman et al.[72], which was commissioned by the National Institute for Health and Clinical Excellence (NICE).

This leaves thus 7 unique reviews:

- 5 reviews on the cost-effectiveness of treatments against AD or dementia:
  - 3 reviews of pharmaceutical treatments only,[72, 109, 110]
  - 1 review of non-pharmaceutical treatments only,[1]
  - 1 review of both pharmaceutical and non-pharmaceutical treatments,[21]
- and 2 reviews critically assessing the models of AD progression used in the economic evaluations.[106, 107]

The articles included in each of those reviews are listed in Table 10.

Table 10: Content of the systematic reviews of pharmacological and non-pharmacological treatments in Alzheimer disease or dementia patients.

Treatment	Reference	HTA's reviews			Economic evaluations' reviews						Models' review	
		SBU, 2008	NICE-SCIE, 2006	Loveman et al., 2006	Oremus, 2008	Wimo et al., Alzh Dem, 2007	Wimo et al., Expert Rev, 2007	Wimo, Int Psycho, 2007	Kirby et al., 2006	Wimo, 2004	Cohen et al., 2008	Green, 2007
Time coverage of the literature review :		*07/2004*	*2006*	*02/2004*	*12/2007*	*07/2004*	*07/2004*	*07/2004*	*07/2004*	*07/2003*	*2005*	*12/2005*
ChEIs	Green C, Picot J, Loveman E, Takeda A, Kirby J, Clegg A. Modelling the cost effectiveness of cholinesterase inhibitors in the management of mild to moderately severe Alzheimer's disease. Pharmacoecon. 2005;23(12):1271-				x						x	x
	Caro J, Getsios D, Migliaccio-Walle K, Ishak J, El-Hadi W, AHEAD Study Group. Rational choice of ChIs for the treatment of Alzheimer's disease in Canada: a comparative economic analysis. BMC Geriatrics 2003; 3:6				x							x
	McDonnell J, Redekop WK, van der Roer N, Goes E, Ruitenberg A, et al. The cost of treatment of AD in The Netherlands: a regression based simulation model. Pharmacoeconomics 2001;19:379 -90										x	
Donepezil	Teipel SJ, Ewers M, Reisig V, Schweikert B, Hampel H, Happich M. Long-term cost-effectiveness of donepezil for the treatment of Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci. 2007;257(6):330-6.				x							
	Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwoods E, et al. AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease: randomized double-blind trial. Lancet. 2004;	((x))		x								x
	Fagnani F, Lafuma A, Pechevis M, Rigaud AS, et al. Donepezil for the treatment of mild to moderate Alzheimer's disease in France: economic implications. Dement Geriatr Cogn Disord. 2004;17(1-2):5–13.			x	(x)						x	x
	Feldman H, Gauthier S, Hecker J, Vellas B, Hux M, Xu Y et al. Donepezil MSAD Study Investigators Group. Economic evaluation of donepezil in moderate to severe Alzheimer disease.Neurology. 2004, 63(4):644-50.	((x))			((x))							
	Wimo A, Winblad B, Engedal K, Soininen H, et al. An economic evaluation of donepezil in mild to moderate AD: results of a 1-year, doubleblind, randomized trial. Dement Geriatr Cogn Disord. 2003; 15:44–54.	((x))		x	((x))							x
	Ikeda S, Yamada Y, Ikegami N. Economic evaluation of donepezil treatment for Alzheimer's disease in Japan. Dement Geriatr Cogn Disord. 2002; 13:33–9.	x		x	x	x	x	x		x	x	x
	Fillit H, Gutterman EM, Lewis B. Donepezil use in managed Medicare: effect on health care costs and utilization. Clin Ther. 1999;21(12):2173-85.	Excluded										
	Jönsson L, Lindgren P, Wimo A, Jönsson B, Winblad B. The cost-effectiveness of donepezil therapy in Swedish patients with Alzheimer's disease: a Markov model. Clin Ther. 1999; 21:1230–40.	x		x	x	x	x	x		x	x	x
	O'Brien BJ, Goeree R, Hux M, Iskedjian M,Blackhouse G, Gagnon M, et al. Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. J Am Geriatr Soc. 1999;47:570–8.	x		x	x	x	x	x		x	x	x
	Neumann PJ, Hermann RC, Kuntz KM, Araki SS, Duff SB, Leon J, et al. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. Neurology 1999;52:1138–45.	x		x	x	x	x	x		x	x	x
	Stewart A, Phillips R, Dempsey G.Pharmacotherapy for people with Alzheimer's disease: a Markov-cycle evaluation of five years'therapy using donepezil. Int J Geriatr Psychiatry 1998;13:445–53.	x		x	x	x	x	x		x	x	x
	Small GW. Donohue JA. Brooks RL. An economic evaluation of donepezil in the treatment of Alzheimer's disease. Clinical Therapeutics 1998; 20(4):838-50, 1998	Excluded			((x))							
	Stein K. Donepezil in the treatment of mild to moderatesenile dementia of the Alzheimer type (SDAT). Development and Evaluation Committee Report,69. Bristol: NHS Executive South and West; 1997.			x								
Rivastigmine	Marin D, Amaya K, Casciano R, Puder KL, Casciano J, Chang S, et al. Impact of rivastigmine on costs and on time spent in caregiving for families of patients with Alzheimer's disease. Int Psy 2003; 15(4):385-98	Excluded			(x)						x	
	Hauber AB, Gnanasakthy A, Snyder EH, Bala MV, Richter A, Mauskopf JA. Potential savings in the cost of caring for Alzheimer's disease - treatment with rivastigmine. Pharmacoeconomics 2000;17:351-60.	(x)		x							x	x
	Hauber AB, Gnanasakthy A, Mauskopf JA. Savings in the cost of caring for patients with Alzheimer's disease in Canada: an analysis of treatment with rivastigmine. Clin Ther 2000;22:439-51.	x		x	(x)	x	x	x		x	x	x
	Fenn P, Gray A. Estimating long term cost savings from treatment of Alzheimer's disease: a modelling approach. Pharmacoeconomics 1999; 16:165-74.	(x)		x	(x)						x	x
	Stein K. Rivastigmine (Exelon) in the treatment of senile dementia of the Alzheimer type (SDAT). Development and Evaluation Committee Report, 89. Bristol: NHS Executive South and West; 1998.			x								

x = full economic evaluation included, (x) = model-based partial economic evaluation included, ((x)) = empirical partial economic evaluation included

Table 10. continued.

Treatment	Reference	HTA's reviews			Economic evaluations' reviews						Models' review	
		SBU, 2008	NICE-SCIE, 2006	Loveman et al., 2006	Oremus, 2008	Wimo et al., Alzh Dem, 2007	Wimo et al., Expert Rev, 2007	Wimo, Int Psycho, 2007	Kirby et al., 2006	Wimo, 2004	Cohen et al., 2008	Green, 2007
Time coverage of the literature review :		*07/2004*	*2006*	*02/2004*	*12/2007*	*07/2004*	*07/2004*	*07/2004*	*07/2004*	*07/2003*	*2005*	*12/2005*
Galantamine	Caro J, Salas M, Ward A, Getsios D, et al. Assessing the health and economic impact of galantamine treatment in patients with AD in the health care systems of different countries. Drugs & Aging 2004; 21(10):677-86				x						x	x
	Migliaccio-Walle K, Getsios D, Caro JJ, Ishak KJ, O'Brien JA, Papadopoulos G, et al. Economic evaluation of galantamine in the treatment of mild to moderate AD in the United States. Clin Ther 2003;25:1806-25.	x		x	(x)	x	x	x		x	x	x
	Ward A, Caro JJ, Getsios D, Ishak K, O'Brien J, Bullock R, et al. Assessment of health economics in Alzheimer's disease (AHEAD): treatment with galantamine in the UK. Int J Geriatr Psychiatry 2003;18:740-7.	x		x	x	x	x	x		x	x	x
	Garfield FB, Getsios D, Caro JJ, Wimo A, Winblad B. Assessment of Health Economics in Alzheimer's Disease (AHEAD): treatment with galantamine in Sweden. Pharmacoeconomics 2002; 20:629-37.	x		x	(x)	x	x	x		x	x	x
	Caro JJ, Salas M, Ward A, Getsios D, Mehnert A. Economic analysis of galantamine in the treatment of patients with mild to moderate Alzheimer's disease in The Netherlands. Dement Geriatr Cogn Disord 2002;14:84-9.	x		x	x	x	x	x		x	x	
	Getsios D, Caro JJ, Caro G, Ishak K. Assessment of health economics in Alzheimer's disease (AHEAD): galantamine treatment in Canada. Neurology 2001;57:972-8.	x		x	(x)	x	x	x		x	x	x
	Caro JJ, Getsios D, Migliaccio-Walle K, Raggio G, Ward A. Assessment of health economics in Alzheimer's disease (AHEAD) based on need for full-time care. Neurology 2001;57:964 -71.										x	x
Memantine	Gagnon M, Rive B, Hux M, Guilhaume C. Cost-effectiveness of memantine compared with standard care in moderate to-severe Alzheimer disease in Canada. Can J Psychiatry. 2007;52(8):519-26.				x							
	Weycker D, Taneja C, Edelsberg J, Erder MH, Schmitt FA, Setyawan J, et al. Cost-effectiveness of memantine in moderate-to-severe AD patients receiving donepezil. Curr Med Res Opin. 2007;23(5):1187-97.				x							
	Antonanzas F, Rive B, Badenas JM, Gomez-Lus S, Guilhaume C. Cost-effectiveness of memantine in community-based AD patients: An adaptation in Spain.[see comment]. Eur J Health Econ. 2006;7(2):137-44.				x							
	Jonsson L. Cost-effectiveness of memantine for moderate to severe Alzheimer's disease in Sweden. Am J Geriatr Pharmacother. 2005;3(2):77-86.				x	x		x			x	x
	François C, Sintonen H, Sulkava R. The costeffectiveness of memantine in moderately severe to severe Alzheimer's disease. A Markov model in Finland. Clin Drug Invest 2004;27:373–84.	x		x	x	x	x	x	x			x
	Jones R, McCrone P, Guilhaume C. Cost effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. Drugs Aging 2004; 21:607–20.	x		x	x	x	x	x	x		x	x
	Wimo A. Winblad B. Stoffler A. Wirth Y. Mobius HJ. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. Pharmacoeconomics 2003; 21(5):327-40	((x))			((x))							
Non-drug	Knapp M, Thorgrimsen L, Patel A, Spector A, Hallam A, Woods B, et al. Cognitive stimulation therapy for people with dementia: cost-effectiveness analysis. British Journal of Psychiatry. 2006;188:574-80.		x									
	Martikainen J, Valtonen H, Pirttila T. Potential cost-effectiveness of a family-based program in mild Alzheimer's disease patients. Eur J Health Econ. 2004;5(2):136-42.	x	x			x		x			x	
	Nocera S, Bonato D, Telser H. The contingency of contingent valuation. How much are people willing to pay against Alzheimer's disease? Int J Health Care Finance Econ 2002;2:219-40.	x				x		x				
	Roberts, J., Browne, G., Milne, C., et al. Problem-solving counseling for caregivers of the cognitively impaired: effective for whom? Nursing Research 1999; 48: 162-172.		x									
	McGuire, R.C. (1998) A case study in CEA for computer technology used in support of caregivers with AD patients. In Information Systems Innovations for Nursing (eds. Moorhead&Delaney). CA: Sage Publications.		x									
	Wimo A, Mattson B, Krakau I, Eriksson T, Nelvig A, Karlsson G. Costutility analysis of group living in dementia care. Int J Technol Assess Health Care 1995;11:49-65.	x				x		x				
	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.	x				x		x				
	Brodaty, H. & Peters, K.E. Cost effectiveness of a training program for dementia carers. International Psychogeriatrics 1991; 3, 11-22.	(x)	x									
	Drummond MF, Mohide EA, Tew M, Streiner DL, Pringle DM, Gilbert JR. Economic evaluation of a support program for caregivers of demented elderly. Int J Technol Assess Health Care 1991;7:209-19.	x	x			x		x				
	Wimo A, Wallin JO, Lundgren K, Ronnback E, Asplund K, Mattsson B, et al. Impact of day care on dementia patients – costs, well-being and relatives' views. Fam Pract 1990;7:279-87.	x				x						

5.1.4.2 Primary full economic evaluations

Table 11 lists the 17 primary economic evaluations published after 2004 and retained.

Table 11: Primary economic evaluations of Alzheimer's disease and dementia treatments (search date: 2004 – August 2008)

References
Cholinesterase Inhibitors (n = 2)
Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, et al. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. Health Technol Assess. 2006;10(1):iii-iv.[72]
Green C, Picot J, Loveman E, Takeda A, Kirby J, Clegg A. Modelling the cost effectiveness of cholinesterase inhibitors in the management of mild to moderately severe Alzheimer's disease. Pharmacoeconomics. 2005;23(12):1271-82.[98]
Donepezil (n = 4)
Fuh JL, Wang SJ. Cost-effectiveness analysis of donepezil for mild to moderate Alzheimer's disease in Taiwan. International Journal of Geriatric Psychiatry. 2008;23(1):73-8.[96]
Teipel SJ, Ewers M, Reisig V, Schweikert B, Hampel H, Happich M. Long-term cost-effectiveness of donepezil for the treatment of Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci. 2007;257(6):330-6.[102]
Feldman H, Gauthier S, Hecker J, Vellas B, Hux M, Xu Y, et al. Economic evaluation of donepezil in moderate to severe Alzheimer disease. Neurology. 2004;63(4):644-50.[94]
Fagnani F, Lafuma A, Pechevis M, Rigaud AS, Traykov L, Seux ML, et al. Donepezil for the treatment of mild to moderate Alzheimer's disease in France: the economic implications. Dementia & Geriatric Cognitive Disorders. 2004;17(1-2):5-13.[93]
Galantamine (n = 1)
Caro J, Salas M, Ward A, Getsios D, Migliaccio-Walle K, Garfield F. Assessing the health and economic impact of galantamine treatment in patients with Alzheimer's disease in the health care systems of different countries. Drugs & Aging. 2004;21(10):677-86.[92]
Memantine (n = 6)
Gagnon M, Rive B, Hux M, Guilhaume C. Cost-effectiveness of memantine compared with standard care in moderate-to-severe Alzheimer disease in Canada. Can J Psychiatry. 2007;52(8):519-26.[97]
Weycker D, Taneja C, Edelsberg J, Erder MH, Schmitt FA, Setyawan J, et al. Cost-effectiveness of memantine in moderate-to-severe Alzheimer's disease patients receiving donepezil. Curr Med Res Opin. 2007;23(5):1187-97.[103]
Antonanzas F, Rive B, Badenas JM, Gomez-Lus S, Guilhaume C. Cost-effectiveness of memantine in community-based Alzheimer's disease patients: An adaptation in Spain. Eur J Health Econ. 2006;7(2):137-44.[91]
Jonsson L. Cost-effectiveness of memantine for moderate to severe Alzheimer's disease in Sweden. Am J Geriatr Pharmacother. 2005;3(2):77-86.[100]
Jones RW, McCrone P, Guilhaume C. Cost-effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. Drugs & Aging. 2004;21(9):607-20.[99]
Francois C, Sintonen H, Sulkava R, Rive B. Cost effectiveness of memantine in moderately severe to severe Alzheimer's disease: A Markov model in Finland. Clinical Drug Investigation. 2004;24(7):373-84.[95]

Non-pharmacological treatments (n = 4)

Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F. Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial. Health Technol Assess.2008, 12(4):iii.[104]

Graff MJL, Adang EMM, Vernooij-Dassen MJM, Dekker J, Jonsson L, Thijssen M, et al. Community occupational therapy for older patients with dementia and their care givers: cost effectiveness study. BMJ. 2008;336(7636):134-8.[43]

Knapp M, Thorgrimsen L, Patel A, Spector A, Hallam A, Woods B, et al. Cognitive stimulation therapy for people with dementia: cost-effectiveness analysis. British Journal of Psychiatry. 2006;188: 574-80.[105]

Martikainen J, Valtonen H, Pirttila T. Potential cost-effectiveness of a family-based program in mild Alzheimer's disease patients. Eur J Health Econ. 2004;5(2):136-42.[101]

The literature search allowed the identification of two recent and comprehensive reviews of economic evaluations of pharmaceutical[109] and non-pharmaceutical[1] interventions (Table 9). Therefore, of the 17 primary economic evaluations identified since 2004 (Table 11), only those not already included in any of both reviews have been summarised in in-house data extraction forms and in the discussion below. This corresponds to 2 economic evaluations of non-pharmaceutical interventions published after 2006 (the time limit of the NICE-SCIE review[1]),[43, 104] and 2 economic evaluations of pharmaceutical interventions (1 evaluations published after the end of 2007, the time limit of the Oremus review,[109] and 1 older evaluation not yet included in this review).[72, 96] The extraction forms of those economic evaluations can be found in appendix.

5.2 OVERVIEW OF THE ECONOMIC EVALUATIONS

In this section we report the main findings of the selected reviews of economic evaluations of pharmacological (research question 1) and non-pharmacological (research question 2) treatments for Alzheimer disease. Whenever appropriate, the methodology and the results of recent primary full economic evaluations are also described. A critical assessment of the assumptions and the methodology used by those studies is provided in the conclusions section.

5.2.1 Research question 1: Pharmacological interventions in AD patients

5.2.1.1 Summary of the systematic reviews

Donepezil, rivastigmine and galantamine in mild to moderately severe AD

Wimo[110] reviewed 11 model-based full economic evaluations of ChEI's in the treatment of AD. There were 5 studies on donepezil, 1 on rivastigmine and 5 on galantamine, all published before 2004 (see Table 10 for the studies reviewed). According to Wimo,[110] ChEIs for mild-to-moderate AD have positive effects in terms of efficacy. Combined with cost data, in most cases models indicate cost-effectiveness but variations in the sensitivity analyses show that the assumed cost-effectiveness is not robust. Also, due to methodological considerations, the validity of the models was difficult to judge. It was further not possible to state that one ChEI is more cost-effective than another. Wimo[110] concludes that although models tend to indicate cost-effectiveness, there is a great need for longer-term empirical data on resource use, costs and outcomes (including quality of life data).

Loveman et al.[72] reviewed 9 full economic evaluations on the cost-effectiveness of donepezil, 4 on rivastigmine and 5 on galantamine. All studies were published before February 2004 and used placebo/usual care as comparator.

Regarding the cost-effectiveness of d*onepezil*, studies have presented a variety of conclusions. While donepezil treatment was mostly reported to be cost saving (often based on the inclusion of informal care), other studies predicted additional incremental costs associated with the treatment. However all studies presented donepezil as having a beneficial effect on delay in disease progression (using MMSE cognitive function scores to define the stages of disease severity),

QALYs gained or as reduced time in need of full-time care. According to Loveman et al.,[72] the wide range of results seen in the literature is not surprising given the diverse country settings, the variations in the perspective of the studies and the differences in the types of resources that were included in the cost estimates; and also given the differences in the way the models were constructed. For studies reporting a cost increase, some interpretation is required on whether the cognitive benefits appear meaningful compared with the additional costs.

The four published economic evaluations reporting on the cost-effectiveness of *rivastigmine* all found patient benefits based almost solely on methods involving MMSE as a measure of cognitive function, with rivastigmine treatment inducing a delay in disease progression. Two studies further report cost savings over time, one without including the costs for rivastigmine and the other form a societal perspective. In the two other studies, rivastigmine treatment was described as cost incurring from an unclear or health sector perspective.

The 5 economic evaluations of *galantamine* included in Loveman et al.[72] all used the same model (the Assessment of Health Economics in Alzheimer Disease - AHEAD[114]) to estimate the cost-effectiveness of galantamine. All studies report results based on a short-term initial 6-month trial period, further extrapolated to a 10-year time-horizon model. The main findings across the economic evaluations of galantamine are patient benefits in terms of a reduction in time spent requiring full-time care (FTC) and of QALYs gained over time. Studies further generally reported cost savings (in 4 studies) or an almost cost neutral profile over time, mainly from a payers' perspective.

Altogether, the HTA report of SBU[21] and the three reviews of Wimo et al.[111-113] derived from the SBU report summarized the conclusions of 11 model-based full economic evaluations of ChEIs treatments for AD. There were 5 studies on the cost-effectiveness of donepezil, 1 on rivastigmine and 5 on galantamine, all published before July 2004 and all with placebo or usual care as the comparison alternative. SBU[21] reports that all models, except those applied in the UK (2) indicate cost savings and a positive outcome (in terms of severity of disease, QALYs or full-time care need) when treatment lasts for 2 years or longer, resulting in an incremental cost-effectiveness ratio (ICER) where treatment dominates. This result was however not robust in most sensitivity analyses. Due to a lack of complete empirical economic evaluations and due to the methodological flows of the model-based evaluations (inconsistent cost calculations, short-term efficacy data and clinical significance), SBU[21] concludes that it is impossible to make any definitive assertion regarding the cost-effectiveness of ChEIs. Their main concern is that model-based economic evaluations are only speculative. SBU's conclusion is further reinforced by the fact that the few (4) empirical cost comparison studies of ChEIs reviewed were of poor quality and did not find any significant cost difference between treated patients and controls. Therefore, since no conclusion on cost-effectiveness is evident, SBU[21] recommends that the focus should be on the clinical value of the treatment.

Of interest, SBU[21] further reported that various types of treatments are generally used in conjunction for the daily care of AD/demented patients, such as caregiver support and drug treatment. Thus it would be logical to consider economic evaluations of combined, i.e. non-pharmaceutical and pharmaceutical, treatment approaches and comparative strategies. Unfortunately, within the literature search time span of the SBU review (up to 2004), no such studies could be identified.

Oremus[109] reviewed 20 economic evaluations (comprising 10 full and 10 partial economic evaluations, i.e. cost comparisons) of ChEI's treatments for AD. There were 10 studies for donepezil, 3 for rivastigmine, 6 for galantamine and 2 for the three ChEIs altogether. The studies reviewed were all published before December 2007 and are listed in Table 10. Oremus[109] reports that treatment with ChEIs was found to be more effective than standard care in all full model-based economic evaluations, with effectiveness being mainly defined as delays to disease progression, delays to institutionalisation or as QALYs gained. In those studies, treatment with donepezil, rivastigmine or galantamine was further found to be either cost-saving or cost-incurring compared to standard care.

By contrast with SBU,[21] Oremus[109] further reports that most of the cost comparison studies showed that ChEIs medications were cost-saving relative to standard treatment. Despite this favourable picture of AD medications, Oremus[109] urges for more robust and transparent models and for the use of longer-term empirical data in the models before any firm conclusion could be drawn on the cost-effectiveness of AD medications.

Memantine in moderately severe to severe AD

Loveman et al.[72] reviewed 2 published (before February 2004) economic evaluations reporting on the cost-effectiveness of memantine. The results of Loveman et al.[72] were also reported in the separate publication of Kirby et al.[108] Compared with placebo, the two economic evaluations report cost savings over time (2 and 4 years time horizon) with memantine from a (assumed) societal perspective. Both studies further report patient benefits in terms of improvement in time spent in an independent state, time in the community and QALYs gained. Loveman et al.[72] and Kirby et al.[108] stress however the difficulty in drawing conclusions on the cost-effectiveness of memantine since both economic evaluations rest on a number of potentially misleading assumptions such as optimistic treatment effects and non-conservative cost assumptions.

SBU[21] and **Wimo et al.[111-113]** reviewed 2 model-based economic evaluations of memantine published before July 2004 (the same studies as those reviewed by Loveman et al.[72]). The studies reported that treatment with memantine provided cost savings due to the expected increase in time to dependency. Just as Loveman et al.[72], SBU[21] reports that the assumptions used in the models probably favoured the drug interventions. SBU[21] concludes that there is insufficient scientific evidence on the cost-effectiveness of memantine.

Oremus[109] reviewed 5 model-based full economic evaluations of memantine compared with standard care or placebo and 1 model-based full economic evaluation of the joint administration of memantine and donepezil in moderate to severe AD patients compared to donepezil alone. The studies were published before December 2007. In all economic evaluations, memantine (alone or in combination with donepezil) was always found more effective that its comparator. Memantine was further reported to be the dominant option (i.e. more effective and less costly) in the 5 studies comparing it with placebo/standard care, mostly from a societal perspective. Compared to donepezil alone, the memantine-donepezil combination therapy was found to be cost incurring even from a societal perspective ($404 per QALY gained, expressed in 2007 US$). Due to the absence of longer-term empirical data to feed the models and the associated questionable validity of the assumptions made, Oremus[109] states that those results should be interpreted cautiously.

5.2.1.2 Summary of recent full economic evaluations

Two recent economic evaluations of ChEIs were identified, which were not included in the literature reviews described above.

The cost-utility analysis of Fuh et al.[96] was a 5-year long model-based evaluation comparing donepezil with usual care in Taiwanese AD patients. The analysis was performed from the perspective of the health care payer, including the direct medical costs of AD care, the drug fee and the patients' out of pocket payments. Donepezil effectiveness was assessed as the delay in disease progression between the AD stages (CDR scale) and was measured by means of an observational study comparing the progression of two cohorts of Taiwanese patients, one with and one without donepezil treatment.[115] QALYs associated with each disease stage were taken from a previously published US study[116, 117] measuring the utilities from 528 AD caregivers via the HUI Mark II questionnaire. The problem of the transferability of those utilities derived from a US population to the Taiwanese population was not assessed by Fuh et al.[115] Utility scores were 0.68 (0.60–0.75), 0.54 (0.45–0.60) and 0.37 (0.25–0.45) for the mild, moderate and severe disease stages.[116, 117] During the 5-year time span, donepezil was predicted to result in a net gain of 0.5 QALYs (or about 38 days per year) and in an incremental cost of US$3647 (costs in 2006 US$). The incremental cost-effectiveness ratio was over US$7000 per QALY gained.

Taking up a societal perspective, i.e. including also the informal caregiver's time, donepezil was both more clinically effective and less costly than (i.e. dominant over) usual care. The confidence intervals around the mean values were not reported, precluding the assessment of the significance of the reported clinical advantage of donepezil.

Furthermore, due to different methodologies and to potentially different patients' profile, the clinical effectiveness of donepezil calculated in Fuh et al.[115] appeared much more favourable than that reported in other studies.[96] Finally, the transferability of the results of this Asian study to our countries is uncertain.

In their HTA report, **Loveman et al.[72]** developed a simple and unique Markov-type disease progression model to assess the cost-effectiveness of the three ChEIs against usual care in a UK context. The perspective of the study was that of the third party payer with a 5-year time-span. The model used was based on the AHEAD model developed by Caro et al.[114] to estimate the cost-effectiveness of galantamine. The rates of progression over time of the AD patients to a stage where they require full-time care (implying institutionalisation for most of them) was derived from a cohort analysis of AD patients.[114] Progression to the full-time care stage was determined by the presence of extrapyramidal symptoms (EPS) and psychotic symptoms, by the age at disease onset, by the duration of AD and by the cognitive function (MMSE). Effectiveness was measured as the mean improvement in cognitive function for each of the three products, as calculated in the meta-analysis of Loveman et al.[72] Utility values for the health states pre-FTC (0.60) and FTC (0.34) were derived and adapted from the US study of Neumann et al.[118] Conform to the current NICE guidance in the UK, future benefits and costs were discounted at a rate of 1.5% and 6% respectively. Loveman et al.[72] found that the incremental QALYs gained by each of the three ChEIs over the 5-year period were small (incremental benefits between 0 and 0.05 QALYs) and that the absolute difference in the disease progression profiles for usual care and the three drug treatment options was small (46% of the usual care cohort in the FTC health state at 5 years against 43.1% to 43.5% of the drug-treatment cohort in FTC at 5 years). Results from the probabilistic analysis showed incremental costs per QALYs of £96 800 for donepezil, £70 500 for rivastigmine and £82 000 for galantamine (£ of the year 2002–2003). Loveman et al.[72] further reported that these results were highly sensitive to a range of alternative inputs, particularly those in relation to effectiveness, health state utility and cost data. Based on those results, Loveman et al.[72] concluded that none of ChEIs appears to be cost-effective in the treatment of mild to moderately severe AD patients.

5.2.1.3 Summary of an older economic evaluation

The economic evaluation of donepezil performed by Stewart et al.[119] is critically assessed in this section of the report despite the fact that this study was published before 2004, the start time of our literature search. We follow here the recommendation of one of the experts of this review to consider this study more specifically.

The cost-effectiveness study of **Stewart et al.[119]** was a UK 5-year-long model-based economic evaluation comparing two treatment regimens with donepezil (5 mg and 10 mg) compared with usual care in patients with mild or moderate AD at the start of the treatment. The perspective of the evaluation was not stated but appeared to be societal. Costs were discounted at 6%. MMSE scores were used to define the AD disease stages. The probabilities of transition between the stages for the disease progression were obtained from epidemiological data for the untreated group and from trial data[120] for the donepezil group. In their trial, Rogers et al.[120] demonstrated a significant impact on the decline in patients' cognitive functions, as seen by the mean change in MMSE scores over 6 months. The outcome measure was reduced time in the severe AD stage (i.e. delay in disease progression). Stewart et al.[119] report that treatment with donepezil resulted in an increase in the time spent in a non-severe AD stage (1.69−1.82 versus 1.57 for mild AD; 0.87−0.98 versus 0.59 for moderate AD) and that treatment groups were almost cost neutral over the 5-year time horizon as costs were only slightly raised with donepezil compared to usual care.

The reported incremental cost-effectiveness ratios were between £1200 and £7000 per year in a non-severe state. The analysis was deterministic so that no confidence intervals were reported around the mean values. Further, there was no probabilistic sensitivity analysis.

5.2.2 Research question 2: Non-pharmacological interventions in AD or dementia patients

5.2.2.1 Summary of the systematic reviews

Patients' intervention

The **systematic review of SBU**[21, 111, 113] reports that there were only a limited number of complete economic evaluations of non-pharmaceutical interventions whose quality was inferior to that of the economic evaluations of drug interventions. SBU reviewed 2 short-term (< 1 year) trial-based[121, 122] and 1 longer-term (8 years) model-based[123] economic evaluations of non-pharmaceutical interventions aimed at dementia patients. The programmes of care evaluated were "day care" or "group living". "Day care" consisted in providing daily (5–7 hours a day) supervision, kinship and care to the AD patient by a trained and professional staff. "Group living" was defined as 24-hour supervision, kinship and care provided by professional staff in a homelike environment, where 4–10 people with dementia usually live in a unit. The patients' AD disease severity was mild in the "day care" programme and mild to moderately severe in the "group living" programme, as assessed by the clinical examination of a geriatrician.

The results of the cost-effectiveness studies were rather heterogeneous. The two trial-based economic evaluations could not demonstrate a significant difference in terms of costs or outcomes (mainly quality of life) between patients "day care" and their comparator (usual care), thereby implying neutrality in the cost-effectiveness of the alternatives considered. The model-based study reported dominance of a "group living" programme over its comparator.

The NICE-SCIE review[1] looked at the health economic evidence of non-pharmaceutical interventions aimed at maintaining the cognitive functions of the demented patient. They identified one RCT-based cost-effectiveness study comparing "cognitive stimulation therapy" (CST) to standard care for UK people with mild to moderate dementia.[105] The study reports a non-significant increase in the cost of CST versus standard care, and a significant improvement in terms of outcome for the patient (MMSE score and QoL-AD). The ICER was £75.3 per additional point on the MMSE (£ of the year 2001). For the quality of life outcome, the ICER was £22.8 per additional point of QoL-AD. NICE-SCIE[1] concludes that this may be reasonable evidence that providing CST alongside usual care for patients with mild to moderate dementia is likely to be cost-effective in the UK. This conclusion lies however on the results of a single RCT-based evaluation whose time horizon was limited to 8 weeks.[105]

Carers' intervention

SBU[21, 111, 113] reviewed 1 short-term (6 months) trial-based[124] and 2 longer-term (> 5 years) model-based[101, 125] economic evaluations of non-pharmaceutical interventions targeted at the informal carers of demented patients. The programme of care evaluated was labelled "caregiver support" and consisted in a programme aimed at supporting the informal caregivers by providing them counselling, education, emotional support and opportunities for contact when needed. The patients' disease severity ranged from mild to moderately severe.

The trial-based economic evaluation did not find any significant change in terms of costs or QoL when the "caregiver support" programme was adopted, in comparison with standard care. However, the two model-based studies found that "caregiver support" was a dominant option, i.e. "caregiver support" was both more effective and less costly than its comparators.

From this, SBU[21, 111, 113] concludes that, since the available studies are of limited quality and size, there is insufficient scientific evidence to assess the cost-effectiveness of non-pharmaceutical programmes for dementia/AD patients or their carers.

The NICE-SCIE review[1] identified 5 economic evaluations assessing a range of caregivers' interventions ("caregiver support",[23, 101] "caregiver training",[124, 126] "caregiver computer support"[127]) compared to standard community care. Just as SBU,[21, 111, 113] NICE-SCIE[1] reports that no firm conclusion can be drawn from these studies, due to their poor quality and statistical power, and the scarce evidence for each type of intervention. The same label may indeed be used for an intervention in different studies but may comprise different components.

5.2.2.2 *Summary of the full economic evaluations*

Carers' intervention

A recent cost-effectiveness study of providing support to caregivers of dementia patient was identified.[104]

The study of **Charlesworth et al.[104]** was a UK RCT-based economic evaluation comparing "social support" versus usual care alone in carers of patients with a primary progressive dementia. Social support was defined as access to a trained befriending facilitator providing one-to-one emotional support (companionship and conversation), generally on a weekly basis, to the caregiver. The monthly cost (including set-up, training, salaries, travel, overhead, stationary…) of this "social support" programme was estimated at £76 (£ of the year 2005) per carer. Two-hundred and thirty-six (236) carers were enrolled in the trial (116 intervention, 120 control). The study was performed from the societal perspective and included all direct medical, direct non-medical and indirect (among others informal care time) costs arising on behalf of the carer and the patient. The main outcomes were QALYs gained by the carer, measured by the EQ-5D questionnaire, and the depression status of the carer, measured by the Hospital Anxiety and Depression Scale (HADS). The time horizon was 15 months. The study found neutrality between the alternatives in terms of incremental costs and outcomes. Compared to usual care, befriending was associated with a non significant increase in total costs (£1 813 per carer; 95%CI: -£11 312–£14 984; £ of the year 2005) and a small (0.017) and non significant (95%CI: -0.051–0.083) gain in QALYs for the carer. There was also no evidence of a significant reduction of the HADS depression score. The ratio of the mean incremental costs on the mean QALYs gained was £106 000 which was much in excess of the upper limit of the UK threshold range (£20 000–£30 000) for cost-effective interventions. The probability that the ICER is below £30 000 per QALY gained was 42.2%. Adding the quality of life gained by the patient to that of the carer only slightly improved the results, with a 51.4% probability that the ICER is below £30 000 per QALY gained. From this Charlesworth et al.[104] conclude that access to a befriending facilitator is neither a cost-effective nor an effective intervention in the support of carers of people with dementia.

Joint intervention on the carers and the patients

The Dutch RCT-based study of **Graff et al.[43]** evaluated the cost-effectiveness of a 10-session occupational therapy focused on both the patient with mild to moderate (Brief Cognitive Rating Scale) dementia and his primary caregiver. Occupational therapy included cognitive and behavioural interventions implemented by trained therapists. It aimed at improving the independence and wellbeing of the patient, and at decreasing the burden on the caregiver while improving his sense of competence. The monthly cost of this intervention was estimated at €394 (costing year not reported) per pair of patient and carer. The timeframe was 3 months. One hundred and thirty-two (132) pairs of patients and carers were included in the study (68 occupational therapy, 67 usual care). The perspective of the study was societal and included direct medical, direct non-medical and indirect costs (including informal care). The outcome was the number of successful treatments, a combined patient and caregiver outcome measure of clinically relevant improvement on process (> 0.5 points on the Assessment of Motor and Process Skills scale), performance (> 20% on the Interview of Deterioration in Daily Activities in Dementia scale) and competence (> 5 points on the Sense of Competence questionnaire) scales. Treatment was considered successful in 25 (37%) patient-carer pairs in the intervention group and in 1 (1.5%) pair in the control group.

This represents a clinically relevant and significant 35% (95%CI: 23–47%) higher proportion of successful treatment with occupational therapy. Compared to usual care, occupational therapy further resulted in mean net savings of -€1 748 per patient (95%CI: -€4 244–€748, costing year not reported), largely due to the reduced informal care and institutionalisation in the intervention group. Graff et al.[43] concludes that occupational therapy is a cost-effective intervention since it dominates (i.e. is both more effective and less costly) usual care with a 94% probability.

5.3 CONCLUSIONS

From the reviews of the literature and the economic evaluations examined here, it appears that the cost-effectiveness studies on the use of donepezil in AD patients have reported a variety of conclusions with studies reporting either cost savings over time (usually from a societal perspective) or cost neutrality as well as incremental costs, alongside with benefits in cognitive function (MMSE) associated with the treatment. Likewise, the results of the cost-effectiveness studies of rivastigmine appear inconclusive, being either cost savings or cost incurring. Further, while most of those studies reported that rivastigmine treatment delays the cognitive decline in AD patients over time, this is based on the assumption that a delay in cognitive decline translates into meaningful long-term patient outcomes. The cost-effectiveness studies of galantamine were rather similar in methods,[114] and reported a delay in time to full-time care need and to institutionalisation associated with a cost saving or cost incurring profile. In moderately severe to severe AD patients, memantine was reported to be the dominant option (i.e. more effective and less costly) in comparison with usual care.

The heterogeneity and unreliability in the studies' conclusions about the cost-effectiveness of AD medications mainly stems from the lack of robustness in the assumptions used to model disease progression and in the final outcomes used to consider patient benefits.

A key assumption in most models estimating the cost-effectiveness of AD medications (donepezil, rivastigmine, memantine and some models for galantamine) is that the severity of the AD states (i.e. the mild, moderate and severe disease stages) and the progression between the states are defined with MMSE scores. There are however concerns about the use of cognition alone to model disease progression over time, since other factors (such as the functional ability) may also be determinant in the progression of the disease or the need for institutionalisation. By contrast, in Loveman et al.[72] and in most models for galantamine, disease progression, though limited to two health states (pre-FTC and FTC), was defined according to both cognitive and non-cognitive criteria.

In a preceding chapter of this short HTA, it was reported that treatments with ChEIs for mild to moderately severe AD or with memantine for moderately severe to severe AD showed statistically significant benefits for some outcome measures in clinical trials (e.g. change in a cognitive scale score). However, the link from those short-term clinical trial outcomes with longer-term, more final patient-related outcomes as used in most economic evaluations (i.e. delay in disease progression, reduction in institutionalisation) is not straightforward and appears to be lacking in the literature so far. Such link is nevertheless assumed in most economic evaluations of AD medication. In this short HTA, we could only identify one high-quality RCT demonstrating a significant reduction in the rate of institutionalisation with non-pharmaceutical treatments (caregiver support) of AD patients' caregivers.[61] In the AD2000 trial, the risk of institutionalisation in persons taking donepezil (5 or 10 mg) was not found to be different from the risk of institutionalisation in persons taking placebo over a 3-year follow-up period.[128] Also, in their recent study, IQWiG reports that no interpretable data are available on the AD medications goal of delay to institutionalisation.[69]

Another common problem across all reported cost-effectiveness modelling studies is the lack of good quality input data, e.g. health state utilities, transition probabilities... Numerous sources of data had thus to be combined from disparate studies to feed the models and many assumptions had to be made to palliate this paucity of data.

Although modelling is necessary when long-term data are lacking, this is still an additional limitation of the modelling approaches for AD, which may then suffer from a lack of internal consistency.

The published literature on the cost-effectiveness of AD medications so far is almost entirely comprised of industry-sponsored studies. Many of those studies are presented from an optimistic societal perspective (i.e. including caregiver time costs and therefore predicting cost savings) and are largely driven by optimistic differences in effectiveness of treatment compared with usual care (i.e. assuming that treatment may delay disease progression).

The results of the economic evaluations assessing non-pharmaceutical interventions in AD patients were rather heterogeneous and inconclusive. Patients' interventions were found neutral both in terms of costs and clinical outcome with a "day care" programme for the patient, while "group living" and "cognitive stimulation therapy" were associated with significant cognitive improvement at an either lower or equal cost compared to usual care. Caregivers support was assessed to be neither a cost-effective nor a clinically effective intervention in two RCT-based studies while it was considered to be the dominant option compared to usual care in two other model-based studies. Finally, based on the results of a single study, an occupational therapy targeting both the patient and his (her) carer was found to be highly cost-effective. Besides the heterogeneity of those results, these studies were further considered to be of poor quality and statistical power, thereby limiting the validity of their findings.

In general, model-based economic evaluations of non-pharmaceutical interventions suffered from the same limitations as those described above for the evaluations of pharmaceutical interventions against AD. The quality of the RCT-based piggy-backed economic evaluations of non-pharmacological AD interventions was also controversial. The short-term outcomes used in those evaluations were changes in the scale score between AD interventions and usual care, for which significant differences were reported in the trial. The limitation with this approach is that such change in scale score do not translate easily into clinically meaningful final outcomes so that the results of such economic evaluations are hardly interpretable.

Therefore, given the lack of consistency in the studies' results and the numerous limitations of the economic evaluations and of their assumptions, more research is needed to draw firmer conclusions on the cost-effectiveness of pharmacological and non-pharmacological interventions in AD patients.

Key points

- **In the economic evaluations, ChEIs and memantine treatments for AD patients were found to be either cost saving or more costly and also more effective than usual care.**
- **Most studies assumed that AD medications were effective in delaying institutionalisation and disease progression. The use of such longer-term endpoints that was modelled in the economic evaluations is controversial given the typically short-term follow-up of the trials of AD medication and given the current lack of evidence on longer-term outcomes in the trials.**
- **Results of the economic evaluations of non-pharmaceutical interventions were heterogeneous, and the quality of the studies was poor.**
- **Although of great interest, no economic evaluation assessing a combined pharmacological and non-pharmacological intervention could be identified. There was also no economic evaluation investigating whether an AD medication is more cost-effective than another.**
- **In the future, ideally, valid data on the medium- to long-term cost and effectiveness of delayed institutionalisation or disease progression should best be available to be used in the economic evaluations of AD interventions.**
- **One step in this direction is the study of Mittleman et al.,[61] a high quality study demonstrating a significant reduction in the rate of institutionalisation with non-pharmacological interventions of AD patients' caregivers. Economic studies based on the results of this study would be highly informative.**

6 ANALYSIS OF BELGIAN DRUG PRESCRIPTION DATA (2002 – 2006)

6.1 INTRODUCTION AND RESEARCH GOALS

6.1.1 Medicines Reimbursed in Belgium

In Belgium the ChEIs (Aricept/donepezil, Reminyl/galantamine, and Exelon/rivastigmine) are reimbursed by the RIZIV/INAMI for mild to moderately severe AD (MMSE > 11) starting mid 2002. Memantine (trade name Ebixa) is reimbursed in moderately severe and severe AD (MMSE >2, <15) starting from 2004. Reimbursement of these medications for AD requires confirmation of the diagnosis (based on DSM-IV criteria) by a psychiatrist, a neurologist, or a geriatrician specialist in internal medicine. The care and support team should include the specialist and the patient general practitioner. Exclusion of other pathology (eg brain infarction) is required using a brain CT or MRI scan. The functional evaluation should include the 6 points ADL Katz scale, the instrumental ADL Lawton scale (9 points), as well as the NPI (Neuro-Psychiatric Inventory) for behaviour. A RIZIV/INAMI registry was planned for AD medication but was never implemented. A patient re-evaluation after the first 6 months of ChEI treatment is required for obtaining continued drug reimbursement.

In Belgium, Ginkgo biloba is also reimbursed for the symptomatic treatment of mild to moderately severe AD (MMSE > 11). Ginkgo biloba is not included in this evaluation because robust trial data are lacking. The number of patients receiving prescriptions for this drug is also limited (as detailed in Pharmanet data below).

6.1.2 Research Goals

The aim was to explore the use of new diagnostic tests and medications in AD patients in Belgium based on the "permanente steekproef / échantillon permanent" (PS/EP) database. In particular this exploration will help to answer the following research goals:

- To quantify the routine use of new proposed diagnostic markers for clinical diagnosis[20] in the 2002-2006 period in Belgium in patients who received a ChEI prescription.
- To describe the patients treated with ChEIs or memantine in Belgium in terms of number, age, gender, place of residence, duration of treatment, co-medication (antipsychotics and antidepressants), and mortality. As the population of patients receiving prescriptions for memantine is lower, data exploration was limited for this group.

6.2 METHODS

6.2.1 Database "permanente steekproef / échantillon permanent"

In Belgium, registered inhabitants in principle have a compulsory health insurance provided by one of the seven national sickness funds and funded by social security contributions withhold on wages and earned incomes. For all sickness funds health care reimbursement data of their members are joined into a large database at the IMA (Intermutualistisch Agentschap/ Agence Intermutualiste). From this population a sample of 1/40 was selected among subjects aged 65 or younger (random selection stratified for age and sex) and a sample of 1/20 among subjects of 66 years and older (random selection stratified for age and sex). This sample contains about 300 000 individuals and was started in 2002. The database was updated every year since and is referred to as "permanente steekproef or échantillon permanent" (PS/EP). For all the individuals in the sample demographic and socio-economic information is updated, in addition to the detailed information on health care expenditures. For reimbursed drug prescriptions two data streams exist and were used for the analyses: the Pharmanet datastream (www.inami.fgov.be/drug/fr/statistics-scientific-information/pharmanet/introduction/pdf/analyticalreport_eng.pdf) which includes prescriptions out of the hospital setting and the Health datastream containing

prescriptions handled by the hospital pharmacy, as well as all other health expenditures covered by the compulsory health insurance.

Most prescriptions for patients in elderly homes (also referred to as ROB/RVT or MR/MRS) are included into Pharmanet, a small part (5% to 12%, depending on the source) of the elderly homes however obtain their medication through a linked hospital pharmacy and are thus included in Health. The codes defining the medication prescribed differ between Pharmanet (APB-CNK code) and Health (RIZIV/INAMI code).

6.2.2 Selection of study population and variables for analysis

We first selected patients included in the PS/EP who had at least one reimbursed prescription for a ChEI or Ebixa/memantine in the 2002-2006 period.

The demographic data analysed for these patients are

- year of birth,
- gender,
- year and month of death (if this occurred in the 2002-2006 period)
- residence type (home, ROB/RVT-MR/MRS).

As stays in an elderly home (ROB/RVT-MR/MRS) are also in part paid by the health insurance (invoiced after each three months period, unless a change of service occurs earlier), it is possible to define the type of residence over time.

We studied individual dates of prescriptions of specific medication for AD (ChEIs and Ebixa), as well as concomitant prescriptions of antipsychotics and antidepressants. Benzodiazepine prescriptions could not be evaluated as these drugs are not reimbursed by the RIZIV/INAMI.

ChEI reimbursement started mid 2002. Ebixa reimbursement started in 2004. A few earlier prescriptions were identified in the database and included.

After the data analyses had been completed and were being validated by a second analyst, it was seen that a small number of prescriptions with the Pharmanet code were unexpectedly present in the dataset Health. It was decided not to repeat the analyses as it concerned a relatively small number of prescriptions and because of the high proportion (a third) of ChEI treatment gaps of over 200 days among the additional patients. The reason for this difference of coding was not clear at the time of writing of the report.

6.2.3 Statistical analyses

The following analyses are performed:

1. Incident cases of patients on ChEI per year from 2002-2006 (number of new patients), and prevalent cases in 2006 (number of patients who received prescriptions in 2006). An extrapolation of the yearly percentage increase of consumption was also performed based on data for 2007, but this was based on data from Pharmanet only.

2. The extrapolation of these results from the PS/EP to the whole population of Belgium is given by:

N patients (≤ 65 years) X 40 + N patients (> 65 years) X 20

3. The setting of the first ChEI prescription: home, hospital or ROB/RVT-MR/MRS. Prescriptions handled by a hospital pharmacy are identified using the RIZIV/INAMI medication codes. Patients in ROB/RVT-MR/MRS are identified using the lump sum paid by the health insurance at three month intervals.

4. The routine use of new diagnostic markers. Recently a revision of the diagnostic criteria for clinical diagnosis has been proposed,[20] reflecting the increasing importance of new markers. We quantified the introduction of these new tests in routine practice in Belgium, using the specific codes of reimbursement as a proxy for the test. The following supportive features were studied (using reimbursement codes):

- presence of medial temporal lobe atrophy on MRI (MRI, of head: 459395, 459406)
- abnormal cerebrospinal fluid biomarkers (amyloid beta1-42, total tau, and phospho-tau) (CSF, lumbar puncture procedure: 355493, 355504)
- a specific pattern on functional neuroimaging with 18F-FDG PET (PET: 442971, 442982, or functional scintigraphic test code used in case centre not registered for PET exams: 442595, 442606) (SPECT technique did not meet criteria for diagnostic accuracy)
- a proven AD autosomal dominant mutation within the immediate family (DNA, genetic test: 588696, 588700)

4. The switch between ChEIs during the study period.

5. The time to discontinuation of ChEI treatment.

The median time between two prescriptions was computed, for patients having at least two prescriptions. Multiple prescriptions on the same date were counted only once. The methodology to compute the time to discontinuation of ChEIs is similar to the one used in the Ontario study.[129] However, we used a 30 day period as treatment period after the last prescription (based on the median time between two prescriptions), and a period of 170 days for drug renewal (and use of remaining medication). Patients without subsequent prescription within 200 days were considered withdrawn from therapy (at the date of last prescription + 30 days). Patients who died within this 200 days period were considered censored for the analysis of time to discontinuation. So were patients who received a last prescription within the 200 day period before the end of our study period (31DEC2006). If there were more than 200 days between two prescriptions, the patient was considered withdrawn from therapy (at the date of last prescription + 30 days), and was not included back in the study. Survival function was estimated with the Kaplan Meier method. Differences in duration of treatment across patient's characteristics were also explored (type of medication, setting of first prescription).

6. The use of concomitant antipsychotics and antidepressants.

The use of antipsychotics and antidepressants was identified from the same databases as those described above. The codes to identify these medications were those in application in 2006. Setting of residence in 2006 (home or ROB/RVT-MR/MRS) was also studied. The concomitant use was defined as any prescription of antipsychotics or antidepressant between (and including) the first and last ChEI prescription date. No treatment period was defined after date of prescription.

7. Survival after start of ChEI treatment.

The survival function after start of ChEI treatment was estimated with the Kaplan Meyer method. The shape of the hazard function was estimated with the life table method.
A Cox proportional hazard (PH) model was fitted to study the influences of some patient's covariates on the hazard function: age, sex, setting of first prescription (hospital, ROB/RVT-MR/MRS, home), institutionalization after start of ChEI treatment, use of concomitant antipsychotics (started before start of ChEI or after) and use of concomitant antidepressants (started before start of ChEI or after). Some of these covariates are defined after the start of ChEI treatment, and are therefore included as a time-depended covariate in the Cox PH model. The assumption of proportional hazards was tested for all covariates by including an interaction term time*covariate in the model, and the model was adapted accordingly. Hazard ratios and 95% CI are presented.

6.3 RESULTS

6.3.1 Patients on ChEIs

6.3.1.1 Baseline demographics

Overall, 2599 patients started ChEI treatment in 2002-2006, defined as a first prescription of a ChEI in the PS/EP. This includes prescriptions with Pharmanet code in the database Health. Without these prescriptions the number of patients on ChEIs is 2502 (2501 with all variables available), and this population was used for most analyses. It will be mentioned each time the study population size of 2599 has been used for the analyses. In terms of demographics there were no noteworthy differences when the population size of 2502 of 2599 was used. Among the 2599 patients, the mean age of the 1749 female patients (67% of all patients) was 79.4 years, and the mean age of the 850 male patients was 78.1 years.

Table 12: Study population

Sex	N	%	Mean age
Female	1749	67%	79.4
Male	850	33%	78.1
All	2599	100%	79.0

The overall mean age was 79.0 years (Standard Deviation: 6.8 years). The percentiles of the age distribution are given below. The proportion of patients under 66 years was 2.9%, and 0.9% of the patients were under 61 years old.

Table 13: Age distribution (percentiles)

P5	P25	P50	P75	P90
68 y	75 y	79 y	83 y	90 y

This compares to a mean age of 80 years and 63% females in a population based study in Ontario, Canada, of patients who started ChEI therapy in the 2000-2002 period.[129] One should note that the mean age in most phase 3 studies with ChEIs was in the 69 to 76 years range.[14] AD patients receiving ChEIs in routine practice are thus on average more than 5 years older compared with patients studied in phase 3 trials of ChEIs.

6.3.1.2 Incidence (first ChEI prescriptions) per year

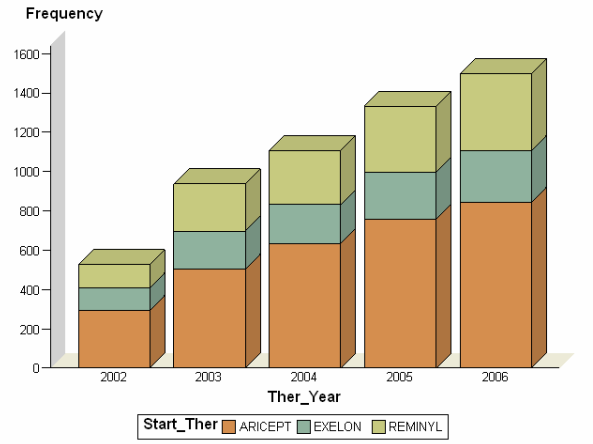
Table 14: Number of patients identified with a first prescription of ChEI by year.

2002	621
2003	499
2004	479
2005	484
2006	516

Extrapolated to Belgium, this means over 10000 AD patients started ChEI therapy per year (incidence). The number of patients starting ChEI treatment each year remained relatively stable over the 2002-2006 observation period.

6.3.1.3 *Prevalence per year (2002-2006)*

Figure 2: Number of patients per year under ChEI treatment (in sample).



Overall, 1038 female and 464 male patients had at least one ChEI prescription in 2006 (prevalence). Extrapolated to the Belgian population these 1502 patients correspond to 30856 patients for 2006 (39 patients were 65 years or younger: x 40 = 1596; plus 1463 patients were 66 years or older: x 20 = 29260).

6.3.1.4 *Extrapolation for prevalence 2007-2008*

Based on the global (i.e. not the PS/EP) Pharmanet data alone (see table below), 27 818 patients received a prescription for a ChEI in 2006 (this number does not take into account patients receiving treatment in a hospital setting). From 2005 to 2006, and from 2006 to 2007 an increase of 13% was seen in the number of patients, increasing to 31 468 in 2007.

Table 15: Pharmanet data, number of patients for Belgium

		2007	2006	2005
donepezil	N06DA02	17170	15460	13960
rivastigmine	N06DA03	4995	4544	4330
galantamine	N06DA04	9303	7814	6406
memantine	N06DX01	3839	3531	3045
gingko biloba	N06DX02	787	742	609

Source: Pharmanet (RIZIV/INAMI)

Starting from the 30856 patients estimated for 2006, our estimate for 2007 would be 34867 patients (13% increase). Assuming a further increase of 13% from 2007 to 2008, the total number of patients would be 39400 in 2008.

In addition, a small part of population living in Belgium did not obtain reimbursement for ChEIs using the obligatory health insurance system during these years and were not included in these numbers. These included subjects who were self-employed workers (and their family) who were not insured for "small risks", and persons employed by institutes such as the European Union, having a separate system of insurance. In the case of ChEIs there are probably also some patients who are not willing to undergo the tests needed to obtain reimbursement, or who receive ChEI out of label. We did not access company sales data to further quantify the number of additional patients receiving ChEIs. Anyhow, the number of AD patients receiving ChEI treatment in Belgium in 2008 is at least 40000, or more than half of the total AD population in Belgium (estimated at 75000 patients).

This compares with nearly a third of the estimated 860 000 AD patients who receive ChEIs in France, mentioned as the highest proportion among the developed countries (Clinical practice guidelines by the French Haute Autorité de Santé, 2008, http://www.has-sante.fr/portail/jcms/c_668822/alzheimer-s-disease-and-related-conditions-diagnosis-and-treatment). Probably, no correction was made for AD versus overall dementia, as the overall prevalence of dementia in France is about 860 000 patients (www.dementia-in-europe.eu). This would mean that the use of ChEIs in Belgium is thus among the highest uses worldwide.

As discussed above, we estimate that about 45% of the Belgian AD patients reside in an elderly home (ROB/RVT-MR/MRS). This corresponds to about 34000 of the 75000 AD patients in 2008.

6.3.2 Institutionalization and ChEI use

The setting of first ChEI prescription is detailed below. The large majority of new treatments are started in ambulatory setting (63.5%). Almost a third (27.9%) of new treatments occurred in the hospital setting, and about 9% of new treatments were started in an ROB/RVT-MR/MRS.

Table 16: Patients on ChEI by setting of first prescription

Setting of first prescription	N	%
Hospital	699	27.9%
ROB/RVT-MR/MRS	214	8.6%
Home (ambulatory)	1588	63.5%
Total	2502	100%

Table 17: Patients grouped based on age and sex, ChEI, and setting of first prescription.

		N	Group			
			<80y,F N	<80y,M N	>=80y,F N	>=80y,M N
Start_Loc	Start_Ther					
HOSP	ARICEPT	424	96	52	199	77
	EXELON	135	39	30	44	22
	REMINYL	140	40	16	54	30
NHOSP	ARICEPT	990	354	168	350	118
	EXELON	326	117	81	90	38
	REMINYL	486	185	114	131	56

HOSP=hospital setting; NHOSP=not in hospital

Note that Aricept and Exelon were more likely to be started in hospital (30% and 29% of first prescriptions) compared with Reminyl (22% of first prescriptions). Age at first prescription was higher for Aricept (mean 79.7 years) compared with Exelon (78.3 years) and Reminyl (78.0 years), while the proportion of male patients was somewhat higher on Exelon (38%) and Reminyl (35%) compared with Aricept (29%).

The analyses below are based on data from mid-2004 to mid 2006 (because at the time of this analysis the codes of lump sums used before 2004 for ROB/RVT-MR/MRS were not available). We selected from the PS/EP 413 patients with a first 3-monthly charge (assumed to be charged 3 month after institutionalization) for stay at an ROB/RVT-MR/MRS institute between 1 october 2004 and 1 october 2006 (2 year period), who received a ChEI prescription during the six months period preceeding or following institutionalisation. Patients were categorized based on institutionalization date and dates of ChEI prescriptions as having discontinued ChEIs in the six months before institutionalization (n=17), continued ChEIs (n=228) or started ChEI withing 6 months after institutionalization (n=168).

One should note that among the 168 patients who started ChEIs within 6 months after institutionalization 101 patients (60%) received their first prescription in a hospital setting. The distribution of the ROB/RVT-MR/MRS types used for the first charge is given below.

Figure 3: ChEI use by ROB/RVT-MR/MRS type

TYPE		Discont'd	Continued	Started
ROB A	N	1	31	33
ROB B	N	4	72	52
ROB C	N	0	5	6
ROB Cd	N	4	32	15
ROB O	N	0	19	29
RVT B	N	4	37	17
RVT C	N	0	2	4
RVT Cd	N	4	30	12
Total	N	17	228	168

These results illustrate ChEIs are prescribed mainly in patients who are not in the highest classes (C) of dependency based on the Katz ADL scale. It should also be noted that the net change in ChEI use associated with institutionalization is thus an increase in the number of patients on ChEIs. The appropriateness of starting ChEIs after institutionalization was questioned by some of the external experts of this project.

Among the patients with ChEI prescriptions in 2006, 466 patients (31%) resided in ROB/RVT-MR/MRS. If we assume that among the 40000 patients on ChEIs in 2008 31% or 12400 patients reside in a ROB/RVT-MR/MRS, the following can be derived. This would mean that 12400 (or 36%) of the estimated 34000 AD patients in ROB/RVT-MR/MRS receive a ChEI. This also means that about 27600 (69%) of the estimated 41000 AD patients residing at home receive a ChEI.

6.3.3 Routine use of new diagnostic markers

The table below shows the patients who are tested, and also shows the number of tests over the period 2002-2006 for the 2502 patients in our study database. We do not know the reason for doing the test nor what analyses were exactly performed.

Table 18: Number of tests and patients tested in 2002-2006 period among the 2502 patients who started ChEI therapy.

Test	N tests	N patients (% of 2502 patients)
MRI	605	472 (18.9%)
CSF	83	65 (2.6%)
PET	78	72 (2.9%)
DNA	42	33 (1.3%)

MRI = MRI of head; CSF = lumbar puncture; PET = PET scan or functional scintigraphic test code used in case centre not registered for PET; DNA = genetic test based on DNA hybridization

Test volumes for Belgium in this patient group can be estimated by multiplying these numbers with a factor of 20. We could not study the reason why the test or procedure was performed, but as the timing of the test/procedure was often close to the start of ChEI therapy in the majority of cases, we can assume that most tests/procedures were performed in the context of dementia diagnostic work-up.

We conclude that the new proposed markers are not routinely used during the study period. According to the external experts consulted for this project these markers, eg CSF markers, are used in selected patients and mainly in university centres.[130]

6.3.4 Switching of ChEIs

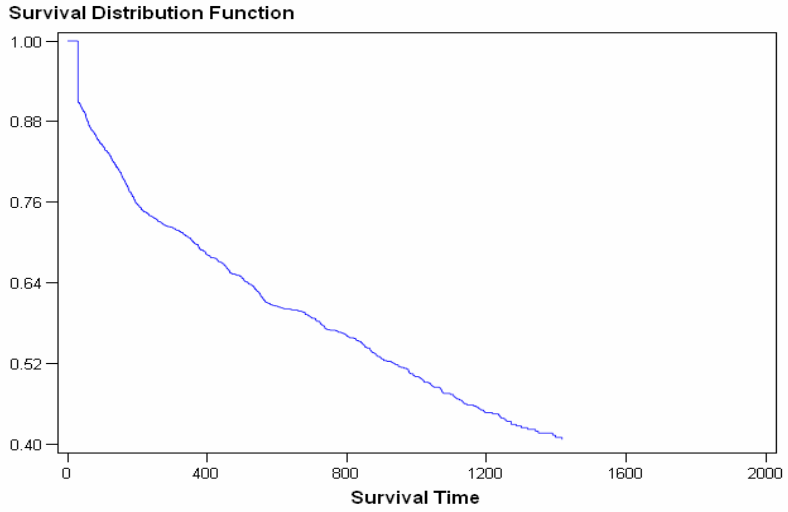
Overall and also when limited to patients who started ChEI treatment in 2003 or before the proportion of patients who switched during the observation period was not higher than 5%. This switch rate of about 5% between ChEI is very similar to the 6% rate reported by Herrmann et al.[129]

6.3.5 Time to discontinuation of ChEI treatment

6.3.5.1 Overall analysis

In our dataset (2502 patients), the median time between two prescriptions was 30 days, and was used as an estimate for the treatment duration (thus added to the last date of the prescription). The median time to treatment discontinuation is 1006 days (95% CI: 905 to 1106), as shown below (using a maximum gap of 200 days between prescriptions, and censoring discontinuation for death or for completed follow up). A total of 294 patients (11.8%) had only one prescription of ChEI during the 2002-2006 study period. In the Ontario study the median time to discontinuation of ChEIs (censored for death or completed follow-up) was 651 days,[129] allowing a grace period of 120 days after the presumed end date of the initial prescription and including a treatment period of 120 days systematically added to the last prescription date. Figure 4 suggests there is no significant impact on drug discontinuation of the patient re-evaluation after the first 6 months of ChEI treatment, which is required for obtaining continued drug reimbursement. When the analysis is not censored for death then the median time to treatment discontinuation is reduced to 594 days (95% CI: 551 to 694).

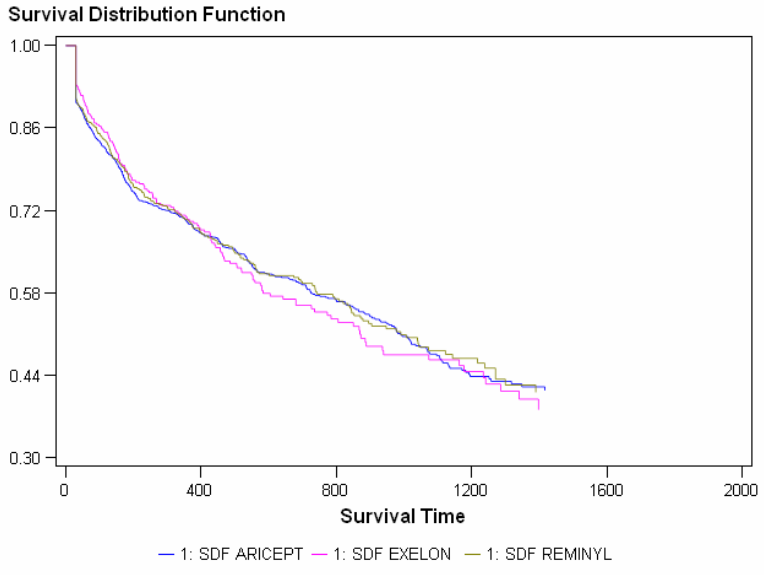
Figure 4: Time to discontinuation of ChEI treatment (censored for death and end of follow-up)



6.3.5.2 *Analysis of time to discontinuation of ChEI treatment, by ChEI*

No significant differences between ChEIs were seen as illustrated below.

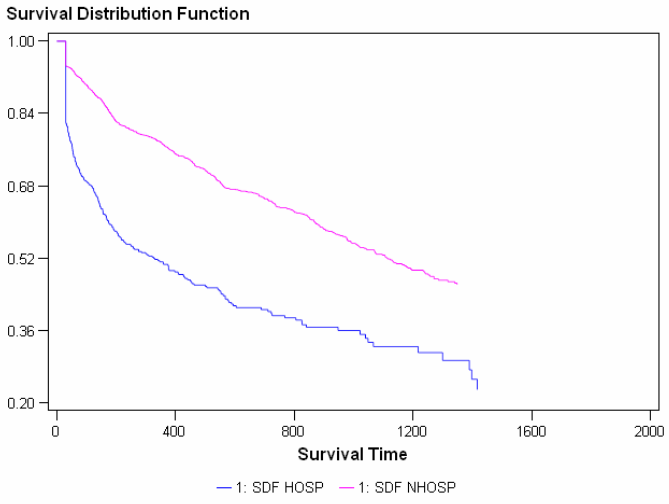
Figure 5: Time to discontinuation by ChEI (censored for death and end of follow-up)



6.3.5.3 *Analysis of time to discontinuation of ChEI, by setting of first prescription*

A major difference in ChEI treatment duration (censored for death and follow-up period as before) was seen according to the setting of the first prescription (hospital vs non-hospital). The median duration of ChEI therapy started in a hospital was 376 days (95%CI: 257 to 505 days) versus 1177 days (95% CI: 1072 to 1348 days) if ChEI treatment was not started in a hospital. The proportion of patients with only one ChEI prescription is also much higher if the first prescription is in the hospital setting.

Figure 6: Time to discontinuation of ChEI, by setting of first prescription



6.3.5.4 *What happens after ChEI therapy is discontinued?*

We selected those patients who started ChEIs in 2002-2006 but for whom there were no ChEI prescriptions during the last 6 months of 2006. Of the 1186 patients thus identified, 310 (26%) died during the 3 month period following the last ChEI prescription, while another 76 patients (6.5%) died 4 to 6 months after the last ChEI prescription. These data suggest ChEI prescriptions are continued in some patients until the end of life.

In this context, monitoring the use of ChEIs in patients with a MMSE < 5 has been suggested as a role of the coordinating physician of the ROB/RVT-MR/MRS (Domino woon en zorgcentrum presentation, "De CRA en het geneesmiddelen verbruik in het RVT", 18 FEB 2009).

6.3.6 Concomitant use of antipsychotics and antidepressants

Table 19: Concomitant use of antipsychotics and antidepressants in AD patients receiving ChEIs (sample, full 2002-2006 period).

		Antipsychotics		Antidepressants	
	N	n	%		%
Any use	2502	844	33.7	908	36.3
Timing of start of medication compared to ChEI					
Before or concomitant to start of ChEI treatment	2502	438	17.5	608	34.3
After start of ChEI treatment	2502	406	16.2	300	12.0
Chronic use (a single versus multiple prescriptions over time)					
Only a single prescription of antipsychotic or antidepressant	2502	125	5.0	99	4.0
By setting of first prescription of ChEI					
Before or concomitant to start of ChEI treatment					
First prescription of ChEI in Hospital	699	264	37.8	271	38.8
First prescription of ChEI in ROB/RVT-MR/MRS	214	46	21.5	71	33.2
First prescription of ChEI in Ambulatory (= care at home)	1588	128	8.1	266	16.7

On the 844 patients receiving antipsychotics concomitantly with ChEI treatment, about half of them started antipsychotics before or concomitantly with the start of ChEI treatment, while for antidepressants this ratio is around two thirds to one third. The proportion of patients with a single prescription is around 5% for antipsychotics and 4% for antidepressants. The use of antipsychotics and antidepressants is also very dependent of the setting of the start of ChEI treatment: 38% of the patients who started their ChEI treatment in a hospital started antipsychotic treatment before the start of ChEI or concomitantly. This percentage is only 8% for patients who started their ChEI treatment at home.

6.3.6.1 *Institutionalization and concomitant use of antipsychotics and antidepressants*

Next, we considered patients who received prescriptions for ChEIs in 2006 and grouped those 1497 patients based on residence status in 2006. We considered for these patient groups the concomitant use (prescription date between first and last ChEI prescription date) of antipsychotics and antidepressants, overall and for 2006 only.

Nearly half (45%) of the institutionalized patients received at least one prescription for a antipsychotic in between prescriptions for a ChEI. This proportion is lower (21%) in non-institutionalised patients. When restricted to the year 2006 these proportions are 24% and 16%.

The most frequently used antipsychotics were Risperdal/risperdon, Haldol/haloperidol, Dominal/prothipendylhydrochloride, Zyprexa/olanzapine, Dipiperon/bipamperon, Buronil/melperonhydrochloride, and Solian/amisulpride.

In 52% of the institutionalized patients prescriptions for antidepressants were identified at some time during the treatment period with a ChEI.

This is the double of the proportion of 26% found in non-institutionalized patients. When restricted to the year 2006 these proportions are 32% and 18%.

The most frequently prescribed antidepressants in patients on ChEIs are Trazolan/trazodonhydrochloride, Sipralexa/escitalopram, Serlain/sertraline, Cipramil/citalopram, Seroxat/paroxetine, Redomex/amitriptyline, Remergon/mirtazapine.

In 2006, 27% of non-institutionalized patients on ChEI (vs 45% and 55% of patients already or being institutionalized) did receive prescriptions for antipsychotics or antidepressants. 12% of institutionalized patients and 7% of non-institutionalized patients received prescriptions for a ChEI, an antipsychotic and an antidepressant, often at the same date. The concomitant use of these three types of medication was highest among patients who were institutionalized the same year (overall 24%: 39% in men and 18% in women).

Table 20: Concomitant use of antipsychotics and antidepressants in AD patients receiving ChEIs (sample 2006 period).

Patients on ChEIs in 2006 by institutionalisation status and concomittant use of neuroleptics and antidepressants in 2006

		Institutionalized before 2006		Institutionalized during 2006		Not institutionalized		Total	
Neuroleptic	Antidepressant	n	%	n	%	n	%	n	%
no	no	191	55,4%	81	44,5%	708	73,0%	980	65,5%
no	yes	71	20,6%	25	13,7%	106	10,9%	202	13,5%
yes	no	43	12,5%	32	17,6%	85	8,8%	160	10,7%
yes	yes	40	11,6%	44	24,2%	71	7,3%	155	10,4%
Total		345	100,0%	182	100,0%	970	100,0%	1497	100,0%

Our analysis is in agreement with the analysis of the Pharmanet data for 2006 as published by INAMI/RIZIV (http://www.inami.fgov.be/drug/fr/statistics-scientific-information/pharmanet/pharmaceutical-tables/index.htm). In 2006, 30 941 patients were identified receiving medication from the class N06D (ChEI, memantine, and Ginkgo biloba) with an average use of 300 DDD (defined daily dose) for the one year period. Concomitant antipsychotic use was found in 36% of the patients (21% atypical antipsychotics, 9 % typical antipsychotics, and 6% association of the two types of antipsychotics).

6.3.7 Patient survival after start of ChEI treatment

The patients survival is 88% 1 year, 78% 2 years, 68% 3 years after the start of a ChEI , as illustrated below. The median survival will be about 5 years but could not be estimated accurately. The hazard function is also shown below. The survival analyses were censored for subjects who were alive at the end of the 2002-2006 observation period.

Figure 7: Survival function (and 95% CI) after start of ChEI treatment (in days)

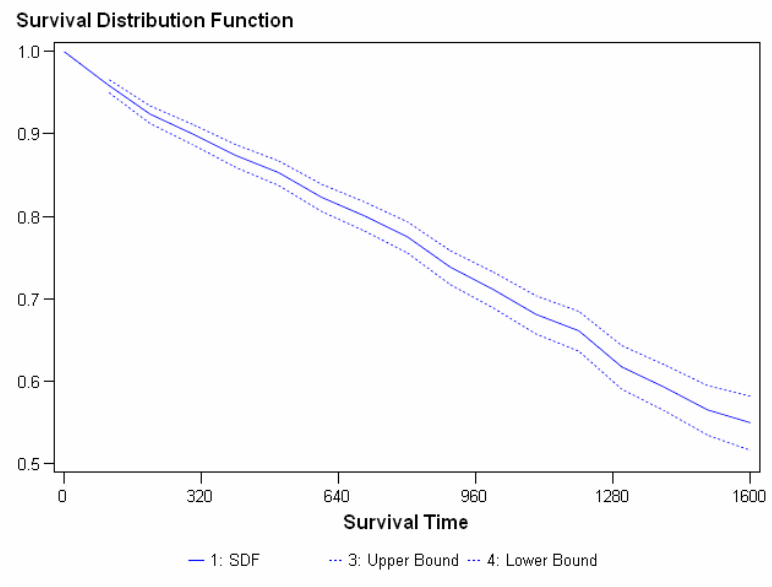


Figure 8: The hazard rate of death (by 6 months periods after ChEI start).

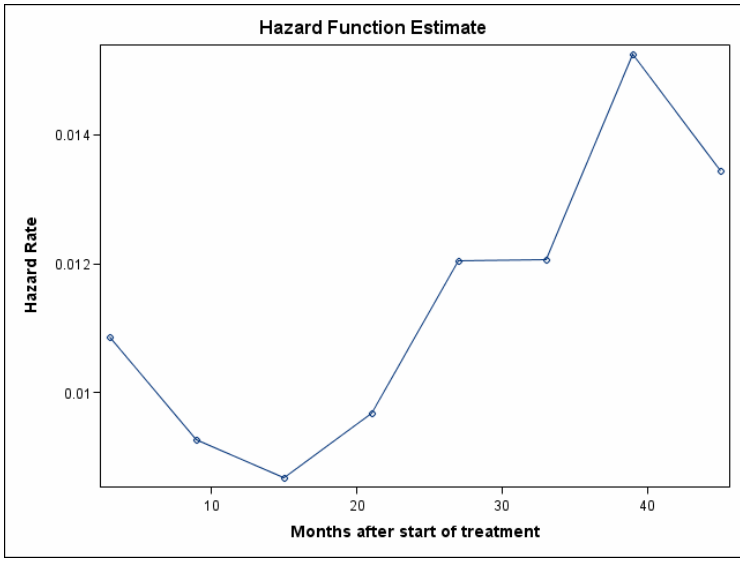
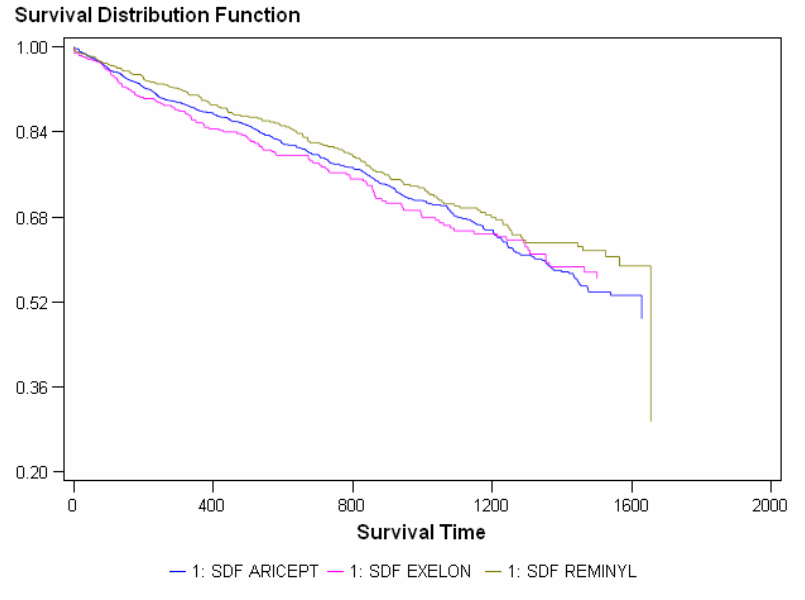


Figure 6 illustrates a gradual increase in the risk of death over time, with a reversed trend (a slightly higher mortality rate) during the first 6 months period.

6.3.7.1 *Survival differences between ChEIs*

There were no significant differences between the three ChEIs as shown below.

Figure 9: Survival (in days) after start of ChEI and hazard function, by ChEI



6.3.7.2 *Survival differences based on setting of ChEI start*

The variable explaining most of the variation was however the setting of the first prescription.

Figure 10: Survival after start of ChEI, by first prescription setting.

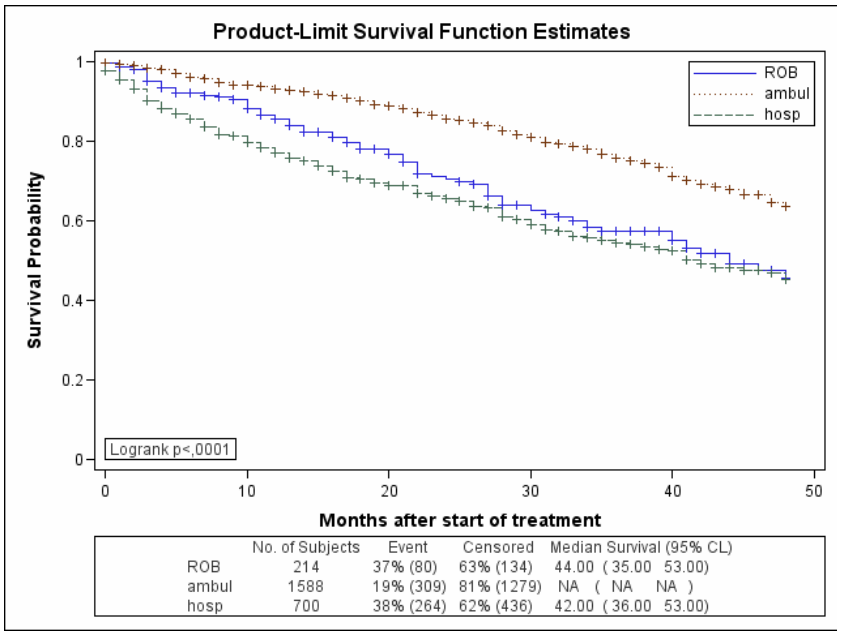
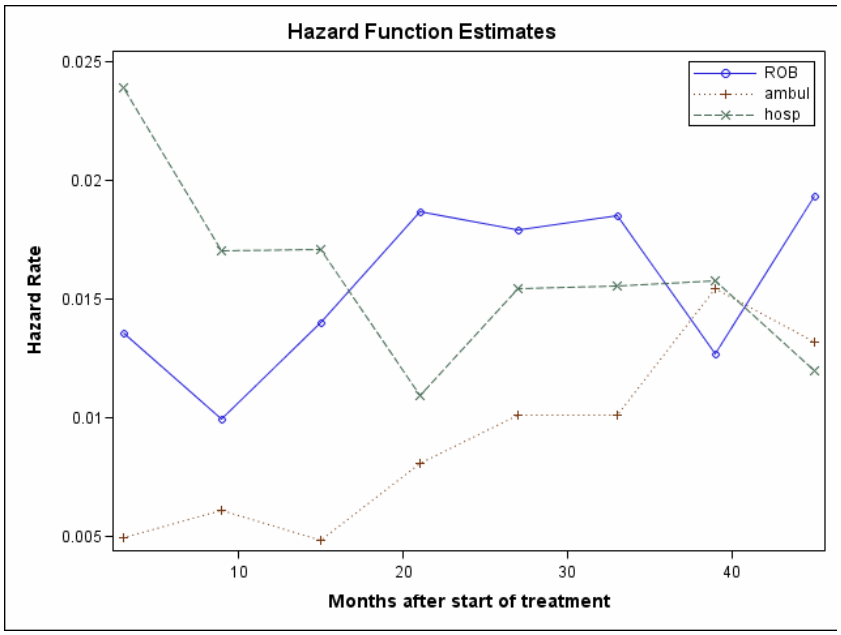


Figure 11: Hazard function by first prescription setting.



The hazard function above illustrates a slight increase in the risk of death in patients starting ChEI in a hospital or an ROB/RVT-MR/MRS setting, compared with starting a ChEI at home. The increased risk of death seems to be somewhat more pronounced in the first months after the start of the start of ChEI treatment in a hospital, most likely related to comorbidity. We also looked at the frequency of pacemaker insertions (RIZIV/INAMI codes 229132 and 229143) during the six months period after the start of ChEI therapy. We did not observe any significant difference from the six month period preceding the start of ChEI treatment in our limited study population.

6.3.7.3 Cox proportional hazard model

We analyzed the impact of patient and treatment characteristics on overall mortality using a Cox Proportional Hazard model. The results of the model are given below.

Table 21: Impact of patient and treatment characteristics on overall mortality using a Cox Proportional Hazard model

Variable	DF	HR	95% CI		Chi Square	p-value
Patients baseline demographics						
Sex (male vs female)	1	2.30	1.96	2.70	103.00	<.0001
Age at start of trt (+ 1 year)	1	1.06	1.04	1.07	66.52	<.0001
Type of treatment						
Aricept vs Reminyl	1	1.00	0.82	1.21	0.00	0.988
Exelon vs Reminyl	1	1.05	0.83	1.34	0.17	0.678
Setting of first ChEI prescription						
Hospital vs ambulatory (= care at home)	1	1.74	1.45	2.10	33.94	<.0001
ROB/RVT-MR/MRS vs ambulatory	1	2.13	1.63	2.78	31.06	<0.001
Institutionalization after start of ChEI treatment						
Institutionalization after start of treatment *	1	1.80	1.49	2.18	35.81	<.0001
Use of Concomitant antipsychotics						
Start date before or equal to start of ChEI	1	1.35	1.12	1.64	9.72	0.002
Start date after start of ChEI *	1	2.08	1.67	2.60	42.57	<.0001
Use of Concomitant antidepressants						
Start date before or equal to start of ChEI	1	0.97	0.81	1.16	0.13	0.719
Start date after start of ChEI *	1	1.18	0.92	1.53	1.66	0.198
* as time dependent variable						

The results of the model can be interpreted as follows:

- Age and male gender are associated with higher hazard of death: male patients have a risk of death which is more than twice that of female patients (p<0.0001). For each one year increase in the age at start of treatment, the hazard of dying increases by 6% (p<0.0001).
- The choice of the ChEI (Aricept, Reminyl, Exelon) prescribed does not significantly impact patient's survival.
- The setting of the first prescription is an important predictor of time of death. Patients who start ChEI therapy in a hospital and patients who start treatment in an ROB/RVT-MR/MRS have an increased risk of death which is about two times higher (p<0.0001) compared with patients treated at home. Patients institutionalized during the course of their treatment have a 80% higher risk of dying at any time after institutionalization, compared to patients who are not institutionalized (p<0.0001)
- Compared with patients without concomitant use of antipsychotics, patients who initiated antipsychotic treatment before or at the same time as the ChEI had a 35% increased risk of death (p=0.002). The death rate is even higher (a hazard ratio of 2.8, p<0.0001) for patients who started antipsychotics after the start of ChEI treatment versus those who did not.
- The use of antidepressants is not associated with higher death rate, both for patients who initiated treatment before ChEI start and for patients who initiated treatment after ChEI start.

6.3.8 Patients on Ebixa

6.3.8.1 Patients and setting of first prescription

As confirmed also by the Pharmanet data listed above, the number of patients receiving Ebixa prescriptions is small compared with the number of patients on ChEIs. The 299 patients receiving Ebixa prescriptions in the PS/EP in the period 2004-2006 are on average 79.9 years old or about 1 year older than those receiving ChEIs (therapeutic indication is moderately severe and severe AD, MMSE < 15 and > 2).

94 patients (about a third of the patients) had a first Ebixa prescription after institutionalization. A total of 211 patients received Ebixa in 2006. This corresponds to an estimated 211x20= 4022 patients on Ebixa in Belgium in 2006. Based on an increase of 9% from 2006 to 2007 in Pharmanet, one can expect about 5000 patients receiving Ebixa in 2008 in Belgium.

In the table below it is shown that 145 out of the 289 patients starting Ebixa during the study period received a ChEI before.

Table 2223: Details of prior ChEI use in 145 patients who started Ebixa.

		Start ARICEPT	EXELON	REMINYL	EBIXA
N		1414	461	626	145
End					
ARICEPT	N	1264	30	29	0
	PctN	47.77	1.13	1.10	0
EXELON	N	22	394	5	0
	PctN	0.83	14.89	0.19	0
REMINYL	N	37	16	560	0
	PctN	1.40	0.60	21.16	0
EBIXA	N	91	21	32	145
	PctN	3.44	0.79	1.21	5.48

Key Points

- **During the 2002-2006 period the number of patients in Belgium starting ChEI therapy every year remained relatively stable at about 10 000 per year.**
- **The recently proposed diagnostic markers for AD were not used routinely in this period.**
- **The mean patient age at the start of ChEI therapy is 79 years and two in three patients are female. Patients receiving ChEIs in routine practice are on average more than 5 years older compared with patients studied in phase 3 trials of ChEIs.**
- **The number of patients on ChEI therapy in Belgium in 2008 can be estimated at over 40 000 patients (or more than half of all Alzheimer patients). One in three of the estimated 34000 AD patients in ROB/RVT-MR/MRS is treated with a ChEI and about 70% of the estimated 41000 AD patients cared for at home.**
- **ChEIs are given for about 1 year when started in a hospital (28% of patients) and for over 3 years (median) in patients not hospitalized at treatment start.**
- **Analysis of overall survival of patients after starting ChEI therapy using a Cox proportional hazard model showed age, male sex, concomitant antipsychotic use, ChEI first prescription in a hospital or ROB/RVT-MR/MRS setting and institutionalization were all significant predictors of mortality. There were no significant differences between ChEIs. Concomitant use of an antidepressant was not a significant predictor of mortality.**
- **In 26% to 32% of patients ChEIs are prescribed until patient death.**
- **We estimated about 5000 patients received Ebixa for severe dementia in Belgium in 2008.**

7 APPENDICES

APPENDIX 1: SEARCH STRATEGIES FOR THE COST-EFFECTIVENESS LITERATURE

In August/September 2008, the websites of HTA institutes and following databases were searched: Medline, Embase, Centre for Reviews and Dissemination (CRD) databases (NHS Economic Evaluation Database - NHS EED - and Health Technology Assessments - HTA), and Econlit. The following tables provide an overview of the search strategies.

SEARCH STRATEGIES FOR THE PHARMACOLOGIC AND NON-PHARMACOLOGIC TREATMENTS IN AD PATIENTS

Table 24: Search strategy and results for CRD HTA

Date	18/08/08
Database	CRD HTA
Date covered	2004 – August 2008
Search Strategy	MeSH Alzheimer Disease EXPLODE 1 2 3
Note	**47** references found

Table 25: Search strategy and results for CRD NHS EED

Date	19/08/08
Database	CRD NHS EED
Date covered	2004 – August 2008
Search Strategy	MeSH Alzheimer Disease EXPLODE 1 2 3
Note	**50** references found

Table 26: Search strategy and results for Medline(OVID)

Date	19/08/08		
Database	Medline (OVID)		
Date covered	2004 to August Week 1 2008		
Search Strategy	**#**	**Search History**	**Results**
	1	economics/	25871
	2	exp "Costs and Cost Analysis"/	140448
	3	"Value of Life"/ec	172
	4	Economics, Dental/	1840
	5	exp "Economics, Hospital"/	15788
	6	Economics, Medical/	7330
	7	Economics, Nursing/	3849
	8	Economics, Pharmaceutical/	1958
	9	or/1-8	183220
	10	(econom$ or cost$ or pric$ or pharmacoeconomic$).tw.	330039
	11	(expenditure$ not energy).tw.	12500
	12	(value adj1 money).tw.	14
	13	budget$.tw.	12656
	14	or/10-13	343364
	15	9 or 14	437889
	16	letter.pt.	672389

	17	editorial.pt.	244652
	18	historical article.pt.	255892
	19	or/16-18	1162209
	20	15 not 19	415771
	21	Animals/	4323884
	22	human/	10639598
	23	21 not (21 and 22)	3250447
	24	20 not 23	389700
	25	(metabolic adj cost).ti,ab,sh.	520
	26	((energy or oxygen) adj cost).ti,ab,sh.	2190
	27	24 not (25 or 26)	387581
	28	Alzheimer Disease/th, ec, dt [Therapy, Economics, Drug Therapy]	8644
	29	27 and 28	649
	30	limit 29 to yr="2004 - 2008"	**235**

Table 27: Search strategy and results for EMBASE

Date	20/08/2008		
Database	EMBASE		
Date covered	2004 – August 2008		
Search Strategy	**#**	**Search History**	**Results**
	#1	'socioeconomics'/exp AND [2004-2008]/py	32139
	#2	'cost benefit analysis'/exp AND [2004-2008]/py	14998
	#3	'cost effectiveness analysis'/exp AND [2004-2008]/py	22522
	#4	'cost of illness'/exp AND [2004-2008]/py	4645
	#5	'cost control'/exp AND [2004-2008]/py	7529
	#6	'economic aspect'/exp AND [2004-2008]/py	200467
	#7	'financial management'/exp AND [2004-2008]/py	51529
	#8	'health care cost'/exp AND [2004-2008]/py	44521
	#9	'health care financing'/exp AND [2004-2008]/py	2514
	#10	'health economics'/exp AND [2004-2008]/py	120613
	#11	'hospital cost'/exp AND [2004-2008]/py	3911
	#12	('finance'/exp) OR ('funding'/exp) OR (fiscal) OR (financial) AND [2004-2008]/py	31658
	#13	'cost minimization analysis'/exp AND [2004-2008]/py	735
	#14	'alzheimer disease'/exp/dm_dm,dm_dt,dm_th /mj AND [2004-2008]/py	3286
	#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	204396
	#16	#14 AND #15	423
	#17	editorial:it OR letter:it AND [2004-2008]/py	248512
	#18	#16 NOT #17 AND [2004-2008]/py	365
	#19	#16 NOT #17 AND [embase]/lim AND [2004-2008]/py	**333**

Table 28: Search strategy and results for Econlit

Date	20/08/2008		
Database	Econlit (OVID)		
Date covered	1969 to August 2008		
Search Strategy	**#**	**Search History**	**Results**
	1	alzheimer disease.mp. [mp=heading words, abstract, title, country as subject]	0
	2	alzheimer.mp. [mp=heading words, abstract, title, country as subject]	3
	3	limit 2 to yr="2004 - 2008"	**1**

SEARCH STRATEGIES FOR THE NON-PHARMACOLOGIC TREATMENTS IN DEMENTIA PATIENTS

Table 29: Search strategy and results for CRD HTA

Date	18/08/08		
Database	CRD HTA		
Date covered	2004 – August 2008		
Search Strategy	**#**	**Search history**	**Results**
	1	MeSH Dementia EXPLODE 1 2	79
	2	MeSH Alzheimer Disease EXPLODE 1 2 3	47
	3	1 not 2	**32**

Table 30: Search strategy and results for CRD NHS EED

Date	10/09/08		
Database	CRD NHS EED		
Date covered	2004 – August 2008		
Search Strategy	**#**	**Search history**	**Results**
	1	MeSH Dementia EXPLODE 1 2 RESTRICT YR 2004 2008	89
	2	MeSH Alzheimer Disease EXPLODE 1 2 3 RESTRICT YR 2004 2008	53
	3	1 not 2	**36**

Table 31: Search strategy and results for Medline(OVID)

Date	9/09/08		
Database	Medline (OVID)		
Date covered	2004 to September Week 1 2008		
Search Strategy	**#**	**Search History**	**Results**
	1	cost-effectiveness.ti,ab,kw.	22261
	2	*cost-benefit analysis/ or *"cost of illness"/	8098
	3	*Dementia/rh, ec, th, nu [Rehabilitation, Economics, Therapy, Nursing]	3421
	4	cost-utility.ti,ab,kw.	1416
	5	1 or 4 or 2	29085
	6	5 and 3	94
	7	limit 6 to yr="2004 - 2008"	**41**

Table 32: Search strategy and results for EMBASE

Date	10/09/2008		
Database	EMBASE		
Date covered	2004 – September 2008		
Search Strategy	**#**	**Search History**	**Results**
	#1	economic evaluation'/exp/mj AND [2004-2008]/py	4504
	#2	dementia'/exp/mj AND [2004-2008]/py	24281
	#3	# 1 AND #2	**52**

Table 33: Search strategy and results for Econlit

Date	10/09/2008		
Database	Econlit (OVID)		
Date covered	1969 to August 2008		
Search Strategy	**#**	**Search History**	**Results**
	1	dementia.mp. [mp=heading words, abstract, title, country as subject]	30
	2	cost-effectiveness.mp. [mp=heading words, abstract, title, country as subject]	1195
	3	cost-benefit.mp. [mp=heading words, abstract, title, country as subject]	5260

	4	cost-utility.mp. [mp=heading words, abstract, title, country as subject]	85
	5	cost.mp. [mp=heading words, abstract, title, country as subject]	44525
	6	cost-minimisation.mp. [mp=heading words, abstract, title, country as subject]	36
	7	cost-minimization.mp. [mp=heading words, abstract, title, country as subject]	246
	8	economic evaluation.mp. [mp=heading words, abstract, title, country as subject]	612
	9	6 or 4 or 3 or 8 or 7 or 2 or 5	44964
	10	9 and 1	6
	11	limit 10 to yr="2004 - 2008"	**2**

RESULTS OF THE SEARCH STRATEGIES FOR PHARMACOLOGIC AND NON-PHARMACOLOGIC TREATMENTS IN AD AND DEMENTIA PATIENTS

80 citations for HTA reports were identified. For the primary or secondary economic evaluations, a total of 750 citations were identified. After removing 196 duplicates, 554 citations were left for assessment (Table 34).

Table 34: Searches results for HTAs and cost-effectiveness studies in Alzheimer or dementia patients

Database	**Research for Alzheimer**	**Research for dementia**	**Total**
Search dates	2004-08/2008	2004-09/2008	
	HTAs reports		
CRD HTA	47	32	79
HTAs website	0	1	1
Total	47	33	80
	Economic evaluations and reviews of economic evaluations		
NHS EED	50	36	86
Medline (OVID)	235	41	276
Embase	333	52	385
Econlit	1	2	3
Total	619	131	750
Duplicates			196
Total			554

APPENDIX 2: CLASSIFICATION OF ECONOMIC STUDIES

		Are both costs (inputs) and consequences (outputs) of the alternatives examined?		
		No		Yes
		Examines consequences only	Examines costs only	
Is there a comparison of at least two alternatives?	No	*Partial evaluation*		*Partial evaluation*
		Outcome description	Cost description	Cost-outcome description
	Yes	*Partial evaluation*		*Full economic evaluation*
		Efficacy or effectiveness evaluation	Cost comparison	Cost-utility analysis (CUA) Cost-benefit analysis (CBA) Cost-effectiveness analysis (CEA) Cost-minimisation analysis (CMA)

Adapted from Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 3d edition; 2005.

APPENDIX 3: DATA EXTRACTION SHEETS

NON-PHARMACOLOGIC INTERVENTIONS

Study	**Graff MJ, Adang E, Vernooij-Dassen M, Dekker J, Jonsson L, Thijssen M, et al. Community occupational therapy for older patients with dementia and their caregivers: cost effectiveness study. BMJ 2008;336(7636):134-8.**		
Country	The Netherlands		
Design	RCT-based economic evaluation Probabilistic evaluation CEA		
Perspective	Societal		
Time window	3 months		
Interventions	Community occupational therapy to both the patients and his caregiver: cognitive and behavioural interventions (= CBT?) to patient and caregiver together Comparator: usual care		
Population	Mild to moderate dementia patients Brief cognitive rating scale (BCRS) – Mild 9-24, moderate 25-40. 132 patients with caregivers included		
Assumptions	Efficacy data from the RCT of Graff et al., BMJ 2006 ITT – LOCF for drops-out and missing data		
Data source for costs	Costing year not reported Diaries (filled in by the primary caregivers) Local direct Dutch costs Friction costs method		
Cost items included	Direct medical costs Direct non-medical costs Indirect costs		
Data source for outcomes	Combination of 3 outcome measures in a "successful treatment outcome": - Patients: Process skills – AMPS "assessment of motor and process skills" (21 items, score -3–4)and Performance scale - "interview of deterioration in daily activities in dementia" IDDD (measures need for assistance, 11 items, score0-44) - Caregiver: Competence skills – SCQ "sense of competence questionnaire" (27 items, score 27-135) "Successful treatment outcome" : Improvement of > 0.5 points, > 20% and > 5 points on the process, performance and competence scales, respectively (= significant clinical improvement)		
Discounting	Not applicable		
Costs	Cost per patient and caregiver	CBT	Usual care
	CBT	€1183	€0
	Total costs (including CBT)	€12563	€14311

Outcomes		CBT	Usual care
	Successful treatment, % of patients	37%	1.5%
Cost-effectiveness	CBT versus usual care: - ICosts: -1748 (-4244 – 748) - Difference in % of patients with a successful treatment: 36% (23 – 47) CE plane: The probability that Occupational therapy is a dominant option is 94% Main cost savings: informal care costs, admissions to hospitals, and nursing homes and homes for elderly (institutionalization)		
Sensitivity analysis	Bootstrap analyses to assess the uncertainty of the results but no formal sensitivity analyses		
Conclusions	"Occupational therapy to both patients and caregivers is cost-effective because, on average, it saved €1748 over three months (with a 94% probability), and yielded significant and clinically relevant improvements in daily functioning (patients) and sense of competence (caregiver)"		
Remarks	Study powered to detect a relevant difference in clinical (not economic) outcome.		

Study	**Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F. Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial. Health Technol Assess. 2008;12(4):iii.**
Country	UK
Design	RCT-based economic evaluation Probabilistic evaluation (bootstrap)
Perspective	Societal
Time window	15 months
Interventions	Social support to caregivers: access to a trained befriending facilitator providing one-to-one emotional support (companionship and conversation) to the caregiver. The role does not encompass instrumental support or activities aimed at increasing community participation. 6 months or longer intervention on a weekly basis Comparator: usual care, i.e. health, social and voluntary services
Population	Carers of patients with a primary progressive dementia (not clear how dementia is assessed) 236 carers included
Assumptions	Efficacy data from the BECCA trial
Data source for costs	Resources used evaluated through questionnaires Costs for both the carers and the patients Costing year: 2005 Direct costs source: national UK references Indirect costs source (time): average UK gross income of the year 2005
Cost items included	Not clearly defined but broadly the following cost categories were included: Intervention's costs Direct medical costs

<table>
<tr><td></td><td colspan="3">Direct non-medical costs
Indirect costs</td></tr>
<tr><td>Data source for outcomes</td><td colspan="3">- Carer well-being: depression measured by the Hospital Anxiety and Depression Scale (HADS)
- Carer health related quality of life: EQ-5D
- Patient health related quality of life: EQ-5D (assessed by the carer)</td></tr>
<tr><td>Discounting</td><td colspan="3">3.5% for both costs and outcomes of the second year</td></tr>
<tr><td rowspan="6">Costs</td><td></td><td>Befriending</td><td>Usual care</td></tr>
<tr><td>Intervention</td><td>£1138 (£395)</td><td>£11 (£65)</td></tr>
<tr><td>Other costs</td><td>…</td><td>…</td></tr>
<tr><td>Informal care time</td><td>£103 398 (£46 625)</td><td>£104 918 (£46 708)</td></tr>
<tr><td>Total costs</td><td>£122 665 (£46 843)</td><td>£120 852 (£45 778)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td rowspan="6">Outcomes</td><td></td><td>Befriending</td><td>Usual care</td></tr>
<tr><td>HADS score</td><td>6.03 (4.00)</td><td>6.71 (4.18)</td></tr>
<tr><td>QALYs - Carer</td><td>0.946 (0.245)</td><td>0.929 (0.260)</td></tr>
<tr><td>QALYs - Patient</td><td>0.365 (0.292)</td><td>0.314 (0.317)</td></tr>
<tr><td>QALYs – Care & Patient</td><td>1.311 (0.416)</td><td>1.243 (0.449)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Cost-effectiveness</td><td colspan="3">Base-case (QoL from the carer) – Befriending + usual care versus usual care alone:
- Decrease in HADS score: 0.468 (-0.5; 1.44)
- QALYs gained: 0.017
- Incremental costs: £1 813 (-£11 312; £14 984)
- Ratio of the mean incremental cost on the mean incremental outcome: £105 954 / QALY gained
CEAC: Prob (ICER) < £30 000 = 42.2%</td></tr>
<tr><td>Sensitivity analysis</td><td colspan="3">Scenario analyses:
- QoL from both the carer and the patient
o Incremental QALYs: 0.068 (-0.045; 0.185)
o Incremental costs: £1 813 (-£11 312; £14 984)
o Ratio: £26 848 / QALY gained
o CEAC: Prob (ICER) < £30 000 = 51.4%
- 24 months follow-up:
o Incremental QALYs: 0.024 (-0.083; 0.136)
o Incremental costs: £9 191 (-£7 864; £26 377)
o Ratio: £380 939 / QALY gained</td></tr>
<tr><td>Conclusions</td><td colspan="3">There was no significant evidence of effectiveness nor cost-effectiveness from the primary analyses on the ITT population</td></tr>
<tr><td>Remarks</td><td colspan="3"></td></tr>
</table>

Study	**Nichols LO, Chang C, Lummus A, Burns R, Martindale-Adams J, Graney MJ, et al. The cost-effectiveness of a behavior intervention with caregivers of patients with Alzheimer's disease. J Am Geriatr Soc. 2008;56(3):413-20.**		
Country	USA		
Design	RCT-based economic evaluation Non probabilistic evaluation CEA		
Perspective	Not stated but limited to a Straff+Caregivers' costs perspective		
Time window	6 months		
Interventions	Caregiver support 6 months intervention including modules focusing on information, safety, caregiver health and well-being, and behaviour management. Organization: 9 individual sessions delivered in the caregiver's home + 3 individual phone sessions + 5 support group sessions of five to six caregivers. Comparators: 2 brief "check-in" phone calls		
Population	Caregivers of patients diagnosed with AD or dementia N = 92 caregivers		
Assumptions	Data from the REACH II trial (Resources for Enhancing Alzheimer's Caregivers Health)		
Data source for costs	Only the intervention direct and indirect costs are considered – no medical costs Local actual costs for direct costs Opportunity costs for indirect costs US$ - Costing year not stated		
Cost items included	Direct costs: - Intervention: staff training, preparation and supervision + staff travel + material - Comparator: staff training, preparation and supervision + material Indirect costs: - Intervention: time spent by the caregiver to assist the interventions' sessions - Control: time spent by the caregiver to assist the phone sessions		
Data source for outcomes	Decrease in the amount of time spent by the caregiver in caregiving activities. Hours of non-caregiving gained or caregiving hours avoided		
Discounting	Not applicable		
Costs		Intervention	Control
	Staff costs	$1047	$50
	Caregiver costs	$167	$4
	Total costs	$1214	$54
Outcomes	Reduction in caregiving hours (baseline versus 6 months): - Intervention: 1.3 hours per day - Control: 0 hours per day		
Cost-	Caregiving hours avoided: 1.3 hours per day (or 234 hours per 6 months)		

effectiveness	ICost: $1160 (over 6 months) ICER: $4.96 / hour of care avoided.
Sensitivity analysis	None performed
Conclusions	According to the authors, this demonstrates that caregiver help is cost-effective. "Intervention costs were only $4.96 per day per caregiver to gain an additional hour of non-caregiving activities"
Remarks	Outcome measure not validated and rather questionable – basically, no medical effectiveness measure are considered. Selection bias since drop-outs and deaths occurring during the follow-up were simply ignored for the data analysis (no ITT analysis) Only the cost of the intervention (or control) is accounted for, no medical costs. Only the costs of the carer and the staff are accounted for – not the costs of the patients Rather poor quality of the study. This is a poor quality cost study – Discarded!

8 REFERENCES

1. NICE-SCIE. Dementia: supporting people with dementia and their carers in health and social care. Care guideline. National Institute for Health and Clinical Excellence (NICE) and Social Care Institute for Excellence; 2006. Clinical Guideline 42 Available from: http://www.nice.org.uk/guidance/cg42
2. Kurz X, Scuvee-Moreau J, Salmon E, Pepin JL, Ventura M, Dresse A, et al. [Dementia in Belgium: prevalence in aged patients consulting in general practice]. Rev Med Liege. 2001;56(12):835-9.
3. Qualidem. Reports of Qualidem I and II projects. 2005. Available from: www.qualidem.be
4. Mitchell A, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia - meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand. 2009.
5. Livingston G, Johnston K, Katona C, Paton J, Lyketsos CG, Old Age Task Force of the World Federation of Biological P. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. Am J Psychiatry. 2005;162(11):1996-2021.
6. Folstein M, Folstein S, McHugh P. Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975;12:189-98.
7. Hasselbalch SG, Baloyannis S, Denislic M, Dubois B, Oertel W, Rossor M, et al. Education and training of European neurologists in dementia. Eur J Neurol. 2007;14(5):505-9.
8. De Lepeleire J, Ylieff M, Buntinx F, Bouckaert F, Steeman E, Van Tichelt K, editors. Omgaan met dementerenden. Aanbevelingen van het Qualidem-project. : Garant; 2007.
9. RIZIV/INAMI. Het doelmatig gebruik van geneesmiddelen bij de behandeling van dementie bij ouderen. Consensus vergadering 24 november 2005. Folia Pharmacotherapeutica 2006;33(7).
10. BCFI. Transparantiefiche. Geneesmiddelen bij Dementie. 2008. Available from: http://www.bcfi.be/pdf/tft/TN_DEM.pdf
11. Wind A, Gussekloo J, Vernooij-Dassen M. NHG-Standaard Dementie (tweede herziening). Huisarts Wet 2003;46(13):754-67.
12. Nederlandse Vereniging voor Klinische Geriatrie. Richtlijn. Diagnostiek en medicamenteuze behandeling van dementie. 2005.
13. Waldemar G, Dubois B, Emre M, Georges J, McKeith IG, Rossor M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol. 2007;14(1):e1-26.
14. SBU. Dementia – Diagnostic and Therapeutic Interventions. A systematic review. Volume 2. June 2008. SBU; 2008. Available from: www.sbu.se
15. Duara R, Loewenstein DA, Potter E, Appel J, Greig MT, Urs R, et al. Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. Neurology. 2008;71(24):1986-92.
16. Nordberg A. Amyloid imaging in Alzheimer's disease. Curr Opin Neurol. 2007;20(4):398-402.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (IV-TR), 4th edn-text revised Washington DC.; 2000.
18. 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(7):939-44.
19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Memantin bei Alzheimer Demenz. Vorbericht A05-19C. Köln: IQWiG; 2008. Available from: http://www.iqwig.de/download/A05-19C_Vorbericht_Memantin_bei_Alzheimer_Demenz.pdf
20. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007;6(8):734-46.
21. SBU. Dementia – Caring, Ethics, Ethnical and Economical Aspects. A systematic review. Volume 3. June 2008. SBU; 2008. Available from: www.sbu.se
22. Harrison J, Minassian SL, Jenkins L, Black RS, Koller M, Grundman M. A neuropsychological test battery for use in Alzheimer disease clinical trials. Arch Neurol. 2007;64(9):1323-9.

23. Roberts J, Browne G, Milne C, Spooner L, Gafni A, Drummond-Young M, et al. Problem-solving counseling for caregivers of the cognitively impaired: effective for whom? Nurs Res. 1999;48(3):162-72.
24. Petrovic M, Hurt C, Collins D, Burns A, Camus V, Liperoti R, et al. Clustering of behavioural and psychological symptoms in dementia (BPSD): a European Alzheimer's disease consortium (EADC) study. Acta Clin Belg. 2007;62(6):426-32.
25. Grasel E, Wiltfang J, Kornhuber J. Non-drug therapies for dementia: an overview of the current situation with regard to proof of effectiveness. Dement Geriatr Cogn Disord. 2003;15(3):115-25.
26. McGonigal-Kenny ML, Schutte DL. Nonpharmacologic management of agitated behaviors in persons with Alzheimer disease and other chronic dementing conditions. J Gerontol Nurs. 2006;32(2):9-14.
27. Czaja SJ, Schulz R, Belle SH, Burgio LD, Armstrong N, Gitlin LN, et al. Data and safety monitoring in social behavioral intervention trials: the REACH II experience. Clin Trials. 2006;3(2):107-18.
28. Rieckmann N, Schwarzbach C, Nocon M, Roll S, Vauth C, Willich S, et al. Concepts of care for people with dementia. HTA report. Köln, Germany: DAHTA, DIMDI; 2009.
29. Frank W, Konta B. Congitive training in dementia and other disorders with cognitive deficits. Köln: DAHTA-DIMDI; 2005. HTA Berichte (26) Available from: www.dimdi.de
30. Sitzer DI, Twamley EW, Jeste DV. Cognitive training in Alzheimer's disease: a meta-analysis of the literature. Acta Psychiatr Scand. 2006;114(2):75-90.
31. Woods B, Spector A, Jones C, Orrell M, Davies S. Reminiscence therapy for dementia. Cochrane Database Syst Rev. 2005(2):CD001120.
32. Hansen RA, Gartlehner G, Lohr KN, Kaufer DI. Functional outcomes of drug treatment in Alzheimer's disease: A systematic review and meta-analysis. Drugs Aging. 2007;24(2):155-67.
33. Nguyen Q-A, Paton C. The use of aromatherapy to treat behavioural problems in dementia. Int J Geriatr Psychiatry. 2008;23(4):337-46.
34. Cameron M, Lonergan E, Lee H. Transcutaneous electrical nerve stimulation (TENS) for dementia. Cochrane Database Syst Rev. 2003(3):CD004032.
35. Peng WN, Zhao H, Liu ZS, Wang S. Acupuncture for vascular dementia. Cochrane Database Syst Rev. 2007(2):CD004987.
36. Sung H-C, Chang AM. Use of preferred music to decrease agitated behaviours in older people with dementia: a review of the literature. J Clin Nurs. 2005;14(9):1133-40.
37. Forbes D, Forbes S, Morgan DG, Markle-Reid M, Wood J, Culum I. Physical activity programs for persons with dementia. Cochrane Database Syst Rev. 2008(3):CD006489.
38. Watson R, Green SM. Feeding and dementia: a systematic literature review. J Adv Nurs. 2006;54(1):86-93.
39. Gitlin LN, Corcoran M, Winter L, Boyce A, Hauck WW. A randomized, controlled trial of a home environmental intervention: effect on efficacy and upset in caregivers and on daily function of persons with dementia. Gerontologist. 2001;41(1):4-14.
40. Gitlin LN, Winter L, Corcoran M, Dennis MP, Schinfeld S, Hauck WW. Effects of the home environmental skill-building program on the caregiver-care recipient dyad: 6-month outcomes from the Philadelphia REACH Initiative. Gerontologist. 2003;43(4):532-46.
41. Gitlin LN, Hauck WW, Dennis MP, Winter L. Maintenance of effects of the home environmental skill-building program for family caregivers and individuals with Alzheimer's disease and related disorders. J Gerontol A Biol Sci Med Sci. 2005;60(3):368-74.
42. Graff MJL, Vernooij-Dassen MJM, Thijssen M, Dekker J, Hoefnagels WHL, Rikkert MGMO. Community based occupational therapy for patients with dementia and their care givers: randomised controlled trial. BMJ. 2006;333(7580):1196.
43. Graff MJ, Adang EM, Vernooij-Dassen MJ, Dekker J, Jonsson L, Thijssen M, et al. Community occupational therapy for older patients with dementia and their care givers: cost effectiveness study. BMJ. 2008;336(7636):134-8.

44. Chapman SB, Weiner MF, Rackley A, Hynan LS, Zientz J. Effects of cognitive-communication stimulation for Alzheimer's disease patients treated with donepezil. J Speech Lang Hear Res. 2004;47(5):1149-63.
45. Onder G, Zanetti O, Giacobini E, Frisoni GB, Bartorelli L, Carbone G, et al. Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: randomised controlled trial. Br J Psychiatry. 2005;187:450-5.
46. Bottino CMC, Carvalho IAM, Alvarez AMMA, Avila R, Zukauskas PR, Bustamante SEZ, et al. Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients: a pilot study. Clin Rehabil. 2005;19(8):861-9.
47. Cahn-Weiner DA, Malloy PF, Rebok GW, Ott BR. Results of a randomized placebo-controlled study of memory training for mildly impaired Alzheimer's disease patients. Appl Neuropsychol. 2003;10(4):215-23.
48. Logsdon RG, McCurry SM, Teri L. Evidence-based psychological treatments for disruptive behaviors in individuals with dementia. Psychol Aging. 2007;22(1):28-36.
49. Ayalon L, Gum AM, Feliciano L, Arean PA. Effectiveness of nonpharmacological interventions for the management of neuropsychiatric symptoms in patients with dementia: a systematic review. Arch Intern Med. 2006;166(20):2182-8.
50. Verkaik R, van Weert JC, Francke AL. The effects of psychosocial methods on depressed, aggressive and apathetic behaviors of people with dementia: a systematic review. Int J Geriatr Psychiatry. 2005;20(4):301-14.
51. Hermans DG, Htay UH, McShane R. Non-pharmacological interventions for wandering of people with dementia in the domestic setting. Cochrane Database Syst Rev. 2007(1):CD005994.
52. Robinson L, Hutchings D, Dickinson HO, Corner L, Beyer F, Finch T, et al. Effectiveness and acceptability of non-pharmacological interventions to reduce wandering in dementia: a systematic review. Int J Geriatr Psychiatry. 2007;22(1):9-22.
53. Bharucha A, Anand V, Forlizzi J, Dew M, Reynolds Cr, Stevens S, et al. Intelligent Assistive Technology Applications to Dementia Care: Current Capabilities, Limitations, and Future Challenges. Am J Geriatr Psychiatry. 2008.
54. Kuske B, Hanns S, Luck T, Angermeyer MC, Behrens J, Riedel-Heller SG. Nursing home staff training in dementia care: a systematic review of evaluated programs. Int Psychogeriatr. 2007;19(5):818-41.
55. Parker D, Mills S, Abbey J. Effectiveness of interventions that assist caregivers to support people with dementia. International journal of evidence-based healthcare 2008;6(2):137-72.
56. Cooper C, Balamurali TBS, Selwood A, Livingston G. A systematic review of intervention studies about anxiety in caregivers of people with dementia. Int J Geriatr Psychiatry. 2007;22(3):181-8.
57. Selwood A, Johnston K, Katona C, Lyketsos C, Livingston G. Systematic review of the effect of psychological interventions on family caregivers of people with dementia. J Affect Disord. 2007;101(1-3):75-89.
58. Thompson CA, Spilsbury K, Hall J, Birks Y, Barnes C, Adamson J. Systematic review of information and support interventions for caregivers of people with dementia. BMC Geriatr. 2007;7:18.
59. Gallagher-Thompson D, Coon DW. Evidence-based psychological treatments for distress in family caregivers of older adults. Psychol Aging. 2007;22(1):37-51.
60. Spijker A, Vernooij-Dassen M, Vasse E, Adang E, Wollersheim H, Grol R, et al. Effectiveness of Nonpharmacological Interventions in Delaying the Institutionalization of Patients with Dementia: A Meta-Analysis. J Am Geriatr Soc. 2008.
61. Mittelman MS, Haley WE, Clay OJ, Roth DL. Improving caregiver well-being delays nursing home placement of patients with Alzheimer disease. Neurology. 2006;67(9):1592-9.
62. Mittelman MS, Roth DL, Clay OJ, Haley WE. Preserving health of Alzheimer caregivers: impact of a spouse caregiver intervention. Am J Geriatr Psychiatry. 2007;15(9):780-9.
63. Miller B, Guo S. Social support for spouse caregivers of persons with dementia. J Gerontol B Psychol Sci Soc Sci. 2000;55(3):S163-72.

64. Smits CH, de Lange J, Droes RM, Meiland F, Vernooij-Dassen M, Pot AM. Effects of combined intervention programmes for people with dementia living at home and their caregivers: a systematic review. Int J Geriatr Psychiatry. 2007;22(12):1181-93.

65. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ginkgohaltige Präparate bei Alzheimer Demenz. IQWiG-Berichte Nr. 39. Köln: IQWiG; 2008. Available from: http://www.iqwig.de/download/A05-19B_Abschlussbericht_Ginkgohaltige_Praeparate_bei_Alzheimer_Demenz.pdf

66. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2009(1):CD003120.

67. DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA. 2008;300(19):2253-62.

68. A. P. A. Work Group on Alzheimer's Disease and other Dementias, Rabins PV, Blacker D, Rovner BW, Rummans T, Schneider LS, et al. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. Am J Psychiatry. 2007;164(12 Suppl):5-56.

69. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Cholinesterase inhibitors in Alzheimer's disease. Final report A05-19A. Köln: IQWiG; 2007.

70. Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D, Levine M, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. 2008;148(5):379-97.

71. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev. 2006(2):CD003154.

72. Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, et al. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. Health Technol Assess. 2006;10(1):iii-iv, ix-xi, 1-160.

73. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006(1):CD005593.

74. Gill SS, Anderson GM, Fischer HD, Bell CM, Li P, Normand S-LT, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. Arch Intern Med. 2009;169(9):867-73.

75. van Dyck CH, Tariot PN, Meyers B, Malca Resnick E, for the Memantine MEMMDSG. A 24-week randomized, controlled trial of memantine in patients with moderate-to-severe Alzheimer disease. Alzheimer Dis Assoc Disord. 2007;21(2):136-43.

76. Winblad B, Jones RW, Wirth Y, Stoffler A, Mobius HJ. Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomised clinical trials. Dement Geriatr Cogn Disord. 2007;24(1):20-7.

77. Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT, Memantine MEMMDSG. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res. 2008;5(1):83-9.

78. Herrmann N, Lanctot KL. Pharmacologic management of neuropsychiatric symptoms of Alzheimer disease. Can J Psychiatry. 2007;52(10):630-46.

79. Thompson S, Herrmann N, Rapoport MJ, Lanctot KL. Efficacy and safety of antidepressants for treatment of depression in Alzheimer's disease: a metaanalysis. Can J Psychiatry. 2007;52(4):248-55.

80. Yury CA, Fisher JE. Meta-analysis of the effectiveness of atypical antipsychotics for the treatment of behavioural problems in persons with dementia. Psychother Psychosom. 2007;76(4):213-8.

81. Zuidema SU, van Iersel MB, Koopmans RTCM, Verhey FRJ, Olde Rikkert MGM. [Efficacy and adverse reactions of antipsychotics for neuropsychiatric symptoms in dementia: a systematic review]. Ned Tijdschr Geneeskd. 2006;150(28):1565-73.

82. Franco KN, Messinger-Rapport B. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. J Am Med Dir Assoc. 2006;7(3):201-2.

83. Ballard C, Waite J, Birks J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev. 2006(1):CD003476.

84. Maidment ID, Fox CG, Boustani M, Rodriguez J, Brown RC, Katona CL. Efficacy of memantine on behavioral and psychological symptoms related to dementia: a systematic meta-analysis. Ann Pharmacother. 2008;42(1):32-8.

85. Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study. BMJ. 2008;337:a1227.

86. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA. 2005;293(5):596-608.

87. Katz I, de Deyn PP, Mintzer J, Greenspan A, Zhu Y, Brodaty H. The efficacy and safety of risperidone in the treatment of psychosis of Alzheimer's disease and mixed dementia: a meta-analysis of 4 placebo-controlled clinical trials. Int J Geriatr Psychiatry. 2007;22(5):475-84.

88. Clegg A, Bryant J, Nicholson T, McIntyre L, De BS, Gerard K, et al. Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimers disease: a rapid and systematic review. Systematic review. The National Coordinating Centre for Health Technology Assessment (NCCHTA) on behalf of Southampton Health Technology Assessments Centre(SHTAC) Southampton.; 2001. Available from: http://www.hta.ac.uk/execsumm/summ501.htm

89. Shukla VK, Otten N. Drug treatments for Alzheimer's disease. III. A review of pharmacoeconomic evaluations. Systematic review. Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2000. Technology Report Issue 11 Available from: https://www.ccohta.ca/

90. Knowles J. Donepezil in Alzheimer's disease: an evidence-based review of its impact on clinical and economic outcomes. Core Evidence. 2006;1(3):195-219.

91. Antonanzas F, Rive B, Badenas JM, Gomez-Lus S, Guilhaume C. Cost-effectiveness of memantine in community-based Alzheimer's disease patients: An adaptation in Spain.[see comment]. Eur J Health Econ. 2006;7(2):137-44.

92. Caro J, Salas M, Ward A, Getsios D, Migliaccio-Walle K, Garfield F. Assessing the health and economic impact of galantamine treatment in patients with Alzheimer's disease in the health care systems of different countries. Drugs & Aging. 2004;21(10):677-86.

93. Fagnani F, Lafuma A, Pechevis M, Rigaud AS, Traykov L, Seux ML, et al. Donepezil for the treatment of mild to moderate Alzheimer's disease in France: the economic implications. Dementia & Geriatric Cognitive Disorders. 2004;17(1-2):5-13.

94. Feldman H, Gauthier S, Hecker J, Vellas B, Hux M, Xu Y, et al. Economic evaluation of donepezil in moderate to severe Alzheimer disease.[see comment]. Neurology. 2004;63(4):644-50.

95. Francois C, Sintonen H, Sulkava R, Rive B. Cost effectiveness of memantine in moderately severe to severe Alzheimer's disease: A Markov model in Finland. Clinical Drug Investigation. 2004;24(7):373-84.

96. Fuh JL, Wang SJ. Cost-effectiveness analysis of donepezil for mild to moderate Alzheimer's disease in Taiwan. International Journal of Geriatric Psychiatry. 2008;23(1):73-8.

97. Gagnon M, Rive B, Hux M, Guilhaume C. Cost-effectiveness of memantine compared with standard care in moderate-to-severe Alzheimer disease in Canada. Can J Psychiatry. 2007;52(8):519-26.

98. Green C, Picot J, Loveman E, Takeda A, Kirby J, Clegg A. Modelling the cost effectiveness of cholinesterase inhibitors in the management of mild to moderately severe Alzheimer's disease.[see comment]. Pharmacoeconomics. 2005;23(12):1271-82.

99. Jones RW, McCrone P, Guilhaume C. Cost effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. Drugs & Aging. 2004;21(9):607-20.

100. Jonsson L. Cost-effectiveness of memantine for moderate to severe Alzheimer's disease in Sweden. Am J Geriatr Pharmacother. 2005;3(2):77-86.

101. Martikainen J, Valtonen H, Pirttila T. Potential cost-effectiveness of a family-based program in mild Alzheimer's disease patients. Eur J Health Econ. 2004;5(2):136-42.

102. Teipel SJ, Ewers M, Reisig V, Schweikert B, Hampel H, Happich M. Long-term cost-effectiveness of donepezil for the treatment of Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci. 2007;257(6):330-6.

103. Weycker D, Taneja C, Edelsberg J, Erder MH, Schmitt FA, Setyawan J, et al. Cost-effectiveness of memantine in moderate-to-severe Alzheimer's disease patients receiving donepezil. Curr Med Res Opin. 2007;23(5):1187-97.

104. Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F. Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial. Health Technol Assess. 2008;12(4):iii.

105. Knapp M, Thorgrimsen L, Patel A, Spector A, Hallam A, Woods B, et al. Cognitive stimulation therapy for people with dementia: cost-effectiveness analysis. British Journal of Psychiatry. 2006;188:574-80.

106. Cohen JT, Neumann PJ. Decision analytic models for Alzheimer's disease: State of the art and future directions. Alzheimer's and Dementia. 2008;4(3):212-22.

107. Green C. Modelling disease progression in Alzheimer's disease: a review of modelling methods used for cost-effectiveness analysis. Pharmacoeconomics. 2007;25(9):735-50.

108. Kirby J, Green C, Loveman E, Clegg A, Picot J, Takeda A, et al. A systematic review of the clinical and cost-effectiveness of memantine in patients with moderately severe to severe Alzheimer's disease. Drugs Aging. 2006;23(3):227-40.

109. Oremus M. Systematic review of economic evaluations of Alzheimer's disease medications. Expert Review of Pharmacoeconomics and Outcomes Research. 2008;8(3):273-89.

110. Wimo A. Cost effectiveness of cholinesterase inhibitors in the treatment of Alzheimer's disease: a review with methodological considerations. Drugs & Aging. 2004;21(5):279-95.

111. Wimo A. Clinical and economic outcomes--friend or foe? Int Psychogeriatr. 2007;19(3):497-507.

112. Wimo A, Norlund A. Cost-effectiveness of treatments for Alzheimer's dementia. Expert Review of Pharmacoeconomics and Outcomes Research. 2007;7(1):83-90.

113. Wimo A, Norlund A. Commentary on "Health economics and the value of therapy in Alzheimer's disease." Cost-effectiveness studies. Alzheimer's and Dementia. 2007;3(3):157-61.

114. Caro JJ, Getsios D, Migliaccio-Walle K, Raggio G, Ward A, Group AS. Assessment of health economics in Alzheimer's disease (AHEAD) based on need for full-time care. Neurology. 2001;57(6):964-71.

115. Fuh J-L, Pwu R-F, Wang S-J, Chen Y-H. Measuring Alzheimer's disease progression with transition probabilities in the Taiwanese population. Int J Geriatr Psychiatry. 2004;19(3):266-70.

116. Neumann PJ, Hermann RC, Kuntz KM, Araki SS, Duff SB, Leon J, et al. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. Neurology. 1999;52(6):1138-45.

117. 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(4):413-22.

118. Neumann PJ, Kuntz KM, Leon J, Araki SS, Hermann RC, Hsu MA, et al. Health utilities in Alzheimer's disease: a cross-sectional study of patients and caregivers. Med Care. 1999;37(1):27-32.

119. Stewart A, Phillips R, Dempsey G. Pharmacotherapy for people with Alzheimer's disease: a Markov-cycle evaluation of five years' therapy using donepezil. Int J Geriatr Psychiatry. 1998;13(7):445-53.

120. 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(1):136-45.

121. 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(6):395-404.

122. Wimo A, Wallin JO, Lundgren K, Ronnback E, Asplund K, Mattsson B, et al. Impact of day care on dementia patients--costs, well-being and relatives' views. Fam Pract. 1990;7(4):279-87.

123. 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(1):49-65.

124. Drummond MF, Mohide EA, Tew M, Streiner DL, Pringle DM, Gilbert JR. Economic evaluation of a support program for caregivers of demented elderly. Int J Technol Assess Health Care. 1991;7(2):209-19.

125. Nocera S, Bonato D, Telser H. The contingency of contingent valuation. How much are people willing to pay against Alzheimer's disease? Int J Health Care Finance Econ. 2002;2(3):219-40.

126. Brodaty H, Peters KE. Cost effectiveness of a training program for dementia carers. Int Psychogeriatr. 1991;3(1):11-22.

127. McGuire RC. A case study in cost-effectiveness analysis for computer technology used in support of caregivers with Alzheimer's disease patients. Information Systems Innovations for Nursing: New Visions and Ventures ed. Moorhead & Delaney, editor. Thousand Oaks, CA: Sage Publications; 1998.

128. 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(9427):2105-15.

129. Herrmann N, Gill SS, Bell CM, Anderson GM, Bronskill SE, Shulman KI, et al. A population-based study of cholinesterase inhibitor use for dementia. J Am Geriatr Soc. 2007;55(10):1517-23.

130. Ivanoiu A, Sindic CJM. Cerebrospinal fluid TAU protein and amyloid beta42 in mild cognitive impairment: prediction of progression to Alzheimer's disease and correlation with the neuropsychological examination. Neurocase. 2005;11(1):32-9.

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