Cholinesterase inhibitors in Alzheimer's disease[1]

- Final report -

[Commission No. A05-19A]

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Executive summary

Background

The Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG]) was commissioned by the Federal Joint Committee to evaluate the benefits and harms of cholinesterase inhibitors (ChEIs) in Alzheimer's disease.

Research questions

The aims of this evaluation were:

- the evaluation of long-term treatment with a ChEI in Alzheimer's disease compared with placebo;
- the evaluation of long-term treatment with a ChEI in Alzheimer's disease compared with treatment with a different drug or non-drug intervention.

The focus of this evaluation was on patient-relevant therapy goals.

Methods

This evaluation was conducted on the basis of randomised controlled trials (RCTs) on the research questions outlined above. For this purpose, a systematic literature search was conducted in the bibliographic databases MEDLINE, EMBASE, and CENTRAL (in each case, coverage up to June 2006), as well as in CHID. In addition, reference lists of relevant secondary publications (systematic reviews, HTA reports, meta-analyses) were searched, and manufacturers of ChEIs were asked to provide information on relevant published or unpublished studies.

The evaluation included RCTs that investigated ChEIs (donepezil, galantamine and rivastigmine) in patients with Alzheimer's disease. The literature screening was conducted by 2 reviewers independently of one another.

After an evaluation of study quality, the results of the individual studies were collated according to therapy comparisons and therapy goals.

IQWiG's preliminary evaluation, the preliminary report, was published on the Internet (www.iqwig.de). Interested parties could submit written comments. Unclear aspects of these written comments were discussed in a scientific debate before production of the final report.

Results

Of all citations viewed, 54 publications on 33 studies were assessed as relevant. Of these publications, 48 publications on 27 studies were included in the evaluation. 22 studies were placebo-controlled (donepezil: 12, galantamine: 6, rivastigmine: 4). Five studies were direct comparisons of different ChEIs. A total of 9883 patients were investigated. Eleven of the relevant publications contained pooled analyses of several studies. Studies comparing ChEIs with other drug or non-drug interventions approved and available in Germany were not identified. Of the studies included, 16 showed minor and 11 showed major deficiencies in respect of study and publication quality.

Except for 2 studies (both on donepezil, duration approx. 1 year), all comparisons with placebo only involved a treatment or observation period of a maximum of 26 weeks. Even though the longer studies did not show fundamentally different results, robust conclusions can essentially only be made for a 6-month period. In contrast, 3 of the 5 studies comparing different ChEIs with each other lasted one year or longer. However, except for one study on donepezil and rivastigmine, validity was restricted due to an unblinded design, while the sample sizes were too small to detect differences or demonstrate equivalence.

Comparisons with placebo

In all studies, a dose-dependent effect was shown. In low-dose interventions, galantamine and rivastigmine showed no or uncertain efficacy (in contrast to donepezil). For galantamine, no noticeable difference was shown between doses of 16 mg and 24 mg. With regard to the reported adverse event rates, a dose-effect association was confirmed.

For the therapy goal "improvement in or prevention of restriction in activities of daily living", indications of a beneficial effect of all 3 drugs in the medium- and/or high-dose range were shown. The average effects determined by means of meta-analyses were about 3 score points on the Disability Assessment for Dementia (DAD) and Progressive Deterioration Scale (PDS) for galantamine and rivastigmine respectively. The corresponding estimates for donepezil cannot be inferred with sufficient certainty, as one must assume an over-estimation of the treatment effect in the corresponding meta-analysis. Nevertheless, indications of a beneficial effect can also be assumed for donepezil.

In respect of the accompanying psychopathology, no indications of a beneficial or detrimental effect of donepezil or rivastigmine can be inferred (for donepezil, due to unconvincing data; for rivastigmine, due to lack of data). There was an indication of a positive effect for galantamine. However, this effect was minor (1-2 score points on the Neuropsychiatric Inventory [NPI] scale).

For all 3 drugs, a beneficial effect on cognition was shown compared with placebo. This effect was about 2 (for donepezil 5 mg or flexible dose) to 3 score points (for donepezil 10 mg, galantamine, rivastigmine) on the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog).

For the therapy goal "improvement or maintenance of health-related quality of life", only data on donepezil were available from 2 studies, which did not show clear indications of either a beneficial or a detrimental effect. No data were available for galantamine or rivastigmine.

No (interpretable) data were available for the therapy goal "prevention of placement in a nursing home" (institutionalisation).

Very few deaths were reported in the studies, and no indications of a beneficial or detrimental effect of ChEIs on mortality can be inferred from these data.

For all drugs, higher discontinuation rates due to adverse events were reported for high-dose therapy. Moreover, more adverse events occurred which are associated with the effects of ChEIs (e.g., nausea, vomiting, diarrhoea). There were no indications that more patients taking ChEIs experienced serious adverse events than those taking placebo. However, it should be noted that the reporting in this regard was in part insufficient. No statements on rare or long-term adverse events can be made, due to the study designs and reporting methods used.

For donepezil, no indications of a beneficial or detrimental effect on caregiver-related quality of life can be inferred from the available results. For galantamine, an indication of a positive effect was shown. However, this effect was minor, with a dimension of 1/10 of the standard deviation. No relevant data were found for rivastigmine.

There were indications that data on rivastigmine for the therapy goal "reduction in the degree of care provided by caregivers or institutions" were collected for all 4 larger phase-III studies. However, so far these data have not been published, so no conclusions can be made in this regard. The data on donepezil were insufficiently robust (mainly for methodological reasons). Therefore, no indications of a beneficial effect on the degree of care can be inferred from them. One study on galantamine showed indications of a positive effect in this regard.

The global clinical impression was consistently improved by all 3 drugs.

For galantamine and rivastigmine, there were indications that the treatment effect was larger in severely impaired patients than in those less severely impaired. No differentiated statements can be made with regard to age, gender, or concomitant diseases.

Comparisons between cholinesterase inhibitors

A quantitive summary (meta-analysis) of comparative results on single outcomes was inappropriate, due to the limited number of studies available and the different study designs and methods used. Only 2 of the 5 studies had a sample size that was sufficiently large to detect moderate differences between treatment groups.

For donepezil vs. galantamine, neither study included provided a clear indication of a superiority of either drug with regard to the effect on activities of daily living, accompanying psychopathology, cognition, and therapy-related adverse events. No comparative or clearly interpretable data were reported for health-related quality of life of patients, institutionalisation, and carer-relevant outcomes.

For donepezil vs. rivastigmine, data from one study indicated a slight superiority of rivastigmine with regard to the effect on activities of daily living (effect estimate about 1/10 of the standard deviation); however, for methodological reasons the validity of these data is doubtful. There was no clear indication of a difference between these 2 drugs in respect of accompanying psychopathology, cognition, and mortality. Substantially higher adverse event rates occurred under rivastigmine, in particular concerning nausea, vomiting, loss of appetite and weight. No comparative data were reported on health-related quality of life and carer-relevant outcomes.

For galantamine vs. rivastigmine, only results of a 3-arm comparison with very low sample sizes were available. In this comparison, no differences were noticeable with regard to the effect on psychopathological outcomes and the occurrence of adverse events. No data were available for other outcomes.

Overall, in the comparative studies, no evidence of the superiority of one drug over the other can be inferred from the non-existing or at most minor differences (which were of insufficient certainty) for efficacy parameters. However, nor can the results be interpreted as showing equivalence between drugs, as the studies were not recognisably designed as equivalence or non-inferiority studies with an a priori definition of "irrelevant differences".

Conclusion

The ChEIs donepezil, galantamine, and rivastigmine have a benefit in patients with mild-to-moderate Alzheimer's disease with regard to the therapy goal "improvement in or maintenance of cognitive function". This applies to all administered doses of donepezil, and only to medium and high doses of galantamine and rivastigmine.

Moreover, for all 3 drugs, there are indications of a benefit in respect of the therapy goal "improvement in or prevention of restriction in activities of daily living".

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

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).

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

All 3 drugs triggered therapy-related adverse events in a dose-dependent manner. An effect on mortality cannot be inferred from the available data; however, the studies were not designed to make conclusions in this regard.

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). Overall, no clear advantage of any of the 3 drugs investigated can be inferred from the available data.

The statements made above mainly refer to a study period of up to 6 months. For a further weighing of benefits and harms, direct comparative studies including other therapy options (other drug or non-drug treatment strategies) would be desirable.

The relevance of ChEIs vs. other drug or non-drug interventions is unclear, due to lack of data.

Key words: cholinesterase inhibitors, donepezil, galantamine, rivastigmine, Alzheimer's disease, systematic review

TABLE OF CONTENTS

Page

LIST OF TABLES XIII

LIST OF FIGURES XV

LIST OF ABBREVIATIONS XVIII

1 BACKGROUND 22

1.1 Description of the underlying disease 22

1.2 Overview of the epidemiology and pathogenesis of Alzheimer's disease 22

1.3 Diagnosis of Alzheimer's disease 23

1.4 Treatment options for Alzheimer's disease 26

1.5 Therapy evaluation in Alzheimer's disease 27

2 AIM OF THE EVALUATION 30

3 PROJECT PROCEDURES 31

3.1 Course of the project 31

3.2 Summary of changes compared with the preliminary report 31

4 METHODS 33

4.1 Criteria for the inclusion of studies in the evaluation 33

4.1.1 Population 33

4.1.2 Test and comparator interventions 33

4.1.3 Outcomes 33

4.1.4 Study types 35

4.1.5 Other study characteristics 35

4.1.6 Inclusion and exclusion criteria 35

4.2 Literature search 36

4.2.1 Literature sources 36

4.2.2 Search for further published and unpublished studies 37

4.2.3 Identification of relevant studies 37

4.2.4 Search for additional information on relevant studies 38

4.2.5 Information from the hearing on the preliminary report 38

4.3 Evaluation of information 38

4.4 Synthesis and analysis of information 41

4.4.1 Study characterisation 41

4.4.2 Comparison of the results of individual studies 42

4.4.3 Meta-analysis 43
4.4.4 Sensitivity analysis 44
4.4.5 Subgroup analysis 44
4.5 Changes compared with the report plan 45
4.5.1 Changes during the preparation of the preliminary report 45
4.5.2 Changes after the publication of the preliminary report 46
5 RESULTS 47
5.1 Results of the literature search 47
5.1.1 Results of the systematic literature search 47
5.1.2 Queries to manufacturers 49
5.1.3 Queries to the authors 50
5.1.4 Resulting study pool 50
5.1.5 Information provided in the hearing 57
5.2 Characteristics of the studies included in the evaluation 57
5.2.1 Donepezil 57
5.2.2 Galantamine 74
5.2.3 Rivastigmine 85
5.2.4 Comparisons between different cholinesterase inhibitors 93
5.3 Results on therapy goals 104
5.3.1 Donepezil 104
5.3.2 Galantamine 133
5.3.3 Rivastigmine 153
5.3.4 Comparisons between different cholinesterase inhibitors 167
5.3.5 Sensitivity analyses 176
5.3.6 Subgroup analyses 177
5.4 Summary 179
6 DISCUSSION 185
7 CONCLUSION 200
8 LIST OF INCLUDED STUDIES 201
9 REFERENCES 207
APPENDIX A: SEARCH STRATEGY 219
APPENDIX B: LIST OF STUDIES PERUSED IN FULL TEXT BUT EXCLUDED (AND REASONS FOR EXCLUSION) 230
APPENDIX C: LIST OF SCREENED SYSTEMATIC REVIEWS 239

APPENDIX D: OVERVIEW OF THE OUTCOME PARAMETERS ASSESSED IN THE STUDIES 241

APPENDIX E: SHORT DESCRIPTION OF THE OUTCOME PARAMETERS USED 245

APPENDIX F: PREVIOUSLY UNPUBLISHED INFORMATION FROM PHARMACEUTICAL COMPANIES 249

APPENDIX G: ADDITIONAL META-ANALYSES 250

APPENDIX H: MEETING MINUTES OF THE SCIENTIFIC DEBATE 256

LIST OF TABLES

Table 1. ICD 10 criteria for Alzheimer's disease 24
Table 2. DSM-IV criteria for Alzheimer's disease 25
Table 3. NINCDS-ADRDA criteria for Alzheimer's disease 26
Table 4. Study pool 51
Table 5. Donepezil studies included 61
Table 6. Main inclusion and exclusion criteria (donepezil) 63
Table 7. Characterisation of the study populations (donepezil) 66
Table 8. Study and publication quality (donepezil) 71
Table 9. Galantamine studies included 76
Table 10. Main inclusion and exclusion criteria (galantamine) 77
Table 11. Characteristics of study populations (galantamine) 79
Table 12. Study and publication quality (galantamine) 83
Table 13. Rivastigmine studies included 87
Table 14. Main inclusion and exclusion criteria (rivastigmine) 88
Table 15. Characteristics of the study population (rivastigmine) 89
Table 16. Study and publication quality (rivastigmine) 92
Table 17. Included direct comparative studies on cholinesterase inhibitors 96
Table 18. Main inclusion and exclusion criteria of the direct comparative studies on cholinesterase inhibitors 98
Table 19. Characterisation of study populations in the direct comparative studies on cholinesterase inhibitors 100
Table 20. Study and publication quality: Comparative studies 103
Table 21. Donepezil: Results on daily living skills 105
Table 22. Donepezil: Results on accompanying psychopathology 109
Table 23. Donepezil: Results on cognitive function 111
Table 24. Donepezil: Study discontinuations, deaths, and adverse events 117
Table 25. Donepezil: Adverse events 119
Table 26. Donepezil: Results on the global clinical impression 132
Table 27. Galantamine: Results on daily living skills 135

Table 28. Galantamine: Results on accompanying psychopathology 137

Table 29. Galantamine: Results on cognitive function 139

Table 30. Galantamine: Study discontinuations, deaths, and number of patients with adverse events 142

Table 31. Galantamine: Adverse events 144

Table 32. Galantamine: Results on quality of life of (caregiving) relatives 149

Table 33. Galantamine: Results of the CIBIC-plus ≤ 4 ("no change" or "improvement") 152

Table 34. Rivastigmine: Results on daily living skills 154

Table 35. Rivastigmine: Results on cognitive function 156

Table 36. Rivastigmine: Study discontinuations, deaths, and number of patients with adverse events 159

Table 37. Rivastigmine: Adverse events 161

Table 38. Rivastigmine: Results for CIBIC-plus ≤ 3 (improvement) 166

Table 39. Rivastigmine vs. donepezil: Results on daily living skills 170

Table 40. Rivastigmine vs. donepezil: Results on cognitive function 171

Table 41. Rivastigmine vs. donepezil: Study discontinuations, deaths, and number of patients with adverse events 173

Table 42. Rivastigmine vs. donepezil: Adverse events 174

Table 43. Number of studies included and patients randomised 179

Table 44. Summary of results on therapy goals from placebo-controlled studies 181

Table 45. Summary of results on therapy goals from comparative studies on ChEIs 183

Table 46. Estimated and observed proportion of responders for the ADAS-cog (response criterion: 4 points) 187

Table 47. Comparison of therapy goals defined in the report plan and outcome parameters used in the studies 242

LIST OF FIGURES

Figure 1. Bibliographic literature search and other literature screening: final study pool for the evaluation 48

Figure 2. Donepezil: Meta-analysis of activities of daily living 107

Figure 3. Donepezil: Meta-analysis of accompanying psychopathology 110

Figure 4. Donepezil: Meta-analysis of cognitive function 113

Figure 5. Donepezil: Meta-analysis of cognitive function – low dose 113

Figure 6. Donepezil: Meta-analysis of cognitive function – flexible dose 114

Figure 7. Donepezil: Meta-analysis of cognitive function – high dose 114

Figure 8. Donepezil: Meta-analysis of study discontinuations due to adverse events – low dose 121

Figure 9. Donepezil: Meta-analysis of study discontinuations due to adverse events – flexible dose 121

Figure 10. Donepezil: Meta-analysis of study discontinuations due to adverse events – high dose 122

Figure 11. Donepezil: Meta-analysis of serious adverse events – low dose 122

Figure 12. Donepezil: Meta-analysis of serious adverse events – flexible dose 123

Figure 13. Meta-analysis of serious adverse events – high dose 123

Figure 14. Donepezil: Meta-analysis of the outcome "nausea" – low dose 123

Figure 15. Donepezil: Meta-analysis of the outcome "nausea" – flexible dose 124

Figure 16. Donepezil: Meta-analysis of the outcome "nausea" – high dose 124

Figure 17. Donepezil: Meta-analysis of the outcome "vomiting" – low dose 125

Figure 18. Donepezil: Meta-analysis of the outcome "vomiting" – flexible dose 125

Figure 19. Donepezil: Meta-analysis of the outcome "vomiting" – high dose 125

Figure 20. Donepezil: Meta-analysis of the outcome "diarrhoea" – low dose 126

Figure 21. Donepezil: Meta-analysis of the outcome "diarrhoea" – flexible dose 126

Figure 22. Donepezil: Meta-analysis of the outcome "diarrhoea" – high dose 127

Figure 23. Donepezil: Meta-analysis of the outcome "lack of appetite" – low dose 127

Figure 24. Donepezil: Meta-analysis of the outcome "lack of appetite" – high dose 127

Figure 25. Donepezil: Meta-analysis of the outcome "dizziness" – low dose 128

Figure 26. Donepezil: Meta-analysis of the outcome "dizziness" – flexible dose 128
Figure 27. Donepezil: Meta-analysis of the outcome "dizziness" – high dose 128
Figure 28. Galantamine: Meta-analysis of activities of daily living 136
Figure 29. Galantamine: Meta-analysis of accompanying psychopathology 138
Figure 30: Galantamine: Meta-analysis of cognitive function 140
Figure 31. Galantamine: Meta-analysis of study discontinuations due to adverse events 146
Figure 32. Galantamine: Meta-analysis of serious adverse events 146
Figure 33. Galantamine: Meta-analysis of the outcome "nausea" 146
Figure 34. Galantamine: Meta-analysis of the outcome "vomiting" 147
Figure 35. Galantamine: Meta-analysis of the outcome "diarrhoea" 147
Figure 36. Galantamine: Meta-analysis of the outcome "lack of appetite" 147
Figure 37. Galantamine: Meta-analysis of the outcome "dizziness" 148
Figure 38. Galantamine: Meta-analysis of quality of life of (caregiving) relatives 150
Figure 39. Rivastigmine: Meta-analysis of daily living skills 155
Figure 40. Rivastigmine: Meta-analysis of cognitive function 157
Figure 41. Rivastigmine: Meta-analysis of study discontinuations due to adverse events 162
Figure 42. Rivastigmine: Meta-analysis of serious adverse events 162
Figure 43. Rivastigmine: Meta-analysis of the outcome "nausea" 163
Figure 44. Rivastigmine: Meta-analysis of the outcome "vomiting" 163
Figure 45. Rivastigmine: Meta-analysis of the outcome "diarrhoea" 163
Figure 46. Rivastigmine: Meta-analysis of the outcome "loss of appetite" 164
Figure 47. Rivastigmine: Meta-analysis of the outcome "dizziness" 164
Figure 48: Association between the effect observed on cognition in placebo-controlled studies and the difference in discontinuation rates between test group and placebo group 189
Figure 49. Rivastigmine: Meta-analysis of daily living skills (including B351; fixed and random effects) 250
Figure 50. Rivastigmine: Meta-analysis of cognitive function (including B351; fixed and random effects) 251
Figure 51. Rivastigmine: Meta-analysis of study discontinuations due to adverse events (including B351; fixed and random effects) 252

Figure 52. Rivastigmine: Meta-analysis of the outcome "nausea" (including B351; fixed and random effects) 253

Figure 53. Rivastigmine: Meta-analysis of the outcome "vomiting" (including B351) 254

Figure 54. Rivastigmine: Meta-analysis of the outcome "dizziness" (including B351) 254

Figure 55. Rivastigmine: Meta-analysis of the outcome "diarrhoea" (including B351) 254

Figure 56. Rivastigmine: Meta-analysis of the outcome "lack of appetite" (including B351)255

LIST OF ABBREVIATIONS

Abbreviation	Meaning
ABS	Adaptive Behavior Scale
ACTS	Allocation of Caregiver Time Survey
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale – cognitive subscale
ADCS-ADL	AD Cooperative Study Activities of Daily Living Inventory
AD-CVD	Alzheimer's disease and concurrent cerebrovascular disease
ADEAR	Alzheimer's Disease Education & Referral Center
ADFACS	AD Functional Assessment and Change Scale
ADL	activities of daily living
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APP	amyloid precursor protein
Aβ	β-amyloid peptide
bADL	(basic) activities of daily living
BADLS	Bristol Activities of Daily Living Scale
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BRDS	Blessed Roth Dementia Scale
CAS	Caregiver Activity Survey
CBS	Caregiving Burden Scale
CDR, CDR-SB	Clinical Dementia Rating Scale, Clinical Dementia Rating Scale – Sum of the Boxes
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CGIC	Clinical Global Impression of Change
CHID	Combined Health Information Database
CI	confidence interval
CIBIC	Clinician's Interview-based Impression of Change

Abbreviation	Meaning
CIBIC-plus	Clinician's Interview-based Impression of Change (with additional caregiver input)
CMBT	Computerized Memory Battery Test
CMCS	Caregiver-rated Modified Crichton Scale
CNS	central nervous system
CSS	Caregiver Stress Scale
CT	computer tomography
CVD	cerebrovascular disease
DAD	Disability Assessment for Dementia Scale
DARE	Database of Abstracts of Reviews of Effects
DEMQOL	Dementia Quality of Life Instrument
DMR	Dementia Questionnaire for Mentally Retarded Persons
DON	donepezil
DRC	Diagnostic Research Criteria
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMBASE	Excerpta Medica Database
EMEA	European Agency for the Evaluation of Medicinal Products
f	female
FAST	Functioning Assessment Staging Scale
FRS	Functional Rating Scale
GAL	galantamine
GAL-PRC	galantamine prolonged release
GAS	Goal Attainment Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GBS	Gottfries-Bråne-Steen Scale
GCP	good clinical practice
GDS	Global Deterioration Scale
HTA	health technology assessment
IADL, iADL	(instrumental) activities of daily living
ICD	International Classification of Diseases
IDDD	Interview for Deterioration in Daily Living Activities in Dementia

Abbreviation	Meaning
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention-to-treat
J-CGIC	Japanese-Clinical Global Impression of Change
LJ	life year
LOCF	last observation carried forward
MCI	mild cognitive impairment
MEDLINE	Medical Literature Analysis and Retrieval System Online
MENFIS	Mental Function Impairment Scale
MMSE (sMMSE)	(standardised) Mini Mental State Examination
MRT	magnetic resonance tomography
N	number
n.r.	not reported
n.s.	not statistically significant
NICE	National Institute for Health and Clinical Excellence
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
NOSGER	Nurses' Observation Scale for Geriatric Patients
NPI	Neuropsychiatric Inventory
NPI-D	Neuropsychiatric Inventory Caregiver Distress Scale
NPI-NH	Neuropsychiatric Interview – Nursing Home
OC	observed cases
p	p-value, probability
PDS	Progressive Deterioration Scale
PET	positron emission tomography
PGAS	Patient Global Assessment Scale
PP	per protocol
PSMS	Physical Self-Maintenance Scale
QoL	quality of life
RCT	randomised controlled trial
RIV	rivastigmine
RUD	Resource Utilization in Dementia

Abbreviation	Meaning
SCGB	Screen for Caregiver Burden
SD	standard deviation
SEM	standard error of the mean
SF-36	Short Form Health Survey (36 items)
SIB	Severe Impairment Battery
SN	Stellungnahme (comment)
VaD	vascular dementia
VFA	Verband Forschender Arzneimittelhersteller (German Association of Research-based Pharmaceutical Companies)
WHO	World Health Organization

1 BACKGROUND

1.1 Description of the underlying disease

The term dementia refers to a chronic and mostly progressive dysfunction of the brain, which leads to a deterioration of memory and other cognitive functions, to a restriction in activities of daily living, and to accompanying psychopathological symptoms of differing severity. Alzheimer's disease (AD) is the most common cause of the dementia syndrome and accounts for about 60% of all cases. Alzheimer's disease also often occurs as mixed-type dementia together with vascular dementia [1-3]. Other causes of dementia (e.g., Pick's disease, Lewy body dementia, Creutzfeldt-Jacob disease), as well as reversible dementia syndromes caused by other diseases, are much rarer.

The dementia syndrome is characterised by dysfunctions in several areas (e.g., memory, cognitive function, emotional control). Whereas Alzheimer's disease in particular is initially noticeable mainly through cognitive symptoms (especially memory dysfunction), restrictions in daily living skills (especially basic skills) determine the degree of care required. In addition, accompanying psychopathological symptoms such as apathy, depression, agitation, anxiety, insomnia, and paranoid symptoms play a key role where quality of life is concerned. Psychopathological symptoms and behavioural changes, which sometimes also occur in early disease stages, can result in a heavy burden for affected patients and their caregiving relatives.

Persons with mild cognitive impairment (MCI) are considered to have an increased risk of developing dementia. Patients with MCI have an impaired memory function, with only a minor restriction of activities of daily living; therefore, one does not refer to this condition as "dementia" (see also the review by Peterson RC 2001 [4])

In the light of the current discussion on the distinction of the term "MCI", studies involving this group of patients are not the subject of the present report. Cholinesterase inhibitors (ChEIs) are not approved for this indication.

A differentiation between Alzheimer's disease and vascular dementia can be made on the ground of clinical criteria; however, misclassifications may occur in individual cases [5,6]. Imaging techniques to identify subclinical cerebral ischaemia may be helpful in this regard. Clinically distinguishable types of dementia either due to Alzheimer's disease or vascular disease are more frequently found in younger patients. Beyond the age of 75, mixed-type pathologies of typical Alzheimer-lesions and vascular lesions are common [7].

1.2 Overview of the epidemiology and pathogenesis of Alzheimer's disease

After correction for the different life expectancy between genders, Alzheimer's disease is slightly more common in women than in men [8]. Besides age and gender, other risk factors

confirmed in studies are a positive family history and the existence of the E4 allele of the ApoE gene.

An evaluation of European epidemiologic studies with operationalised diagnostic criteria showed the following prevalence rates for dementia syndromes: 1% (65 to 69-year-olds), 4% (70 to 74-year-olds), 6% (75 to 79-year-olds), 13% (80 to 84-year-olds), 22% (85 to 89-year-olds) and 32% (90 to 94-year-olds) [9]. The disease progresses continuously and is associated with an increased mortality risk. The mean survival time after diagnosis is substantially lower than in the general population of the same age and is comparable to that of other serious geriatric diseases [10]. Due to increasing efforts in the early diagnosis of Alzheimer's disease, increased public awareness, and increasing services such as "memory consultation hours", an apparent extension of disease duration may occur through earlier diagnosis [11,12]. If the disease is diagnosed early, in the first 6 months only slight progression is usually noticeable.

The metabolism of the amyloid precursor protein (APP) and its degradation to β-amyloid peptides play a predominant role in the pathogenesis of Alzheimer's disease. The corresponding evidence was inferred from studies on human gene mutations of the amyloid metabolism and on transgenic mice [13-15]. In addition to a primary defect in APP metabolism with an increased formation of Aβ (in particular, in early disease associated with a genetic predisposition), a primary defect in the degradation of Aβ as the cause of sporadic types of Alzheimer's disease is also discussed. Especially in older age or with progressive pathology, numerous connections to further tissue-damaging processes seem to exist (oxidative stress, cell damage through glutamatergic excitotoxicity, inflammatory processes, formation of neurofibrils, neuronal apoptosis, etc.). Initial neuropathological changes precede manifest cognitive dysfunction by many years.

Alzheimer's disease is classified into different disease severities, for example by means of the Mini Mental State Examination (MMSE) scores or the Global Deterioration Scale (GDS). Most affected patients are diagnosed in the stage of mild to moderate dementia [16]. A shift to earlier diagnosis may occur in the near future for the reasons stated above (change in public awareness, potential new treatment options, new diagnostic tests) [11,12].

1.3 Diagnosis of Alzheimer's disease

In clinical practice, no sufficiently sensitive and specific surrogate parameters are currently available to diagnose Alzheimer's disease. Besides evidence of typical clinical symptoms, the diagnosis is made by exclusion of potential alternative causes. On an international level, the diagnosis of Alzheimer's disease is made according to ICD-10 (Table 1) or the related DSM-IV criteria (Table 2). ICD-9 and DSM-III-R are previous versions of the ICD-10 and DSM-IV classification systems.

The ICD-10 criteria require the existence of a dementia syndrome with an insidious onset and slow deterioration, the exclusion of other neurological or systemic causes (such as endocrine diseases, vitamin-B12 deficiency, neurosyphilis or hydrocephalus) and the lack of an acute onset, or of focal neurological symptoms such as hemiparesis and loss of visual field. The definite diagnosis of Alzheimer's disease can only be made post mortem by a brain autopsy or, in the rare case of the dominantly inherited type, by a gene mutation analysis.

Table 1. ICD 10 criteria for Alzheimer's disease

Presence of dementia	1. Memory impairment
	2. Additional cognitive impairment
	3. Resulting restrictions in daily living
	Symptoms occurring not only during a delirium Continuation of symptoms > 6 months increases diagnostic accuracy
Course of disease progression	Insidious, no sudden onset.
Other diseases	No indication/exclusion of other diseases (e.g., endocrine-metabolic disorders, normal-pressure hydrocephalus, subdural haematoma)
No early occurrence of neurological focal signs	E.g., hemiparesis, ataxia, hemianopsia
Coding	F00.0 AD early onset (< 65 years) F00.1 AD late onset (≥ 65 years)

according to [17]

ICD-10 and DSM-IV distinguish between 2 subtypes of Alzheimer's disease: early-onset Alzheimer's disease (< 65 years), and late-onset Alzheimer's disease (≥ 65 years). This differentiation is not relevant with regard to symptoms, course of disease, and neuropathology. Genetically associated forms of Alzheimer's disease are usually of early onset. However, they are rare, even in patients with early-onset disease.

Table 2. DSM-IV criteria for Alzheimer's disease

Criterion A1	Memory impairment
Criterion A2	Further cognitive disorder A2a Aphasia A2b Apraxia A2c Agnosia A2d Disturbance in executive functioning
Criterion B	Decline from a previous level of functioning and impairment in daily functioning
Criterion C	Gradual onset and continuing cognitive decline.
Criterion D	The cognitive deficits are not due to any of the following: D1 Other central nervous system conditions D2 Systemic conditions D3 Substance-induced conditions
Criterion E	The deficits do not occur exclusively during the course of a delirium
Criterion F	The disturbance is not accounted for by another Axis I disorder (e.g., major depressive disorder, schizophrenia)
Coding	290.10 AD early onset (≤ 65 years) 290.0 AD late onset (> 65 years)

according to [18]

Besides the ICD-10 and DSM-IV criteria, the criteria applied most often in clinical studies are those of the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [19]. The diagnosis is classified as "definite" (clinical diagnosis with histological confirmation), "probable" (typical clinical symptoms without histological confirmation), and "possible" (with atypical symptoms; possible alternative cause which, however, is not regarded as the cause of dementia in the individual case). The sensitivity and specificity for the diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria are about 0.65 and 0.75 respectively (Table 3).

Table 3. NINCDS-ADRDA criteria for Alzheimer's disease

Clinical diagnosis of possible AD

- Dementia syndrome with atypical symptoms or atypical course without noticeable other neurological or internal cause of dementia
- Dementia syndrome in the presence of another disease sufficient to produce dementia, but in this case is not considered the decisive cause of dementia
- Progressive deficit in single area of cognition

Clinical diagnosis of probable AD

I. Necessary requirements:

- Signs of dementia established by clinical examination and by neuropsychological tests (e.g. MMSE)
- Deficits in 2 or more areas of cognition
- Progressive worsening of memory and other cognitive function
- No disturbance of consciousness
- Onset between ages 40 and 90
- Exclusion of other physical or neurological disease that could account for the symptoms

II. Supportive findings:

- Progressive deterioration of language (aphasia), motor skills (apraxia) and perception (agnosia)
- Impaired activities of daily living and altered patterns of behaviour
- Positive family history of Alzheimer's disease, particularly if confirmed neuropathologically
- Normal lumbar puncture, unspecific EEG changes, progression of cerebral atrophy confirmed by CT

III. Other features consistent with the diagnosis of probable Alzheimer's disease:

- Plateaus in the course of progression of the illness
- Associated symptoms such as depression, insomnia, incontinence, delusions, illusions, hallucinations, "catastrophic" outbursts, sexual disorders, weight loss
- Especially with more advanced disease: increased muscle tone, myoclonus, gait disorder, seizures
- CT normal for age

IV. Symptoms and patient history that make the diagnosis of Alzheimer's disease unlikely:

- Sudden, apoplectic onset
- Focal neurological deficits: hemiparesis, visual field deficits, ataxia early in the course of the disease
- Seizures or gait disturbances early in the course of the disease

according to [19]

1.4 Treatment options for Alzheimer's disease

Treatment options for Alzheimer's disease comprise various areas, for example, according to Cummings 2004 [20]:

- Establishment of activities to maintain and promote physical and mental health;
- Coordination of the collaboration between therapists, relatives, and other caregivers;
- Use of antidementia drugs (ChEIs, N-methyl-D-aspartate [NMDA] antagonists, and ginkgo biloba) in the dementia stages for which these drugs are approved in Germany;

- Non-drug interventions or psychopharmacological agents to treat psychopathological symptoms and behavioural disorders.

In the 1970s, a markedly decreased activity of central cholinergic neurons was shown in post-mortem examinations of the brain of patients with advanced Alzheimer's disease [21]. An association of these findings with cognitive deficits, disease severity [22], and mental symptoms is assumed [23]. Subsequently, together with the observation that centrally active anticholinergic drugs led to a reduction in cognitive function, many efforts were made to treat dementia symptoms in Alzheimer's disease by intensifying cholinergic neurotransmission. Whereas acetylcholine precursors in the form of nutritional additives did not show an effect, and cholinergic agonists (cholinergic stimulating agents) are so far not available for clinical use, 3 ChEIs are currently available in Germany out of the numerous ChEIs tested in clinical studies (donepezil, approved 1996; rivastigmine, approved 1998; galantamine, approved 2001). The ChEI tacrine, which was approved in Germany in 1995 under strict requirements, is no longer available. These 3 ChEIs are also approved in most other European countries and the United States.

1.5 Therapy evaluation in Alzheimer's disease

There are evident problems in assessing the needs of patients with Alzheimer's disease and the impairments they suffer. On the one hand, impairments fluctuate or are only evident in specific situations; on the other, the disease-related loss of communication skills can restrict the adequate formulation of needs or preferences by the affected patient. Another specific problem of dementia is that some patients have a lack of self-awareness with regard to their deficits and need for help. According to some experts, this disease-related lack of self-awareness can also lead to a severe external misjudgement of potential impairments and needs [24].

The impact of Alzheimer's disease and the efficacy of treatment can be assessed by the patients themselves (with the limitations stated above), by clinicians, and by relatives or other carers. The assessment of the extent of disease symptoms and the resulting impairments can vary according to the area of evaluation and the evaluator [25].

In view of the complex and changing requirements of patients (depending on disease progression), therapeutic measures can be classified into 3 areas. Psychopharmacologic agents (antidementia drugs or other psychotropic drugs) aim to directly change cognitive or psychological abilities of patients with dementia. Psychological-behavioural interventions aim to modify behavioural patterns or develop coping strategies in the early stage of disease. Social interventions (counselling/training of relatives, daycare centres, nursing services, home care, etc.) are important interventions in moderate to severe dementia. All 3 intervention levels – chemical (antidementia drugs and other psychopharmacologic agents), psychological

(e.g., cognitive strategies) and social (work with relatives, provision of care) interact substantially.

It is still controversially discussed which instruments can appropriately evaluate the efficacy of drug and non-drug therapies in Alzheimer's disease [24,26,27]. In most therapy studies, the treatment result is evaluated on the basis of cognitive function, especially by means of the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-cog) scale [28] or the Mini Mental State Examination (MMSE) scale [29]. In addition, global evaluation scales are used, such as the Clinician's Interview-based Impression of Change (CIBIC) [30,31]. In order to consider the complexity of the disease, scales are also employed that measure daily living skills (activities of daily living: ADL [32]), often further divided into basic ADL (bADL) and instrumental ADL (iADL) [33]. Instrumental ADL areas (handling money, making phone calls, etc.) are often affected at the early stage of disease, whereas basic ADL areas (e.g., washing and dressing) are closely associated with the increasing need of care in the moderately severe disease stage. A further scale that measures restrictions in daily activities is the Progressive Deterioration Scale (PDS). To measure the accompanying psychopathology, which can be evident in all stages of disease but mainly becomes noticeable from the moderate stage onwards, specific interviews are conducted with caregivers (e.g., NPI; Neuropsychiatric Inventory [34]).

The ADAS-cog scale is completed by an experienced rater based on a direct examination of the patient and the observed response to questions. The ADL, PDS and NPI are based on information provided by relatives. Studies on the reliability and validity of these commonly used scales are available and in part show slightly deviating results [35-38].

So far only few instruments are available to measure health-related quality of life in Alzheimer's disease, which is due to the difficulties in gaining reliable information directly from affected patients. A negative impact of the disease on quality of life has, however, often been reported [39], as well as the ability of affected patients to speak about their subjective experience [40]. In a recent study, instruments to assess quality of life were evaluated and a new disease-specific instrument was developed and validated [24]. It was shown that marked deviations may exist regarding the assessment of patients' health-related quality of life, depending on whether this was assessed by patients or relatives/nursing staff. Agreement is higher in patients who live closely with relatives and lower if strong cognitive impairment or marked affective symptoms exist [41].

The impact of Alzheimer's disease on relatives and caregivers increases with the progression of disease. The everyday need of care, as well as behavioural problems, communication difficulties and possible social stigmatisation, may place a heavy burden on relatives. However, the intensity of care, in particular the time invested, does not necessarily reflect the mental and physical burden placed on relatives. The impact of the disease on relatives can, for example, be measured with quality of life scales.

The literature on Alzheimer's disease is inconsistent regarding the criteria for the efficacy of interventions. As criteria for efficacy, regulatory authorities often require the assessment of cognitive function (e.g., measured on the ADAS-cog scale), the global clinical impression, as well as daily living skills. A change in more than one assessment criterion is desirable. To what extent an intervention should influence such a criterion to be able to speak of a benefit of an intervention is, however, a matter of controversy.

Ideally, all instruments for assessing efficacy should show acceptable psychometric characteristics, such as reliability, validity (construct validity) and sensitivity to change.

2 AIM OF THE EVALUATION

The aims of this evaluation result from the wording of the commission awarded by the Federal Joint Committee (Gemeinsamer Bundesausschuss), as well as the availability and approval status of ChEIs in Germany.

The aims of this evaluation were:

- the evaluation of long-term treatment with a ChEI in Alzheimer's disease compared with placebo,

and

- the evaluation of long-term treatment with a ChEI in Alzheimer's disease compared with treatment with a different drug or non-drug therapy option.

The focus of this evaluation was on patient-relevant therapy goals.

In this report, the term "cholinesterase inhibitors" refers to all drugs of this class that are approved and available in Germany for treatment of Alzheimer's disease:

- Donepezil
- Galantamine
- Rivastigmine

This evaluation was conducted on the basis of the comparison and weighing of desired and undesired effects of the separate drugs (weighing of benefits and harms).

3 PROJECT PROCEDURES

3.1 Course of the project

The Federal Joint Committee (Gemeinsamer Bundesausschuss) commissioned IQWiG in writing on 22.02.2005 to evaluate the benefits and harms of different drugs approved for the treatment of Alzheimer's disease. This also includes the evaluation of ChEIs. The nature of this commission was specified with the Federal Joint Committee in advance on the basis of a draft of the commission on 02.02.2005.

External experts were involved in the commission, and contributed to the production of the report plan, the literature search and its evaluation, as well as to the production of the preliminary report.

In order also to consider the opinion of relatives in the definition of patient-relevant outcomes in the evaluation, a meeting took place with representatives of the German Alzheimer's Disease Society. The representatives of this society were relatives of patients with dementia. Direct questioning of affected patients did not take place. The subsequent discussion was held within IQWiG's internal project group.

The report plan was finalised on the 02.06.2005, forwarded to the Federal Joint Committee, and then published on the Internet. On 12.06.2006, an amendment on the report plan was finalised and published on 19.06.2006. The preliminary evaluation, the preliminary report, was published on the Internet on 08.09.2006. Comments on this preliminary report could be submitted until the 06.10.2006 by all interested persons, institutions and societies, including private persons, scientific societies and commercial enterprises. Unclear aspects of the written comments were then discussed with the persons submitting comments in an oral scientific debate on 14.11.2006 with regard to their relevance to the final report. The meeting minutes of this scientific debate are provided in Appendix H. In addition, an external review of the preliminary report was performed.

After the scientific debate, IQWiG produced the present final report, which was published on the Internet 8 weeks after being forwarded to the Federal Joint Committee.

3.2 Summary of changes compared with the preliminary report

After the hearing, the following changes were made to the preliminary report and included in the final report:

- Modified evaluation of study quality due to additional information provided by the manufacturers, as well as corrections;

- Supplementation of single results due to additional information provided by the manufacturers;

- For study results on galantamine: supplementation of a meta-analytic summary of the results on the quality of life of (caregiving) relatives.

4 METHODS

4.1 Criteria for the inclusion of studies in the evaluation

4.1.1 Population

Due to the epidemiology of Alzheimer's disease and the approval status of ChEIs, patients with mild to moderately severe Alzheimer's disease and patients with mixed-type dementia (Alzheimer's disease and vascular brain damage) were to be included in the evaluation. This definition also allowed, for example, the concomitant diagnosis of vascular dementia and Alzheimer's disease. The confirmation of diagnosis had to be conducted according to generally accepted criteria (e.g., ICD-9, ICD-10, DSM-III-R, DSM-IV or NINCDS-ADRDA) as described in the relevant EMEA publication [42]. The determination of disease severity was based on the corresponding definition used in the study. The classifications used were not necessarily consistent with other classification schemes, and there were also minor deviations between studies. A rough classification was that a score of least 10 was mostly required in the MMSE for "moderately severe dementia", and a score of at least 20 (to a maximum of 26) for "mild dementia".

Studies were not considered that solely included patients with MCI, vascular dementia, dementia due to Parkinson's disease, Lewy body disease, Creutzfeldt-Jacob disease, or other rare causes.

4.1.2 Test and comparator interventions

The test interventions considered were the ChEIs donepezil, galantamine, and rivastigmine in all approved forms and doses.

Placebo therapy, any other drug interventions (including a different ChEI from the ChEI used in the test intervention), or non-drug interventions for Alzheimer's disease were considered as comparator interventions.

4.1.3 Outcomes

The outcomes investigated in this evaluation were parameters that enabled an assessment of the following patient-relevant therapy goals:

- Improvement in or prevention of restrictions in activities of daily living;
- Improvement or normalisation of concomitant psychopathological symptoms (e.g., depression, sleep-wake reversal, mania, agitation);
- Improvement or maintenance of cognitive function;

- Improvement or maintenance of health-related quality of life;
- Prevention of placement in a nursing home (institutionalisation);
- Reduction in mortality;
- Reduction in treatment-related adverse events.

In addition, parameters were used as outcomes that enabled an assessment of the following therapy goals relevant to relatives:

- Improvement or maintenance of the quality of life of (caregiving) relatives[2]
- Reduction in the degree of care provided by one or several caregiver(s) or institutions(s)

As supplementary information, results are also reported that refer to the "improvement or maintenance of the clinical disease stage according to the clinical impression".

Results on therapy goals relevant to relatives and results that refer to the "improvement or maintenance of the clinical disease stage according to the clinical impression" are not primarily considered in the evaluation. However, conclusions may possibly be drawn regarding the association between changes in these outcomes and changes in patient-relevant outcomes.

[2] In this text, the term "relatives" as a rule refers to all direct relatives, but also to other caregiving persons ("caregivers").

4.1.4 Study types

Randomised controlled trials (RCTs) provide the most reliable results for the evaluation of the benefits of a medical intervention, as they are least prone to produce uncertainty of results, insofar as they have been conducted with appropriate methods and in accordance with the relevant research question. An evaluation within the framework of RCTs is possible and feasible in practice for all therapy goals listed in Section 4.1.3 and the interventions listed in Section 4.1.2. Therefore, only RCTs were included in this evaluation as relevant scientific literature.

4.1.5 Other study characteristics

When drugs for cognitive disorders are administered for the first time, the Drug Commission of the German Medical Profession recommends a control examination after 12 weeks in order to assess therapy success [43]. EMEA recommends a study duration of at least 24 weeks for the assessment of short-term effects of ChEIs [42]. In order to meet both recommendations, a minimum observation period of at least 16 weeks was specified for this report, as within this period a response to therapy can be expected and a longer term effect can be observed.

4.1.6 Inclusion and exclusion criteria

Studies that fulfilled all of the inclusion criteria and none of the exclusion criteria listed below were included in the evaluation.

Inclusion criteria

I1	Patients with mild or moderately severe Alzheimer's disease, also including mixed-type dementia with, for example, vascular dementia. Confirmation of diagnosis following EMEA [42] or generally accepted criteria (e.g., ICD-9, ICD-10, DSM-III-R, DSM-IV or NINCDS-ADRDA).
I2	Comparison of a ChEI (donepezil, galantamine, rivastigmine) with placebo or a different drug or non-drug intervention (as described in 4.1.2).
I3	Outcomes that can be inferred from the therapy goals formulated in 4.1.3.
I4	Randomised controlled trials (RCTs).

Exclusion criteria

E1	Studies with an observation period < 16 weeks.
E2	Studies that exclusively considered patients with vascular dementia, dementia due to Parkinson's disease, Lewy body disease, Creutzfeldt-Jacob disease, or other rare causes.
E3	Studies or publications that only contained data from uncontrolled open-label follow-up phases.
E4	Duplicate publications not containing relevant additional information.
E5	No full-text publication available.[1]
1: In this context, full-text publications also include the non-confidential provision of clinical study reports to the Institute or the non-confidential provision of other reports on a study to the Institute that fulfil the CONSORT[3] criteria [44] and enable the evaluation of the study.	

4.2 Literature search

The aim of the literature search was to identify full-text published and unpublished studies that provided relevant information on the evaluation of the benefits and harms of ChEIs in mild to moderate Alzheimer's disease.

4.2.1 Literature sources

The literature search for relevant published studies was conducted in the following sources:

- Bibliographic databases: MEDLINE,[4] EMBASE,[5] CENTRAL,[6] CHID via ADEAR,[7]
- Reference lists of relevant secondary publications (systematic reviews, HTA[8] reports, meta-analyses).

The search strategies applied in the search in bibliographic databases can be found in Appendix A. The search was conducted in 3 steps:

- Primary search on 13.04.2005 (MEDLINE and EMBASE), 14.04.2005 (Cochrane databases), and 25.04.2005 (CHID via ADEAR);

[3] Consolidated Standards of Reporting Trials
[4] Medical Literature Analysis and Retrieval System Online
[5] Excerpta Medica Database
[6] Cochrane Central Register of Controlled Trials
[7] Combined Health Information Database via Alzheimer's Disease Education & Referral Center, www.alzheimers.org
[8] Health technology assessment

- First search update on 03.11.2005 for the period 4/2005 to 10/2005 (all databases);

- Second search update on 12.06.2006 by means of a modified search strategy in MEDLINE, EMBASE, and the Cochrane databases. The database CHID was no longer available at the time of this update.

The search for relevant secondary publications (systematic reviews, HTA reports, meta-analyses) was conducted in MEDLINE and EMBASE parallel to the search for relevant primary literature. In addition, a search was conducted in the specialised databases CDSR,[9] DARE,[10] and the HTA database (primary search and search updates as above).

4.2.2 Search for further published and unpublished studies

Inquires were made to the manufacturers of ChEIs in Germany to identify further published and unpublished studies. The following companies were contacted:

- Eisai GmbH, Frankfurt (donepezil, Aricept®)
- Novartis Pharma GmbH, Nuremberg (rivastigmine, Exelon®)
- Janssen-Cilag GmbH, Neuss (galantamine, Reminyl®)

4.2.3 Identification of relevant studies

Title and abstract screening of the retrievals from bibliographic databases

The citations identified in bibliographic databases were evaluated with regard to their relevance by 2 reviewers independently of each other on the basis of their titles, and, if available, their abstracts. Publications viewed by both reviewers as potentially relevant were perused with regard to their relevance using the full text. Citations that were regarded by at least one reviewer as potentially relevant were perused again by both reviewers and, after discussion, were either classified as irrelevant or also perused with regard to their relevance using the full text.

Assessment of potentially relevant full texts

The assessment of the relevance of the publications on the basis of the full text was also performed independently by 2 reviewers. After this step, studies assessed as relevant for this report were defined as:

- Studies that were assessed as relevant by both reviewers;

[9] Cochrane Database of Systematic Reviews
[10] Database of Abstracts of Reviews of Effects

- Studies that were initially assessed as relevant by only one reviewer, but after subsequent discussion were assessed as relevant by both reviewers.

Search in reference lists of secondary publications

Reference lists of relevant secondary publications were searched in order to identify any further primary publications. The full texts of the publications identified in these reviews were assessed for their relevance by 2 reviewers, as described above.

Multiple publications

The publications to be included were screened with regard to whether they represented multiple publications of one and the same study. If multiple publications existed, all publications were allocated to the corresponding studies, and all data that were evaluable and provided information on the outcomes listed in Section 4.1.3 were assessed.

4.2.4 Search for additional information on relevant studies

The studies identified in the literature search were, if appropriate, supplemented by additional relevant studies from the documents described in Section 4.2.2. Moreover, the documents found following the search described in Section 4.2.2 were screened for additional information on studies already identified in the literature search.

Authors of publications and sponsors of studies were also contacted, if queries that could not be answered by the publications arose during the course of the evaluation concerning the studies included.

4.2.5 Information from the hearing on the preliminary report

After the publication of the preliminary report, a written hearing was conducted by means of written comments, which, among other things, could refer to the completeness of the literature search. Relevant information from this hearing could be included in the evaluation.

4.3 Evaluation of information

The evaluation of the studies included was conducted on the basis of the information available and was therefore strongly dependent on the quality of the relevant publications and additional sources of information.

The evaluation was conducted in 3 steps:

- Data extraction;

- Evaluation of the consistency of data within the publication itself and between the publication and other sources of information (e.g., information provided in the publication and in regulatory documents);

- Evaluation of the quality of the studies and publications.

Data extraction

Data extraction from published studies was conducted with standardised data extraction forms. Two reviewers performed the data extraction independently of one another. Subsequently the extracted data were compared, and a mutually agreed data extraction form for each study was prepared.

Details on the following aspects of study quality were systematically extracted:

- Randomisation process and allocation concealment

The randomisation process was classified as "unclear" if only the term "randomised" was mentioned, and as "inadequate" if the process was described in the publication, but regarded as inappropriate. The process was classified as "adequate" if detailed information on an adequately conducted process was available.

In the assessment of allocation to treatment groups, "unclear" means that no information was provided on whether allocation to groups was conducted in a concealed manner. It was classified as "adequate" if an adequate procedure was described, and as "inadequate" if a procedure was described that was clearly not adequate. However, in actual double-blind studies, a preferably exact description of concealment of allocation to groups is presumably of less relevance than in open studies, even though details in this regard would be desirable and also easy to provide.

- Blinding of treating staff, patients, and the outcome evaluation

As the vast majority of studies was conducted in a double-blind manner, it is described in each case whether the publication provided information in this regard and whether the persons who evaluated outcomes in patients were blinded, particular with regard to other study results and the occurrence of adverse events in these patients.

- Sample size planning

Sample size planning was classified as "adequate" if the outcome, the size of the expected effect, the power, the significance level, and the calculated sample size were reported. In addition, it was regarded as desirable if information was provided on the expected variability in the sample, the type of statistical test employed, and on whether the test was one- or two-

sided. If the required information was available, but there was a relevant deviation in the conduct of the study from the planned procedure (e.g., if the actual sample size was substantially smaller than the planned one), then this was classified as "(yes)". If no information was provided in the publication on sample size planning, it was assumed that none was performed, and this was classified as "no". If some details were missing, this was classified as "unclear".

- Description of study discontinuations

It is described for each study whether information on the number of participants who discontinued the study in the different treatment groups, as well as the corresponding reasons for discontinuation, were provided in the publication.

- Deviation from the intention-to-treat (ITT) principle

It was assessed whether a relevant violation of the ITT principle was present. If a small proportion of patients had been excluded from the data analysis, this was not seen as a relevant violation within the framework of the IQWiG report. In cases where a "relevant" violation of the ITT principle was noted, the rate of patients not considered in the primary analyses of the study was at least 11% (rounded off) or the difference in non-consideration rates between treatment groups was at least 5 percentage points (rounded off). In these cases, the proportions of patients not considered in the analyses (ITT analyses, as far as stated) were documented, so that the decisions presented (relevant deviation from the ITT principle: yes/no) were comprehensible in each case. If a relevant violation of the ITT principle was noted, this led to a devaluation of the study/publication quality ("major deficiency").

Assessment of data consistency

Following the data extraction, if appropriate, a comparison took place between these data and the data obtained by the additional searches for published studies described in 4.2.2 and 4.2.3. Insofar as discrepancies were detected (also discrepancies between multiple data provided on an aspect within the publication itself) that may have had a substantial effect on the study results or on their interpretation, this is presented in the corresponding parts of the results section.

Evaluation of study and publication quality

Finally, under consideration of the aspects stated above and individual aspects (presented for each case), an evaluation of the study and publication quality was conducted by means of a scale comprising 4 grades (biometric quality).

Possible grades comprised:

- No identifiable deficiencies,
- Minor deficiencies,
- Major deficiencies,
- Unclear.

The grades were predefined as follows:

- "No identifiable deficiencies": at most irrelevant deficiencies are evident;
- "Minor deficiencies": it is assumed that their correction will not substantially influence the results and the overall conclusion of the study;
- "Major deficiencies": the overall conclusion of the study is to be questioned, as a correction of the deficiencies may possibly lead to different conclusions;
- "Unclear": based on the available documents, no clear conclusion on the biometric quality of the study can be made.

As described above, the evaluation of study quality is directly influenced by the quality and consistency of the available information. Therefore the classification "major deficiencies" does not necessarily describe the quality of the study itself, but may also be due to the quality of the underlying publication(s).

The quality grading was, if appropriate, to provide a basis for a sensitivity analysis within the framework of a meta-analysis.

4.4 Synthesis and analysis of information

4.4.1 Study characterisation

In this report the studies are described by means of design characteristics (study design, study duration, study location and period, number of randomised and analysed patients, relevant outcomes). In addition, the test intervention(s) and the comparator intervention(s) are described. The study populations are described by demographic data (age, gender), the characteristics of dementia (Alzheimer's disease or mixed type, disease severity), and the number of study discontinuations.

4.4.2 Comparison of the results of individual studies

The results of individual studies were collated according to therapy goals and outcomes. The following outcomes were considered:

Therapy goal	Outcome
Patient-relevant therapy goals	
Improvement in or prevention of restriction in activities of daily living	- Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL) - Alzheimer's Disease Functional Assessment and Change Scale (ADFACS) - Blessed-Roth Dementia Scale (BRDS) - Bristol Activities of Daily Living Scale (BADLS) - Caregiver-rated Modified Crichton Scale (CMCS) - Disability Assessment for Dementia Scale (DAD) - Instrumental Activities of Daily Living (IADL) - Interview for Deterioration in Daily Living in Dementia (IDDD) - Physical Self-Maintenance Scale (PSMS) - Progressive Deterioration Scale (PDS)
Improvement in/normalisation of accompanying psychopathological symptoms	- Neuropsychiatric Inventory (NPI) - Nurses' Observation Scale for Geriatric Patients (NOSGER) - Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)
Improvement in or maintenance of cognitive function	- Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) - Mini Mental State Examination (MMSE) - Severe Impairment Battery (SIB)
Improvement in or maintenance of health-related quality of life	- Quality of Life Scale (QoL Scale)
Prevention of placement in a nursing home (institutionalisation)	- Time up to admission to a nursing home - Proportion of patients admitted to a nursing home after a specific treatment period
Reduction in mortality	- Proportion of patients who died within a specific period
Reduction in (therapy-related)	- Overall adverse event rate

Therapy goal	**Outcome**
adverse events	- Serious adverse events - Study discontinuation due to adverse events - Common adverse events
Therapy goals relevant to relatives	
Improvement or maintenance of quality of life of (caregiving) relatives	- Caregiving Burden Scale (CBS) - Caregiver Stress Scale (CSS) - Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D) - Screen for Caregiver Burden (SCGB)
Reduction in the degree of care provided by one or more caregivers or institutions	- Allocation of Caregiver Time Survey (ACTS) - Caregiver Activity Survey (CAS) - Resource Utilization in Dementia (RUD)
Additional information	
Improvement or maintenance of the clinical disease stage	- Clinical Dementia Rating Scale (CDR) - Clinical Global Impression of Change Scale (CGIC) - Clinician's Interview-Based Impression of Change (with input of the caregiver: CIBIC-plus) - Global Deterioration Scale (GDS) - Gottfries-Bråne-Steen Scale (GBS)

The table included in Appendix D gives an overview of all outcomes in the studies included that can be allocated to one of the therapy goals.

If several scales for one therapy goal (e.g., cognitive function) were reported in the studies, then in general only one scale in each case (preferably the scale used most) was analysed and presented in this evaluation. Therefore, in the tables describing the included studies, only those outcomes are listed that were considered in the evaluation in this report (in addition to the primary outcome of the study).

A short explanation of all evaluated scales is presented in Appendix E.

4.4.3 Meta-analysis

Data on an outcome were to be summarised in a quantitive manner by means of meta-analysis provided that, on the basis of the available evidence, this was seen as a meaningful procedure regarding methodology and content. A meta-analysis was conducted if at least 3 studies with valid statistical measures were available or at least calculable with sufficient exactness, or

were assessable from the figures. Deviating from this, meta-analyses were also conducted to describe data on adverse events in more detail if at least 2 studies were available (as described above).

In the first step, a fixed effects model was used. If there were indications of possible heterogeneity in the individual studies ($I^2 > 50$ % or $p < 0.2$ in the heterogeneity test), in a second step, the calculations were performed by means of a model with random effects, and these results are presented. Relevant deviations from these results regarding the fixed effects model are discussed in the text.

The statistical analysis primarily considered results of the ITT analyses as described in the publications. In studies including several intervention groups with different doses or frequency of administration, the group with the highest dose or most frequent administration was selected for the comparison with placebo in the meta-analytical summary (unless otherwise noted).

For continuous variables, the standardised mean difference (Cohen's d) was used as an effect measure in order to be able to compare scores of different scales. For binary variables, meta-analyses were conducted by means of the absolute risk difference as well as the odds ratio. However, in this report, only the results for the odds ratio are presented, as they were much more homogeneous compared with the absolute risk difference.

The case that no event occurred in either treatment group did not present itself in any meta-analysis for binary data. If no patient experienced an event in only one of the treatment groups, a correction factor of 0.5 was added to each cell frequency in the underlying 2x2 table.

4.4.4 Sensitivity analysis

According to the report plan, sensitivity analyses regarding the following factors were planned within the meta-analyses:

- Statistical quality assessment (see Section 4.3);
- If possible, per-protocol (PP) analyses described in the publications (versus ITT analyses); and
- A (statistical) fixed effects versus a random effects model.

4.4.5 Subgroup analysis

If feasible, subgroup analyses were planned for the following characteristics:

- Gender

- Age
- Disease severity
- ChEI dose
- Different concomitant diseases
- Characteristics that were responsible for relevant heterogeneity

No or very few differentiated analyses were available for the characteristics gender, age, disease severity, and different concomitant diseases. Therefore, corresponding subgroup analyses were not possible.

In the case of noticeable heterogeneity (see above) in a meta-analysis, a subgroup analysis was to be conducted, if appropriate, for characteristics that were possibly responsible for heterogeneity. In those cases where heterogeneity was observed within the framework of this evaluation, explanatory characteristics could not be found or the number of studies was too small. Therefore, subgroup analyses within this study pool were not meaningful.

4.5 Changes compared with the report plan

4.5.1 Changes during the preparation of the preliminary report

During the course of the project, changes and amendments took place in the procedures followed in the evaluation, which meant a deviation from those defined in the report plan (including the methodology presented in the amendment of 19.06.2006). These changes mainly concerned the following points:

Changes of content compared with preplanned procedures

- The Cochrane Dementia and Cognitive Improvement Group was not contacted to identify further studies.

Changes without relevant consequences of content (specification of the preplanned procedures)

- The data sources screened to identify systematic reviews, meta-analyses, and HTA-reports were explicitly named.
- Treatment with placebo and any other drug intervention (including a different ChEI from that used in the relevant test intervention) and non-drug intervention for Alzheimer's disease were investigated as comparator interventions.

- The exclusion criterion "E5: Only abstract publication" was specified to clarify that only full-text publications were considered ("E5: No full-text publication"). In this context, full-text publications also included the non-confidential provision of clinical study reports to the Institute or the non-confidential provision of other reports on a study to the Institute that fulfilled the CONSORT criteria [44] and enabled the evaluation of the study.

4.5.2 Changes after the publication of the preliminary report

The comments on the preliminary report did not lead to a change of the methodology specified in the report plan.

5 RESULTS

5.1 Results of the literature search

5.1.1 Results of the systematic literature search

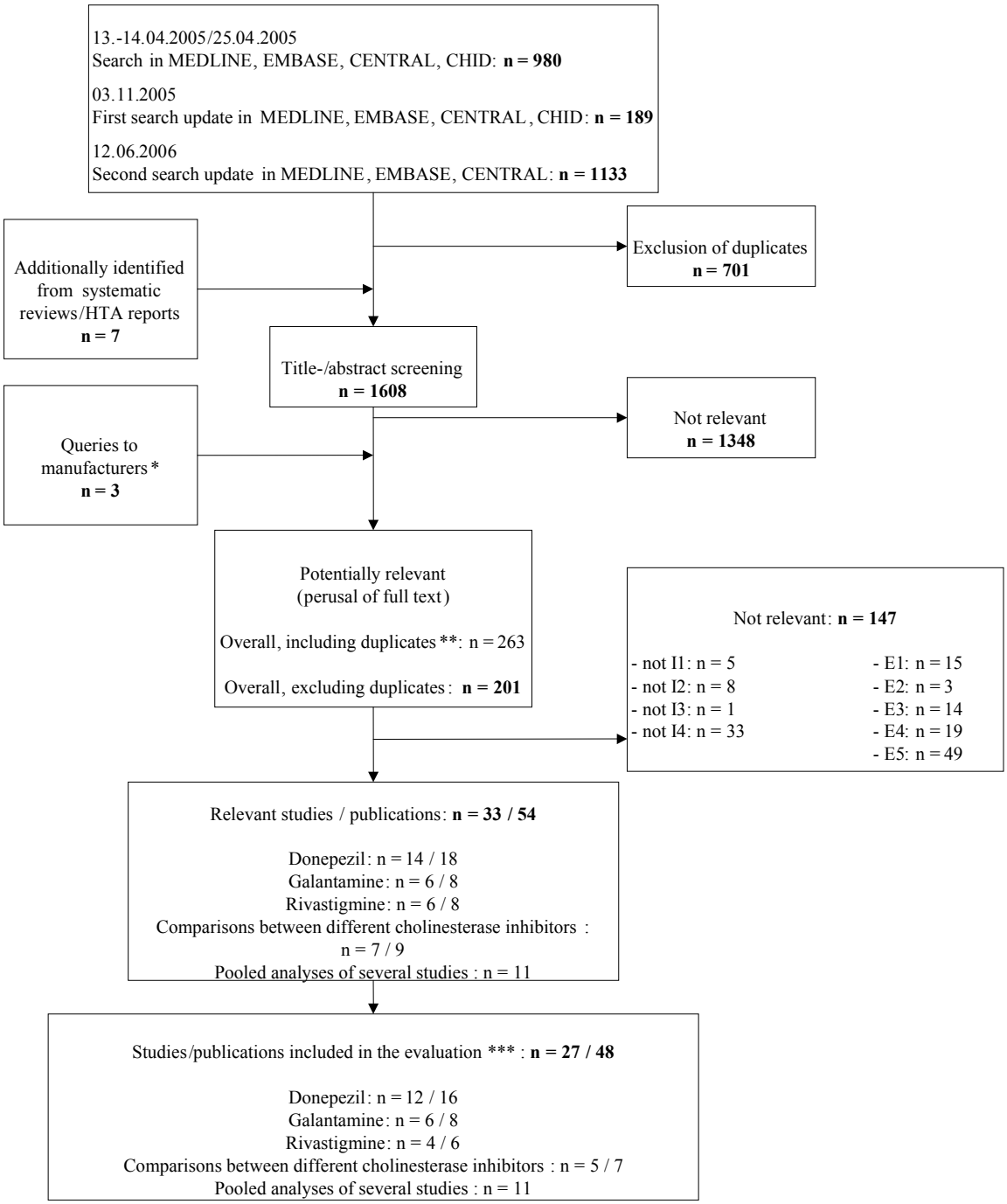
Figure 1 shows the results of the systematic literature search in bibliographic databases and the literature screening according to the inclusion and exclusion criteria.

After exclusion of 701 duplicates, the primary search, the first and second search update and the search in systematic reviews and HTA reports resulted in a total of 1608 hits. The database CHID was screened by using the substance names. The search strategies applied in MEDLINE, EMBASE, and CENTRAL are presented in Appendix A. Within the framework of the second search update, it was shown that the applied search strategies contained, among other things, incorrect links and field names. Consequently, a substantial revision was necessary. The second search update was therefore conducted with the revised search strategy (see Appendix A) for the databases MEDLINE, EMBASE, and CENTRAL without restriction of the search period. At the time of this search update, the database CHID was no longer available. Of 1608 hits, a total of 1348 were assessed as being "not relevant". Queries to the manufacturers resulted in references to a further 3 potentially relevant studies.

A total of 263 potentially relevant references were identified. As the primary search and second search update covered a common time period, several citations were identified in both search steps. After exclusion of these duplicates, 201 full-text publications were reviewed, of which 147 were excluded, being assessed as "not relevant". The citations of these non-relevant publications, perused in full text, can be found in Appendix B, including the reasons for exclusion.

Of the reviewed articles, 54 publications on 33 studies were assessed as being relevant; of these articles, 48 publications on 27 studies were included in the evaluation.

A total of 22 studies were placebo-controlled (donepezil 12, galantamine 6, rivastigmine 4), 5 studies were direct comparisons between different ChEIs. 11 of the publications included contained pooled analyses of several studies.



* See Section 5.1.2 (Queries to manufacturers).
** Duplicates were retrieved as the 2nd search update included the period of the primary search. Moreover, a study already identified in the literature search was also identified by the query to the manufacturer (Tai 2000).
*** In 6 studies, the information provided was insufficient for use in the evaluation (see Section 5.1.4).

Figure 1. Bibliographic literature search and other literature screening: final study pool for the evaluation

5.1.2 Queries to manufacturers

In May 2005, EISAI GmbH, the manufacturer of donepezil, Janssen-Cilag GmbH, the manufacturer of galantamine, and Novartis Pharma GmbH, the manufacturer of rivastigmine, were asked to provide an overview on ChEI studies. All companies subsequently provided lists of studies. In the meantime, it had become necessary to achieve a regulated and uniform procedure with regard to the transmission of study information from pharmaceutical companies to IQWiG. In the following months, a general agreement in this regard was prepared, which was to be concluded between IQWiG and the manufacturers before the transmission of documents. The agreement concerning the transmission and utilisation of data was signed by all the above companies.

EISAI GmbH

After signing the agreement on the transmission of documents, following a request from IQWiG, EISAI provided the Expert Report of the approval document for donepezil and confirmed the completeness of the lists of studies submitted. A review of the Expert Report and the lists showed that all relevant studies had been published and had already been identified in the literature search.

Janssen-Cilag GmbH

After conclusion of the agreement on the transmission of documents, the documents already provided by Janssen-Cilag could be used for IQWiG's evaluation. These documents referred to a Clinical Expert Report and a Clinical Overview from the approval procedure for galantamine, to lists of studies, as well as to documents Janssen-Cilag had provided to the UK National Institute for Health and Clinical Excellence (NICE) for the evaluation of galantamine [45,46]. After a request by IQWiG, Janssen-Cilag also provided details on statistical calculations from studies on galantamine.

A review of the documents submitted did not reveal references to unpublished or published studies not already identified.

Information from the documents considered in the IQWiG evaluation that did not originate from the publications on galantamine, but from the NICE dossier or from Janssen-Cilag directly, is marked separately in the report.

Novartis Pharma GmbH

After the agreement on the transmission of documents had been signed, the Expert Report on the approval of rivastigmine provided by Novartis, as well as a list of studies conducted after approval were used to identify relevant studies. A review of the documents showed 3 studies that had not been published, or had only been published as abstracts.

Study	Publication status
B304	Unpublished
B351	Unpublished
Tai 2000	Abstract publication [47]

In March 2006, the clinical study reports of the studies named were requested from Novartis. The report on B304 [48] was provided; the study was therefore considered in this evaluation. The study report on B351 had not been provided by Novartis by the end of July 2006; therefore the study could not be presented and adequately considered in this evaluation. Single results on B351 have been published in a Cochrane Review [49]. These data show that the results of this study were negative. As far as possible, sensitivity analyses using data from B351 obtained from the Cochrane Review were conducted for the present report, in order to assess the influence of this study on the overall conclusions of the evaluation. The results of the sensitivity analyses are presented in the corresponding sections of this report and in Appendix G. Novartis did not have the clinical study report on Tai 2000; therefore this study was not considered, either.

Information from non-publicly accessible documents provided by the manufacturers is presented in italics in the tables.

5.1.3 Queries to the authors

Authors of the following studies were contacted and asked to provide additional information on full-text publications: AD2000 (e-mail of 07.07.2006 and 09.08.2006, letter of 09.08.2006), Karaman 2005 (e-mail of 25.07.2006), Kim 2002 (e-mail of 25.07.2006), Kemp 2003 (e-mail of 26.07.2006), Thomas 2001 (e-mail of 01.08.2006), and Wang 2001 (e-mail of 31.07.2006).

A response was only received from P. Kemp (e-mail of 31.07.2006). Queries concerning studies conducted by manufacturers with whom a confidentiality agreement existed were directly addressed to the manufacturers.

5.1.4 Resulting study pool

Table 4 shows the study pool resulting from the various search steps.

Table 4. Study pool

Test drug(s) Study	Full-text publication	Identified by	Inclusion in report
Donepezil vs. placebo			
AD 2000	Courtney C et al. Lancet 2004; 363: 2105-2115 [50]	Bibliographic literature search	no[(a)]
Burns 1999	Burns et al. Dement Geriatr Cogn Disord 1999; 10: 237-244 [51]	Bibliographic literature search	yes
Gauthier 2002	Gauthier S et al. Curr Med Res Opin 2002; 18: 347-354 [52] Feldman H et al. Neurology 2001; 57: 613-620 [53] Feldman H et al. J Am Geriatr Soc 2003; 51; 737-744 [54]	Bibliographic literature search	yes
Homma 2000	Homma A et al. Dement Geriatr Cogn Disord 2000; 11: 299-313 [55]	Bibliographic literature search	yes
Kemp 2003	Kemp et al. J Neurol Neurosurg Psychiatry 2003; 74: 1567-1570 [56]	Bibliographic literature search	no[(b)]
Krishnan 2003	Krishnan KR et al. Am J Psychiatry 2003; 160: 2003-2011 [57]	Bibliographic literature search	yes
Mohs 2001	Mohs RC et al. Neurology 2001; 57: 481-488 [58]	Bibliographic literature search	yes
Moraes 2006	dos Santos Moraes et al. Sleep 2006: 199-205 [59]	Bibliographic literature search	yes
Prasher 2002	Prasher VP et al. Int J Ger Psychiatry 2002; 17: 270-278 [60]	Bibliographic literature search	yes
Rogers 1998	Rogers et al. Neurology 1998; 50: 136-145 [61]	Bibliographic literature search	yes
Seltzer 2004	Seltzer B et al. Arch Neurology 2004; 61: 1852-1856 [62]	Bibliographic literature search	yes
Tariot 2001	Tariot PN et al. J Am Geriatr Soc 2001; 49: 1590-1599 [63]	Bibliographic literature search	yes
Tune 2003	Tune L et al. Am J Geriatr Psychiatry 2003; 11: 169-177 [64]	Bibliographic literature search	yes
Winblad 2001	Winblad B et al. Neurology 2001; 57: 489-495 [65] Wimo A et al. Curr Med Res Opin 2004; 20: 1221-1225 [66] Wimo 2003 Dement Geriatr Cogn Disord 2003; 15: 44-54 [67]	Bibliographic literature search	yes

(continued)

Table 4 (continued). Study pool

Test drug(s) Study	Full-text publication	Identified by	Inclusion in report
Galantamine vs. placebo			
Brodaty 2005	Brodaty H et al. Dement Geriatr Cogn Disord 2005; 20: 120-132 [68]	Bibliographic literature search	yes
Erkinjuntti 2002	Erkinjuntti T et al. Lancet 2002; 359: 1283-1290 [69]	Bibliographic literature search	yes
Raskind 2000	Raskind MA et al. Neurology 2000; 54: 2261-2268 [70]	Bibliographic literature search	yes
Rockwood 2006	Rockwood K et al. CMAJ 2006; 174: 1099-1105 [71]	Bibliographic literature search	yes
Tariot 2000	Tariot PN et al. Neurology 2000; 54: 2269-2276 [72] Cummings JL et al. Am J Psychiatry 2004; 161: 532-538 [73] Galasko D et al. J Am Geriatr Soc 2004; 52: 1070-1076 [74]	Bibliographic literature search	yes
Wilcock 2000	Wilcock GK et al. BMJ 2000; 321: 1445-1449 [75]	Bibliographic literature search	yes
Rivastigmine vs. placebo			
B304 1998	Novartis Pharma AG. Study ENA B304 Final Study Report. 1998 [48]	Query to manufacturer	yes
B351		Query to manufacturer	no[(c)]
Corey-Bloom 1998	Corey-Bloom J et al. Int J Ger Psychopharmacol 1998; 1: 55-65 [76] Kumar et al. Eur J Neurol 2000; 7: 159-169 [77]	Bibliographic literature search	yes
Forette 1999	Forette F et al. Eur J Neurol 1999; 6: 423-429 [78]	Bibliographic literature search	yes
Karaman 2005	Karaman et al. Dement Geriatr Cogn Disord 2005; 19: 51-56 [79]	Bibliographic literature search	no[(a)]
Rösler 1999	Rösler M et al. BMJ 1999; 318: 633-638 [80] Erkinjuntti et al. Int J Clin Pract 2002; 56: 791-796 [81]	Bibliographic literature search	yes

(continued)

Table 4 (continued): Study pool

Test drug(s) Study	Full-text publication	Identified by	Inclusion in report
Comparison between different cholinesterase inhibitors			
Galantamine vs. donepezil			
Wilcock 2003	Wilcock G et al. Drugs Aging 2003; 20: 777-789 [82]	Bibliographic literature search	yes
Rivastigmine vs. donepezil			
Bullock 2005	Bullock R et al. Curr Med Res Opin 2005; 21: 1317-1123 [83] Bullock et al. Curr Med Res Opin 2006; 22: 483-494 [84] Touchon et al. Curr Med Res Opin 2006; 22: 49-59 [85]	Bibliographic literature search	yes
Fuschillo 2001	Fuschillo C et al. Arch Gerontol Geriatr 2001: 7: 151-158 [86]	Bibliographic literature search	yes
Kim 2002	Kim et al. Int Psychogeriatr 2002; 14: 187-195 [87]	Bibliographic literature search	no[(d)]
Thomas 2001	Thomas et al. Clin Neuropharmacol 2001; 24: 31-42 [88]	Bibliographic literature search	no[(a)]
Wang 2001	Wang Y et al. Chinese Journal of Neurology 2001; 34: 210-213 [89]	Bibliographic literature search	yes
Rivastigmine vs. donepezil vs. galantamine			
Cumbo 2005	Cumbo E. Prim Care Comm Psych 2005; 10: 95-102 [90]	Bibliographic literature search	yes
Publications on several studies (pooled analyses)			
Anand et al. Int J Ger Psychopharmacol 2000; 2: 68-72 [91]		Bibliographic literature search	yes
Burns et al. Int J Geriatr Psychiatry 2004; 19: 243-249 [92]		Bibliographic literature search	yes
Kurz et al. Alzheimer Dis Assoc Disord 2004; 18: 123-128 [93]		Bibliographic literature search	yes
Marcusson et al. Alzheimer Dis Assoc Disord 2003; 17 Suppl 3: S86-S91 [94]		Bibliographic literature search	yes

(continued)

Table 4 (continued). Study pool

Publications on several studies (pooled analyses)	Identified by	Inclusion in report
Orgogozo et al. Curr Med Res Opin 2004; 20: 1815-1820 [95]	Bibliographic literature search	yes
Potkin et al. Prog Neuropsychopharmacol Biol Psychiatry 2002; 26: 713-720 [96]	Bibliographic literature search	yes
Pratt et al. Int J Clin Pract 2002; 56: 710-717 [97]	Bibliographic literature search	yes
Sano M et al. Int J Ger Psychiatry 2003; 18: 942-950 [98]	Bibliographic literature search	yes
Schneider et al. Int J Ger Psychopharmacol 1998; 1: S26-S34 [99]	Bibliographic literature search	yes
Whitehead et al. Int J Geriatr Psychiatry 2004; 19: 624-633 [100]	Bibliographic literature search	yes
Wilkinson et al. Int J Clin Pract 2002; 56: 509-514 [101]	Bibliographic literature search	yes

a: Study could not be included, as relevant questions concerning its interpretation could not be clarified before finalisation of the preliminary report (a query to the authors was not answered).
b: Study could not be included, as relevant data analyses for the research questions of this report were either not conducted or could not be made available (information provided by P. Kemp on 31.07.2006).
c: This unpublished study could not be included, as the clinical study report had not been provided by Novartis by the end of July 2006.
d: The study could not be included, as the publication did not provide relevant data analyses for the relevant research question of this report; a query to the authors was not answered.

Relevant fully published studies identified in the literature search were included in the evaluation. The following studies are exceptions that (so far) could not be included in the evaluation.

AD2000:

The AD2000 study included 565 patients with mild-to-moderate Alzheimer's disease, and compared donepezil with placebo. The study was conducted in 22 centres in England and investigated patients over a maximum period of about 4 years up to placement in a nursing home or to a defined degree of loss of activities of daily living (primary outcomes). AD2000 was solely funded by the UK National Health Service (NHS). The study was reported to be randomised and double-blind. The results on the primary outcomes (time to event) were analysed using survival time analyses. In contrast to the usual randomised 2-group comparisons, most patients in the AD2000 study were randomised twice. At the start of the study, all patients included were randomised to the donepezil 5 mg or placebo group. After 12 weeks, patients were randomised again, this time into the 3 groups: donepezil 5 mg, donepezil 10 mg, and placebo. According to this distribution into 3 treatment arms, patients were investigated in up to 4 phases lasting 48 weeks each. Between each phase, a 4-6 week washout phase took place. This unusual rerandomisation after 12 weeks led to a switch of about 43% of patients in the donepezil to the placebo group or vice versa. About 11% switched to higher-dose donepezil (from 5 mg to 10 mg) and only about 32% of patients remained in the original group. About 14% either died within the first 12 weeks of the study or discontinued for other reasons. The percentages stated originate from our own calculations based on the data in the publication.

Various aspects of study design and reporting of results in the publication [50] restrict the evidential value of results.

- **Allocation to treatment:** Due to the double randomisation, a mixed study population was formed with regard to treatment received, consisting of treatment group switchers, patients who received higher dose treatment, and patients who did not switch treatment groups. It cannot therefore be excluded that results are biased by hangover effects, in particular by the fact that no wash-out phase was included before the second randomisation. Even though the authors state in the methods section of the publication that the analysis technique used ("standard mixed model technique") considers these effects, this is at best possible for the secondary outcomes (various characteristics on a continuous numerical level). However, this is not presented in a comprehensible manner in the publication. With regard to the evaluation of primary outcomes, the use of Kaplan-Meier estimates and the log-rank test do not meet the study design. In the publication, all results are solely presented as a 2-group comparison (donepezil vs. placebo), and the start of the observation period is the time of the first randomisation. No separate results are

presented for both doses of donepezil nor are analyses reported where the time of the second randomisation is the baseline.

- **Washout phases:** Whereas a washout phase after the first 12 weeks to reduce possible hangover effects would have been meaningful, the authors do not provide an explanation for the 4-6 week washout phases between treatment periods.

In order to clarify these aspects, a query by e-mail was sent to the AD2000 Collaborative Group asking for further details on study design, conduct, and analyses. This request was repeated by e-mail and by letter. However, there was no response. Due to the aspects described, the interpretability of results is so strongly limited that it seemed appropriate not to present the results of this study in this report and not to consider them in the IQWiG evaluation.

B351:

Study B351, which together with study B304 was identified as a potentially relevant study in the documents provided by Novartis, could also not be considered in the evaluation. It could be inferred from the publications on rivastigmine [49,99] that study B351 (with regard to the study design applied and the outcomes investigated) contained relevant results for this evaluation. The study reports on both studies were requested from Novartis on 27.03.2006. Novartis provided the study report on study B304; this study was therefore considered in the evaluation. No documents on study B351 had been provided by the end of July 2006.

Karaman 2005:

Essential issues on design remain open in this publication, among other things regarding the allocation of patients to treatment groups, the number of randomised patients, as well the treatment in both the placebo and in the test group after the first 8 weeks. A query to the authors was not answered.

Kemp 2003:

The publication did not present data suited to answer the research questions of this report. According to the authors, the data sets were no longer available, so the corresponding analyses could not be provided.

Kim 2002:

The publication did not present data suited to answer the research questions of this report. A query to the authors was not answered.

Thomas 2001:

Essential issues on the study design remain open in this publication. Among other things, it is not clearly described whether the treatment in the rivastigmine and donepezil groups took place in parallel. A query to the authors was not answered.

All studies included compared ChEIs with placebo or with each other. No randomised studies were identified that compared the benefit of a ChEI with another drug or non-drug intervention in Alzheimer's disease.

In the following sections, the results of studies are presented separately for the different ChEIs.

5.1.5 Information provided in the hearing

The following information relevant to the evaluation was provided in the hearing:

- Additional information on the methodology of some of the studies, which was considered in the evaluation of the study and publication quality, as well as

- Additional information on the results of single studies, which was included in the presentation of the results on the separate therapy goals.

Further aspects presented in the written comments and the scientific debate are outlined in Section 6 (Discussion).

No studies fulfilling the inclusion and exclusion criteria that had not already been considered in the preliminary report were named in the written comments.

5.2 Characteristics of the studies included in the evaluation

5.2.1 Donepezil

5.2.1.1 Study design, doses, study populations

In total, 14 relevant studies comparing donepezil and placebo, of which 12 were included in the evaluation, were identified (Table 4). Details on the design and basic characteristics of the studies included are presented in Table 5.The following text summarises the main aspects.

Except for 4 smaller studies, all studies had a multicentre design. Most studies lasted 24 weeks. In 2 studies, the drugs were administered in a controlled and blinded manner over a period of one year (Winblad 2001) and 13.5 months (Mohs 2001). Daily doses of 5 mg and 10 mg donepezil were used. Three studies, mainly in patients with severe disease, allowed the investigator responsible the option of either increasing or reducing the dose to 10 mg and

5 mg respectively (Winblad 2001) or allowed a dose reduction to 5 mg in patients who did not tolerate the prior dose increase to 10 mg (Gauthier 2002, Tariot 2001). In higher-dose studies, the increase in dose from 5 mg to 10 mg took place at the earliest after a week (Burns 1999), and mainly within 6 weeks.

Gauthier 2002 was a subgroup analysis of the study by Feldman et al 2001, which included patients with moderate to severe Alzheimer's disease (MMSE 5–17). For this report, according to the indication for ChEIs, only the subpopulation of patients with moderate dementia (MMSE 10–17) was considered. This subpopulation comprised about 71% of the total study population.

The number of patients included in the studies lay between 153 (Seltzer 2004) and 818 (Burns 1999, 3-arm study), except for 4 studies with substantially lower patient numbers. Overall, about 1700 patients were treated with donepezil and 1300 patients were treated with placebo.

In part, the studies varied substantially concerning inclusion and exclusion criteria (Table 6); these differences are reflected in the actual patient populations investigated (Table 7) and are therefore presented in detail in the following text.

Most studies included patients with probable Alzheimer's disease according to NINCDS-ADRDA criteria; the MMSE mainly lay between 10 and 26 points.

Over 80% of the patients in the Burns 1999 study suffered from mild dementia (CDR 1); the average MMSE was 20 points. The patient populations in Rogers 1998 and Winblad 2001, as well as in the smaller studies Krishnan 2003 and Tune 2003, were comparable to those in this study. Patients included in Mohs 2001 also showed comparable disease severity on the CDR scale (80% of participants were in CDR stage 1), even though they had a lower average MMSE (17 points). This can be explained by the higher requirements in the inclusion criteria for coping with activities of daily living. In Homma 2000, a higher proportion of patients had moderate disease (CDR 2: about 35% of patients; average MMSE: about 17 points). In this study, a markedly lower cognitive impairment in the test group compared with the placebo group was noticeable at baseline (difference between groups: MMSE +1.2 points, $p = 0.035$; ADAS-cog –3.9 points, $p = 0.001$). However, the study results are interpretable, as the individual progression (baseline vs. end of study) was investigated, and the baseline value was considered as a factor in an (additional) covariate analysis (ANCOVA) (and, according to the authors, did not influence the study results).

The study by Seltzer 2004 included only very mildly impaired patients (MMSE 21–26). The patients in the upper range (25–26) may presumably also be referred to in part as patients with MCI; however, there is no sharp distinction between MCI and mild Alzheimer's disease. About 32% of patients were in CDR stage 0.5, which is consistent with MCI; the remaining patients had mild dementia (CDR 1). In this study (also in the placebo group) only a minimal

progression of cognitive impairment was observed, as is common in patients with initially only mild cognitive impairment.

Gauthier 2002 reported a subgroup analysis of patients with moderate disease (MMSE 10–17) within the framework of a study that also included patients with severe disease [53]. In the following text, as far as possible, only the data on this subgroup are presented. The separate results of the subgroup and whole group during the course of treatment were comparable. This also applies to Tariot 2001, which investigated patients with mild to severe Alzheimer's disease (MMSE 5–26) who, according to the study protocol, all lived in nursing homes. As 75% of patients had mild to moderate disease (MMSE 10–26), the study is sufficiently suited to draw conclusions for this population. Insofar as separate analyses for the subgroup with mild to moderate disease were conducted, only these are presented in the following text. These analyses also showed comparable results between the subgroup and whole group. In both of these studies, the provision of brain imaging pictures at the start of the study was not compulsory; therefore, more patients with concomitant vascular pathology may be expected.

Prasher 2002 included a specific study population (patients with trisomy 21 and possible Alzheimer's disease). According to the Summary of Product Characteristics, the use of donepezil is not specifically excluded in patients with trisomy 21 (see [102]). Therefore this study was included in the evaluation, even though this group of patients only represents a small minority of patients with Alzheimer's disease. In this group, Alzheimer's disease was diagnosed according to specific criteria (WHO Diagnostic Research Criteria), whose validity is unclear. Whether specific pharmacogenetic features of trisomy 21 influence the effects of ChEIs is also unclear. However, due to noticeable unequal distribution of potentially relevant prognostic factors between randomised groups, the relevance of the study results is per se also unclear for people with trisomy 21.

The most important exclusion criteria in the individual studies were other potential causes of dementia, other neurological or psychiatric diseases, as well as other relevant uncontrolled diseases such as insulin-dependent diabetes, and respiratory, haematological or oncological diseases.

In 5 studies, ADAS-cog and/or CINIC-plus were the primary outcomes (Table 5). In 2 studies (Krishnan 2003 and Tune 2003, including 67 and 28 participants respectively), the primary outcomes were changes in neurobiological markers (measured by means of magnet resonance tomography and –spectroscopy and positron emission tomography) or the change in REM-sleep under donepezil (Moraes 2006, including 35 participants). However, these studies also presented results on the predefined patient-relevant therapy goals outlined in this report. Table 5 shows the primary outcomes of all studies, as well as the patient-relevant outcomes listed in Section 4.1.3. In most studies, the scales applied were primarily evaluated in a continuous manner, often without defining a response criterion.

In the (small) study by Tune 2003, a statistically significant unequal distribution of a baseline characteristic (NPI) was shown. However, for the evaluation of this outcome, the difference at the start of treatment was assessed and adjusted for the (different) baseline values (ANCOVA). In the (small) study by Moraes 2006, a 3-point difference between groups in the ADAS-cog was not considered in the analysis. The baseline differences in SIB between groups in the Prasher 2002 were evidently not considered in the analysis, either.

The study by Mohs 2001 had a particular design: the participants were not followed over a fixed period, but until they reached a pre-defined (primary) outcome, which was also defined as the end of study for each affected patient. The results were analysed by means of a survival analysis. This design did not allow the certain interpretation of results outside this survival analysis, as patients were either successively lost for the corresponding evaluations or the values were used at the time of reaching the outcome; this meant the "missing at random" principle was violated.

In Mohs 2001, a defined deterioration of basic activities of daily living or of several instrumental activities of daily living (more than 20% of the performable iADL at the start of study) were defined as the clinical outcome. An alternative definition for reaching the outcome (increase in the CDR by one point) was only used for a small subgroup, which was of similar size in both treatment arms.

Table 5. Donepezil studies included

Study **(additional study names)**	**Study design**	**Study duration (monitored administration of test drug)**	**Intervention group and number of randomised patients**	**Study location and number of centres**	**Main outcomes[a]**
Burns 1999 (E044-304)	RCT, parallel, double-blind, multicentre	6 months	1. Donepezil 5 mg: n=271 2. Donepezil 10 mg: n=273 3. Placebo: n=274	AUS, B, CAN, F, D, GB, IRL, NZ, ZA (total: 82 centres)	**ADAS-cog, CIBIC-plus** IDDD (modified), QoL, adverse events
Gauthier 2002[b] (MSAD; Don-NY-96-002-324)	RCT, parallel, double-blind, multicentre	6 months	Subgroup with moderate AD: 1. Donepezil (5-) 10 mg: n=102 2. Placebo: n=105	CAN (22), AUS (6), F (4) (total: 32 centres)[c]	**CIBIC-plus** sMMSE, DAD, IADL+, PSMS+, NPI, CSS[d], adverse events
Homma 2000	RCT, parallel, double-blind, multicentre	6 months	1. Donepezil 5 mg: n=136 2. Placebo: n=132[e]	Japan (54 centres)	**ADAS-J-cog[f], J-CGIG** CMCS, adverse events
Krishnan 2003	RCT, parallel, double-blind, single centre	6 months	1. Donepezil 10 mg: n=34 2. Placebo: n=33	USA (1 centre)	**N-acetyl-aspartate-concentration** ADAS-cog, adverse events
Mohs 2001 (A001-312; The Functional Survival Study)	RCT, parallel, double-blind, multicentre, *survival analysis*	13.5 months	1. Donepezil 10 mg: n=214 2. Placebo: n=217	USA (31 centres)	**Time to clinically manifest deterioration[g]** ADFACS, CDR-SB, MMSE, adverse events
Moraes 2006	RCT, parallel, double-blind, bi-centre	6 months	1. Donepezil 10 mg: n=17 2. Placebo: n=18	Brazil (2 centres)	**REM-sleep** ADAS-cog

(continued)

Table 5 (continued). Donepezil studies included

Study **(additional study names)**	**Study design**	**Study duration (monitored administration of test drug)**	**Intervention group and number of randomised patients**	**Study location and number of centres**	**Main outcomes[(a)]**
Prasher 2002 (UK Down Syndrome Ageing Study)	RCT, parallel, double-blind, single centre	6 months	1. Donepezil 10 mg: n=16 2. Placebo: n=15	GB (1 centre)	**DMR** SIB, NPI, adverse events
Rogers 1998 (A001-302)	RCT, parallel, double-blind, multicentre	6 months	1. Donepezil 5 mg: n=154 2. Donepezil 10 mg: n=157 3. Placebo: n=162	USA (20 centres)	**ADAS-cog, CIBIC-plus** QoL, adverse events
Seltzer 2004 (E2020-A001-402)	RCT, parallel, double-blind, multicentre	6 months	1. Donepezil 10 mg: n=96 2. Placebo: n=57	USA (17 centres)	**ADAS-cog13** CDR-SB
Tariot 2001	RCT, parallel, double-blind, multicentre	6 months	1. Donepezil (5-) 10 mg: n=103 2. Placebo: n=105 Subgroup with mild to moderate AD 1. Donepezil (5-) 10 mg: n=76 2. Placebo: n=80	USA (27 nursing homes)	**NPI-NH** CDR-SB, MMSE, PSMS, adverse events
Tune 2003	RCT, parallel, double-blind, single centre	6 months	1. Donepezil 10 mg: n=14 2. Placebo: n=14	USA (1 centre)	**Brain metabolism** (PET) ADAS-cog, NPI
Winblad 2001 (DON-NY-96-001)	RCT, parallel, double-blind, multicentre	12 months	1. Donepezil (5-) 10 mg: n=142 2. Placebo: n=144	DK, FIN, N, S, NL (total: 28 centres)	**GBS** PDS, MMSE, NPI

a: Primary and other main outcomes according to Section 4.1.3 (in **bold** print if defined as "primary" in the corresponding study).
b: Unless otherwise stated, all information refers to the publication by Gauthier 2002 [52], which reports on a subgroup of patients with moderate disease (MMSE 10–17) of the original study by Feldman 2001 [53].
c: Information provided in Feldman 2001 [53].
d: Data on CSS are published in Feldman 2003 [54] for the total population of the original study by Feldman 2001 (MMSE 5–17).
e: Number of patients in groups inferred from information on safety provided on p. 307 of the publication.
f: Japanese version of ADAS-cog.
g: "Clinically evident decline" criterion from ADFACS or CDR.

Table 6. Main inclusion and exclusion criteria (donepezil)

Study	Main inclusion criteria	Main exclusion criteria[a]
Burns 1999	- Mild to moderate AD (probable) - MMSE: 10-26; CDR: 1-2 - CT or MRT - Good overall state of health	- Other neurological or psychiatric diseases - Severe uncontrolled gastrointestinal, renal, hepatic, endocrine or oncological diseases; asthma
Gauthier 2002[b]	- Moderate AD (probable or possible) - MMSE: 10-17 - FAST: ≤ 6 - CT or MRT	- Other potential causes of dementia - Other primary neurological or psychiatric diagnosis - Delirium, depression or other diagnosis that could impair study participation - Clinically relevant obstructive respiratory disease or asthma, haematological or oncological diseases, vitamin B12 or folic acid deficiency, gastrointestinal, renal, hepatic, endocrine or cardiovascular diseases - Substance abuse in the last 10 years - Complete need of care Other comorbidities such as controlled diabetes, hypertension, or thyroid disease were permitted.
Homma 2000	- Mild to moderate AD - MMSE: 10-26; CDR: 1-2 - ADAS-J-cog: ≥ 15 - Hachinski Score[c]: ≤ 4 - CT and MRT - Caregiver available	- Neurological diseases (e.g., Parkinson), prior head injury with unconsciousness - Depression - Serious complications - Stomach/intestinal ulcers
Krishnan 2003	- Mild to moderate AD (probable) - MMSE: 10-26; CDR: 1-2 - Hachinski Score[c]: ≤ 4 - Good overall state of health - Suitable for MRT (e.g., no pacemaker)	- Cerebrovascular disease - Other psychiatric primary diagnosis - Any unstable disease

(continued)

Table 6 (continued). Main inclusion and exclusion criteria (donepezil)

Study	Main inclusion criteria	Main exclusion criteria[a]
Mohs 2001	- Mild to moderate AD (probable) - MMSE 12-20 or 21; CDR: 1-2 - Hachinski Score[c]: ≤ 4 - Minimum number of preserved activities of daily living - Caregiver available	- Other neurological or psychiatric diseases - Complications of dementia (organic disease, delirium, depression, delusion) - Prior substance abuse
Moraes 2006	- Mild to moderate AD (probable) - CDR: 1-2	- Other causes of dementia - Other serious medical or psychiatric diseases - Moderate to severe sleep disorders - Apnoea-Hypopnoea Index (AHI) > 10 periodic limb movement index (PLMI) > 5 per hour
Prasher 2002	- Down syndrome - Mild to moderate AD according to DRC-10 - Living with a caregiver	- Significant diseases (e.g., insulin-dependent diabetes or other untreated metabolic disorder, asthma, obstructive lung disease, relevant uncontrolled neurological, gastrointestinal, hepatic or cardiovascular disease, Vitamin B12 or folic acid deficiency) Controlled epilepsy, treated thyroid disease, and stable psychotropic medication were permitted.
Rogers 1998	- Mild to moderate AD (probable) - MMSE: 10-26; CDR: 1-2 - Caregiver available	- Insulin-dependent diabetes or other endocrine disorder - Asthma or obstructive lung disease - Clinically significant, uncontrolled gastrointestinal, hepatic or cardiovascular disease
Seltzer 2004	- Mild AD (probable) - MMSE: 21-26; CDR: 0.5-1 - Hachinski Score[c]: ≤ 4 - Only minor restriction in activities of daily living	- Memory impairment, possibly caused by other psychiatric or neurological disorder or head injury.

(continued)

Table 6 (continued). Main inclusion and exclusion criteria (donepezil)

Study	Main inclusion criteria	Main exclusion criteria[a]
Tariot 2001	- Mild to moderate[d] AD (probable or possible) with or without a vascular component - MMSE: 5-26 - NPI-NH: at least one symptom several times a week - Living in nursing home for at least a month - Medically stable (concomitant disease permitted)	- Other neurological diseases, Parkinson's disease, vascular dementia - Uncontrolled diseases, as well as clinically relevant obstructive respiratory disease, asthma, vitamin B12 deficiency, haematological or oncological diseases, hemiparesis or aphasia - Hospital admission in the last 3 months - Substance abuse within the last years, secondary alcohol-related dementia
Tune 2003	- Mild to moderate AD (probable) - MMSE: 10-26; CDR: 1-2 - Hachinski Score[c]: ≤ 4 - CT or MRT	No details provided
Winblad 2001	- Mild to moderate AD (probable or possible) - MMSE: 10-26 - Good overall state of health - Caregiver available	- Other neurological or psychiatric primary diagnoses (in particular depression or vascular dementia) - Clinically relevant and uncontrolled active gastrointestinal, renal, hepatic, endocrine or cardiovascular disease - Hypothyroidism - Neoplasms, insulin-dependent diabetes, obstructive respiratory disease, asthma, haematological/oncological diseases, pernicious anaemia, vitamin B-12 or folic acid deficiency - Substance abuse within the last 10 years

a: Beyond the usual contraindication (e.g., drug intolerance) and exclusion criteria (e.g., competing concomitant medication).
b: Information provided in Feldman 2001 [53].
c: The Hachinski Scale was used for the differential diagnosis between Alzheimer's disease and vascular dementia.
d: Most patients included (about 75 %) had mild to moderate Alzheimer's disease (MMSE 10–26). Insofar as separate analyses were reported for these subgroups, these data are presented.

Table 7. Characterisation of the study populations (donepezil)

Study	Age (years) [a]	Gender f (%)	MMSE[a]	NPI[a]	Comment (on comparability etc.)	Discontinuations N (%)
Burns 1999						
DON 5 mg	72 (8.2)[b]	61	20 (4.9)[b]	-		60 (22)
DON 10 mg	72 (8.3)[b]	57	20 (3.3)[b]	-		72 (26)
Placebo	71 (8.3)[b]	55	20 (5.0)[b]	-		55 (20)
Gauthier 2002						
DON (5-) 10mg	74 (52-92)	69	14 (2.9)[b]	18 (17.1)[b]		19[c] (19)
Placebo	74 (48-90)	57	14 (2.7)[b]	17 (16.4)[b]		12[c] (11)
Homma 2000					Only baseline data of the PP group provided; impact of the difference in baseline MMSE and ADAS-cog analysed with ANCOVA	
DON 5 mg	70 (7.6)[d]	68[d]	18 (3.9)[d]	-		17 (13)[c]
Placebo	69 (8.8)[d]	66[d]	17 (3.9)[d]	-		22 (17)[c]
Krishnan 2003						
DON 10 mg	74 (7.0)	74	20 (4.8)	-		6 (18)
Placebo	72 (10.1)	70	19 (4.6)	-		10 (30)
Mohs 2001						
DON 10 mg	75 (8.8)	61	17 (2.9)	-		60 (28)
Placebo	75 (8.8)	65	17 (3.0)	-		56 (26)

(continued)

Table 7 (continued). Characterisation of the study populations (donepezil)

Study	Age (years) [a]	Gender f (%)	MMSE[a]	NPI[a]	Comment (on comparability etc.)	Discontinuations N (%)
Moraes 2006						
DON 10 mg	77 (6.6)	76	-	-	Donepezil group slightly less severely impaired[g]	n.d.
Placebo	75 (9.8)	61	-	-		n.d.
Prasher 2002						
DON 10 mg	53 (8.0)	37	-	8 (5.8)	Substantial differences regarding gender and SIB (cognition)	2 (13)[f]
Placebo	55 (4.6)	64	-	8 (7.6)		2 (13)[f]
Rogers 1998						
DON 5 mg	73 (7.5)[b]	63	19 (5.0)[b]	-		23[e] (15)
DON 10 mg	75 (7.5)[b]	62	19 (5.0)[b]	-		50[e] (32)
Placebo	73 (7.6)[b]	61	19 (5.1)[b]	-		32[e] (20)
Seltzer 2004						
DON 10 mg	73 (9.6)	50	24 (1.7)	-		26 (27)
Placebo	75 (8.8)	60	24 (1.3)	-		11 (19)
Tariot 2001						
DON (5-) 10mg	85 (64-98)	83	14 (5.4)	21 (14.5)[h]		19 (18)
Placebo	86 (65-102)	82	14 (5.8)	21 (14.7)[h]		27 (26)
Tune 2003						
DON 10 mg	74 (62-83)	79	21 (3.7)	18 (12.4)	Differences between groups in NPI; considered in ANCOVA for the evaluation of NPI	0 (0)
Placebo	72 (53-92)	71	21 (4.1)	9 (9.8)		2 (14)

(continued)

Table 7 (continued). Characterisation of the study populations (donepezil)

Study	Age (years) [(a)]	Gender f (%)	MMSE[(a)]	NPI[(a)]	Comment (on comparability etc.)	Discontinuations N (%)
Winblad 2001						
DON (5-) 10mg	72 (8.6)	70	19 (4.4)	13 (13.8)		47 (33)
Placebo	73 (8.0)	59	19 (4.5)	12 (12.2)		47 (33)

a: Mean value with SD (standard deviation) or range.
b: Own calculation of the SD from the standard error.
c: Information provided by the manufacturer Eisai within the framework of the submission of comments on the preliminary report (see comments: SN Eisai).
d: Data only provided for the per-protocol population.
e: N calculated from percentages.
f : % calculated from N.
g: Baseline data: ADAS-cog = 36 (donepezil); ADAS-cog = 39 (placebo).
h: NPI-NH.

DON = donepezil, f = female, N = number, n.d. = no details provided
As baseline data on ADL scales were only available for one study (Gauthier 2002), these are not reported here.

5.2.1.2 Study and publication quality

Overall, the study and publication quality was average. Details are presented in Table 8. In the subsequent assessment of biometric quality, 8 studies showed "minor deficiencies" and 4 showed "major deficiencies" (see Section 4.3). The most important aspects are summarised in the following text.

All studies were described as randomised, double-blind and placebo-controlled. The exact procedure followed regarding randomisation and concealment of allocation was often not reported in the publications. For most studies affected, the company Eisai provided further information within the framework of the submission of comments on the preliminary report (see comments: SN Eisai[11]). Overall, randomisation and allocation concealment were nearly always assessed as being adequate.

It was not always obvious from the publications whether or how the outcome raters were blinded with regard to other patient data. This is particularly relevant, as, due to the typical adverse effects of ChEIs, a post-randomisation unblinding would otherwise have been possible. In the comments on the preliminary report, the manufacturers noted that the assessment of CIBIC-plus was in each case performed by an independent rater who was blinded with regard to all other study results (see comments: SN Pfizer, p. 3). For ADAS-cog, it was reported that this scale was not usually assessed by the principal investigator, but by another member of the study team, normally before other assessments were made. According to the manufacturer, a formal blinding of the ADAS-cog rater was therefore not necessary, particularly as these persons generally did not have access to other study results (see comments: SN Eisai, p. 9, as well as meeting minutes). Therefore, certain blinding with regard to adverse events and other study outcomes is only given for the evaluation of CIBIC-plus. Further limitations of Moraes 2006 and Prasher 2002 are noted accordingly.

No information on sample size planning was provided in the publications on the 2 larger studies by Seltzer 2004 and Homma 2000; however, relevant information was later provided in the comments by Eisai (see comments: SN Eisai). Nor was information on sample size planning provided in the 2 smaller studies on imaging (Krishnan 2003, Tune 2003); however, these studies were pilot studies. Some issues on sample size planning remained unclear in Moraes 2006, Rogers 1998, and Tariot 2001. The other studies included a sample size calculation for a primary outcome, mainly CIBIC-plus. In Burns 1999, due to the high variance of baseline data, the sample size estimation was corrected upwards during the ongoing study. None of the studies provided information on how the problem of multiple testing was handled if several outcomes were assessed (e.g., statistical α-adjustment or the

[11] For references to comments, in cases where comments were submitted by manufacturers, the name of the company is noted; if comments were submitted by scientific societies, associations, working groups, etc., in each case, the first signatory is named (see Appendix I).

reason for not applying such an adjustment), even when more than one primary outcome had been defined. In particular for the patient populations investigated in Gauthier 2002, results of 10 assessment tools (mainly presenting both continuous as well as categorical evaluations) with different responder definitions were reported, without correction for multiple testing.

Information on study discontinuations, reasons for discontinuation, as well as patient flow charts, were presented in nearly all studies.

In almost all studies, a last observation carried forward (LOCF) analysis (referred to by the authors as an ITT analysis) was performed. In this context, at least one post-baseline measurement was mainly required for inclusion in the ITT population. In most cases this led to the exclusion of few (< 5%) randomised patients. Therefore, in most studies (assuming that the LOCF strategy was an appropriate strategy to consider missing values) an adequate ITT analysis was performed. A relevant deviation from the ITT principle[12] was ultimately only noticeable in 2 studies (Homma 2000, Prasher 2002). For Burns 1999, it remained unclear whether the ITT principle was followed, as it was only reported in the methods section of the publication that an analysis following ITT LOCF was to be performed, but otherwise no information on the patients actually analysed was provided. In the comments on the preliminary report, information on patients not considered was provided for ADAS-cog analyses (see comments: SN Eisai), but not for CIBIC-plus, even though this also represented a primary outcome. Eisai also provided information on the number of patients at risk after the start of treatment for Mohs 2001, which assessed the time to reach a specified outcome (see comments: SN Eisai).

Few relevant data inconsistencies were shown in these studies. The Prasher 2002 study contained inconsistent information on the number of serious adverse events.

[12] This can in general only be judged with some certainty for the outcomes named as primary, and this judgement implies that the procedure following the LOCF method is regarded as the adequate replacement method for the clinical situation investigated here and the outcomes used.

Table 8. Study and publication quality (donepezil)

Study	Randomisation / concealment adequate	Blinded outcome evaluation	Sample size planning adequate	Study discontinuations reported / Reasons for discontinuation reported	Relevant deviation from the ITT principle	Relevant data inconsistency within the publication	Study and publication quality
Burns 1999	yes[a]/yes[a]	(yes)[b]	yes[c]	yes/yes	unclear[d]	no	major deficiencies
Gauthier 2002	yes[e]/yes[a]	(yes)[b]	yes[e,f]	yes/yes[g]	no	no	minor deficiencies
Homma 2000	yes[a]/yes[a]	(yes)[b]	yes[a]	yes[a]/yes[a]	yes[h]	no	major deficiencies
Krishnan 2003	yes/yes[a]	(yes)[b]	no	yes/yes	no	no	minor deficiencies
Mohs 2001	yes[a]/yes	yes	yes	yes[a]/yes	(no)[i]	no	minor deficiencies
Moraes 2006	unclear/unclear	(yes)[j]	unclear	unclear	no	no	major deficiencies
Prasher 2002	yes/unclear	(yes)[k]	(yes)[l]	yes/yes	yes[m]	yes[n]	major deficiencies
Rogers 1998	yes/yes[a]	(yes)[o]	unclear	yes/(yes)[p]	no	no	minor deficiencies
Seltzer 2004	yes[a]/yes[a]	(yes)[b]	yes[a]	yes/yes	no	no	minor deficiencies
Tariot 2001	yes/yes[a]	(yes)[b]	unclear	yes/yes[a]	*no*[q]	no	minor deficiencies
Tune 2003	yes[a]/yes[a]	(yes)[b]	no	yes/yes	no[r]	no	minor deficiencies

(continued)

Table 8 (continued). Study and publication quality (donepezil)

Study	Randomisation / concealment adequate	Blinded outcome evaluation	Sample size planning adequate	Study discontinuations reported / Reasons for discontinuation reported	Relevant deviation from the ITT principle	Relevant data inconsistency within the publication	Study and publication quality
Winblad 2001	yes/yes[a]	(yes)[b]	*yes*[a]	yes/yes	no	no	minor deficiencies

a: The assessment is based on information provided by Eisai and Pfizer in the comments on the preliminary report (see comments: SN Eisai, Pfizer).
b: The study is described as double-blind; no information was provided in the publication on the type of blinding for outcome raters. In the comments on the preliminary report, the manufacturer stated that the blinding of the CIBIC raters regarding other study outcomes was ensured in each case (see comments: SN Pfizer). For ADAS-cog, it was reported that this scale was usually assessed not by the principal investigator, but by another member of the study team, usually before other assessments were made. According to the manufacturer, a formal blinding of the ADAS-cog rater was therefore not necessary, in particular as these persons generally did not have access to other study results; no information on the rating of other outcomes was made (see comments: SN Eisai).
c: Sample size planning was performed for CIBIC-plus, not for the second primary outcome ADAS-cog. The additional recruitment of about 500 patients took place due to the high variance of baseline values in the ADAS-cog.
d: It was not reported in the publication how many patients were included in the primary analysis. In the comments on the preliminary report, Eisai provided information on the primary outcome ADAS-cog, but not on CIBIC-plus, the second primary outcome (see comments: SN Eisai).
e: Information on this issue is provided in the publication by Feldman 2001 [53].
f: Sample size planning only took place for CIBIC-plus and did not take place for the investigated subgroup (MMSE 10-17), but only for the underlying total population (MMSE 5-17).
g: The reasons for discontinuation in the subgroup investigated were provided by Eisai (see comments: SN Eisai).
h: Overall, 11% of the randomised patients were not included in the ITT-LOCF analysis of the primary outcome ADAS-cog (donepezil group 7%; placebo group 14%).
i: Information on patients at risk during the course of the study were provided by EISAI (see comments: SN Eisai). The information provided on the analyses applied (Kaplan-Meier Analysis, Life-Table Method) are not completely comprehensible.
j: The study is described as double blind; regarding blinding of outcome raters, only blinding of the evaluation of sleep outcomes is mentioned.

(continued)

Table 8 (continued). Study and publication quality (donepezil)

k: It is described that all persons involved in the study were blinded towards allocation concealment throughout the whole study period; however, it is not presented how blinding was maintained.
l: The planned sample size was not achieved in the study.
m: Overall, 13% of randomised patients were not included in the ITT-LOCF analysis of the primary outcome DMR (donepezil group 13%; placebo group 13%).
n: Data inconsistencies regarding adverse events.
o: Study is described as double blind; regarding the blinding of the outcome raters, only the blinding of the CIBIC-plus rater in respect of the outcomes of the psychometric tests, laboratory values, and adverse events is mentioned.
p: Reasons for discontinuation are only partially reported.
q: After a query by IQWiG, the manufacturer Eisai stated that 103 patients each in the donepezil group and in the placebo group were included in the analysis of the primary outcome NPI-NH.
r: Even if the criterion for violating the ITT principle was formally fulfilled (rate of non-considered patients in the test group 0/14 = 0% and in the placebo group 1/14 = 7%), this difference between groups was not seen as a relevant deviation, as only one single patient in the whole study was not included in the analysis.

5.2.2 Galantamine

5.2.2.1 Study design, doses, and study populations

Six studies comparing galantamine and placebo fulfilled the inclusion criteria of this systematic review (Brodaty 2005, Erkinjuntti 2002, Raskind 2000, Rockwood 2006, Tariot 2000, Wilcock 2000; see Table 4). Study design and investigated patient populations of the included studies are presented in Tables 9 and 11. In addition to the publications, the manufacturer Jansen-Cilag provided data. These unpublished data are marked separately in the report. In the following text, the main aspects of the studies are summarised.

All studies had a multicentre design. The controlled observation period in the studies included (randomised phases) varied between 4 and 6 months. Some studies had an open-label follow-up phase including all interested participants of the blinded phase. Data from these uncontrolled phases were not considered in the present evaluation. In all studies, galantamine doses of 8 mg, 16 mg, 24 mg, and 32 mg were investigated; the dose of the unretarded form was always taken as 2 tablets (one per morning and one per evening). As galantamine in a 32 mg dose is not approved for Alzheimer's disease in Germany, the corresponding results are not presented here. The most commonly used dose was the 24 mg/day dose. The medication was increased at different paces, with an increase of 8 mg per week (Wilcock 2000, Raskind 2000) or 4 mg per week (Erkinjuntti 2002) or 8 mg every 4 weeks (Brodaty 2005, Tariot 2000, Rockwood 2006). In 2 studies, flexible dose regimens were permitted (16 or 24 mg galantamine) (Brodaty 2005, Rockwood 2006). In Brodaty 2005, conventional galantamine (twice-daily administration) as well as galantamine prolonged release (GAL-PR), which enabled a once-daily morning administration, were investigated.

Between 130 and 978 patients participated in the studies. Overall, 2000 patients took galantamine and 1200 patients took placebo.

Five studies included patients with probable Alzheimer's disease according to the NINCDS-ADRDA criteria (Table 10). This did not apply to Erkinjuntti 2002, which included both patients with probable vascular dementia (VaD) and patients with Alzheimer's disease and additional cerebrovascular disease (AD-CVD). In this latter group with mixed dementia (AD-CVD), both the diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria had been made and cerebral imaging had shown significant cerebrovascular damage. According to the authors, this AD-CVD group did not overlap with patients with Alzheimer's disease from other studies on galantamine, in which patients diagnosed with significant vascular damage based on imaging were excluded. Some AD-CVD subgroup analyses were outlined separately in the publication and are considered here in the overview of studies. Further unpublished data from this study were provided by Janssen-Cilag after a request by IQWiG and were also provided in the comments on the preliminary report (see comments: SN Janssen-Cilag). When interpreting these results, it should be considered that there may be

differences in the course of disease between patients with Alzheimer's disease and additional cerebrovascular dementia and Alzheimer's disease only (e.g., increased mortality and morbidity, as well as faster progression of disease [103]).

All studies included patients with mild to moderate Alzheimer's disease. Disease severity was assessed with the MMSE scale, and patients with scores between 10-25 were included. At the same time, a minimum number of errors in the ADAS-cog was required (≥ 12 or ≥ 18) to ensure that patients in the upper MMSE range (MMSE 24/25) already showed minimum cognitive impairment.

There were slight variations regarding the other inclusion and exclusion criteria. In general, patients were included who had concomitant diseases such as hypertension, cardiac failure, or diabetes type 2, as long as the disease was well controlled. In some studies, patients with stomach ulcers, micturition disorders, as well as cardiac disease that may lead to syncope, were explicitly excluded. Patients with other relevant psychiatric or neurological diseases were generally not included. In most studies, concomitant psychiatric medication was permitted.

According to the MMSE range included in the individual studies, the mean MMSE score and the mean age varied only slightly between studies (Table 11). In Erkinjuntti 2002, patients in the placebo group were slightly more impaired regarding activities of daily living (DAD) at baseline (66 points vs. 71 points in the galantamine group). It is unclear whether this difference was considered in the analysis. In Rockwood 2006, the patients in the placebo group also showed more severe impairment in the DAD and ADAS-cog (27.9 in the placebo group vs. 24.2 in the galantamine group). The results did not change after consideration of these differences.

In 5 studies, ADAS-cog and CIBIC-plus were primary outcomes (Table 9). The degree of achieving individually determined outcomes, measured with the Goal Attainment Scale (GAS), was a primary outcome only in Rockwood 2006. Further, secondary outcomes were daily living skills, which were measured by means of 2 different scales (ADCS-ADL [2 studies] and DAD [4 studies]). In 3 studies, the accompanying psychopathology was measured by means of the NPI. Summarised data on caregiver time from 2 studies was published in an additional paper [98]. In one study, caregiver burden was assessed with the Caregiving Burden Scale (CBS) (Rockwood 2006).

Overall, the 6 studies were comparable regarding methodology and characteristics of study participants.

Table 9. Galantamine studies included

Study (additional study ID)	**Study design**	**Study duration (controlled administration of test drug)**	**Intervention groups and number of randomised patients**	**Location and number of centres**	**Main outcomes[a]**
Brodaty 2005 (GAL-INT-10)	RCT, parallel, double-blind, multicentre	6 months	1. Galantamine Prolonged Release (PRC) 16-24 mg: n=320 2. Galantamine unretarded (GAL) 16-24 mg: n=327 3. Placebo: n=324	USA (66 centres), CAN, AUS, ZA, NZ (total: 93 centres)	**ADAS-cog**, **CIBIC-plus** ADCS-ADL, NPI, NPI-D, adverse events
Erkinjuntti 2002[b] (GAL-INT-6)	RCT, parallel, double-blind, multicentre	6 months	1. Galantamine 24 mg: n=188 2. Placebo: n=97	CAN, DK, FIN, F, D, IRL, NL, Israel, PL, GB (total: 62 centres)	**ADAS-cog, CIBIC-plus** NPI, NPI-D, DAD, adverse events
Raskind 2000 (GAL-USA-1)	RCT, parallel, double-blind, multicentre	6 months	1. Galantamine 24 mg[c]: n=212 2. Placebo: n=213	USA (33 centres)	**ADAS-cog, CIBIC-plus** DAD, adverse events
Rockwood 2006	RCT, parallel, double-blind, multicentre	4 months	1. Galantamine 16-24 mg: n=64 2. Placebo: n=66	CAN (14 centres)	**GAS** ADAS-cog, CIBIC-plus, DAD, CBS
Tariot 2000 (GAL-USA-10)	RCT, parallel, double-blind, multicentre	5 months	1. Galantamine 8 mg: n=140 2. Galantamine 16 mg: n=279 3. Galantamine 24 mg: n=273 4. Placebo: n=286	USA (no details provided on number of centres)	**ADAS-cog, CIBIC-plus** ADCS-ADL, NPI, NPI-D, adverse events
Wilcock 2000 (GAL-INT-1)	RCT, parallel, double-blind, multicentre	6 months	1. Galantamine 24 mg[c]: n=220 2. Placebo: n=215	CAN, NOR, FIN, F, D, S, NL, GB (total: 86 centres)	**ADAS-cog, CIBIC-plus** DAD, adverse events

a: Primary and other main outcomes according to Section 4.1.3 (in **bold print** if defined as "primary" in the corresponding study).
b: Subpopulation of patients with Alzheimer's disease plus cerebrovascular disease (AD-CVD); data obtained directly from the manufacturer (Janssen-Cilag).
c: The study also included an intervention group using 32 mg; however, this group is not presented here as the drug is not approved in this dose in Germany.

Table 10. Main inclusion and exclusion criteria (galantamine)

Study	Main inclusion criteria	Main exclusion criteria [(a)]
Brodaty 2005	- Mild to moderate AD (probable) - MMSE: 10-24 - ADAS-cog: ≥ 18 - Progressive deterioration of cognitive function for ≥ 6 months - Availability of a caregiver	- Other neurodegenerative diseases, cognitive impairment due to other cause, vascular dementia - Clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, endocrine, or cardiovascular diseases - Micturition disorder, stomach or intestinal ulcer - Epilepsy
Erkinjuntti 2002	Subpopulation AD+CVD: - Mild to moderate AD (possible) - CVD (probable; neuroradiologic imaging) - MMSE: 10-25 - ADAS-cog: ≥ 12 - Availability of a caregiver	- Other neurodegenerative diseases, cognitive impairment due to other cause - Cardiovascular disease that would endanger the completion of the study - Clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, endocrine, or cardiovascular diseases - Stomach or intestinal ulcer - Epilepsy or former substance abuse
Raskind 2000	- Mild to moderate AD (probable) - MMSE: 11-24 - ADAS-cog: ≥ 12 - Progressive deterioration of cognitive function for ≥ 6 months - Availability of a caregiver	- Other neurodegenerative diseases, cerebrovascular diseases - Cardiovascular disease that would endanger the completion of the study - Clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, or endocrine diseases - Micturition disorder, stomach or intestinal ulcer - Epilepsy or former substance abuse Stable and well-controlled concomitant diseases such as hypertension, non-insulin dependent diabetes or hypothyroidism were permitted.
Rockwood 2006	- Mild to moderate AD (probable) - Progressive deterioration of cognitive function for ≥ 6 months - MMSE: 10-25 - ADAS-cog: ≥ 18 - Availability of a caregiver	- Other possible causes of dementia - Living in a nursing home - Relevant communication disorder (speech, hearing or visual ability) - Other diseases

(continued)

Table 10 (continued). Main inclusion and exclusion criteria (galantamine)

Study	Main inclusion criteria	Main exclusion criteria [a]
Tariot 2000	- Mild to moderate AD (probable) - MMSE: 10-22 - ADAS-cog: ≥ 18 - CT or MRT - Availability of a caregiver	- Other neurodegenerative diseases, cerebrovascular disease - Cardiovascular disease that would endanger the completion of the study - Clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, or endocrine diseases - Micturition disorder, stomach or intestinal ulcer - Epilepsy or former substance abuse Stable and well-controlled concomitant diseases such as hypertension, non-insulin dependent diabetes or hypothyroidism were permitted
Wilcock 2000	- Mild to moderate AD (probable) - Progressive deterioration of cognitive function for ≥ 6 months - MMSE: 11-24 - ADAS-cog: ≥ 12 - Availability of a caregiver	- Other neurodegenerative diseases, multi-infarct dementia or other cerebrovascular disease - Cardiovascular disease that would endanger the completion of the study - Clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, or endocrine diseases - Micturition disorder; stomach or intestinal ulcer - Epilepsy or former substance abuse Stable and well-controlled concomitant diseases such as hypertension, non-insulin dependent diabetes or hypothyroidism were permitted
a: Going beyond the usual contraindications (e.g., drug intolerance) or exclusion criteria (e.g., competing concomitant treatment with other drugs)		

Table 11. Characteristics of study populations (galantamine)

Study	Age (years) [a]	Gender f (%)	MMSE[a]	NPI[a]	ADL[a]	Comments (on comparability etc.)	Study discontinuations N (%)
Brodaty 2005[b]							
GAL PRC 16-24 mg	77 (7.6)	205 (64)	18 (4.0)	*11 (13.8)[c,d]*	*53 (15.9)[c,d,e,f]*		69 (22)
GAL 16-24 mg	77 (7.8)	208 (64)	18 (4.1)	*13 (13.6)[c,d]*	*52 (16.4)[c,d,e,f]*		76 (23)
Placebo	76 (8.0)	205 (64)	18 (4.1)	*10 (11.7)[c,d]*	*55 (15.6)[c,d,e,f]*		58 (18)
Erkinjuntti 2002[c,g]							
GAL 24 mg	*76 (6.8)*	*99 (53)*	*21 (4.0)*	*11 (11.6)*	*71 (23.6)[d,h]*	*Patients in the placebo group were slightly more impaired regarding ADL*	34 (18)[i]
Placebo	*78 (5.9)*	*49 (51)*	*20 (3.6)*	*11 (11.8)*	*66 (24.3)[d,h]*		10 (10)[i]
Raskind 2000							
GAL 24 mg	76 (7.3)	139 (66)	20 (4.4)	-	71 (21.8)[h]		68 (32)
Placebo	75 (8.8)	131 (62)	19 (4.4)	-	70 (23.4)[h]		41 (19)
Rockwood 2006							
GAL 16-24 mg	77 (8)	41 (64)	21 (3.3)	-	76 (19.7)[h]	Patients in the placebo group were more severely impaired [j]	11 (17)
Placebo	78 (8)	41 (62)	20 (4.2)	-	71 (21.4)[h]		10 (15)
Tariot 2000							
GAL 8 mg	76 (7.1)	90 (64)	18 (3.5)	13 (14.2)	54 (14.2)[e]		32 (23)
GAL 16 mg	76 (8.4)	174 (62)	18 (3.3)	12 (13.4)	52 (15.0)[e]		60 (22)
GAL 24 mg	78 (6.6)	183 (67)	18 (3.3)	12 (13.2)	52 (16.5)[e]		61 (22)
Placebo	77 (8.5)	178 (62)	18 (3.4)	11 (11.8)	52 (15.2)[e]		46 (16)
Wilcock 2000							
GAL 24 mg	72 (8.3)	139 (63)	20 (3.4)	-	70 (21.4)[h]		44 (20)
Placebo	73 (7.6)	132 (61)	19 (3.5)	-	67 (22.5)[h]		29 (13)

(continued)

Table 11 (continued). Characteristics of study populations (galantamine)

a: Mean value with SD (standard deviation) or range.
b: The information on the study population refers to the group of randomised and treated patients (GAL-PRC: n=319, GAL: n=326, placebo: n=320).
c: Data obtained directly from the manufacturer Janssen-Cilag.
d: Data only available for the ITT-LOCF population.
e: ADCS-ADL.
f: Standard deviation calculated from the standard error using the number of randomised patients, as no information was available regarding the number of patients in the ITT-LOCF population.
g: Subpopulation of patients with Alzheimer's disease plus cerebrovascular disease.
h: DAD.
i: Information provided by Janssen-Cilag in the comments on the preliminary report (see comments: SN Janssen-Cilag).
j: The difference was considered in the analysis and did not influence the result.

f = female, GAL = galantamine, GAL-PRC = galantamine prolonged release, N = number

5.2.2.2 Study and publication quality

There were minor differences in methodological and publication quality between studies (with one exception). Overall, the quality can be described as satisfactory. Details are presented in Table 12. In 5 cases, the biometric quality was assessed as having "minor deficiencies"; in one case "major deficiencies" were noted. In the following text, the main aspects of the study and publication are summarised.

All studies were reported to be randomised. Most publications reported a computer-generated randomisation. In half of the publications, it was unclear to what extent allocation to treatment groups had been concealed. Additional documents provided by the manufacturer showed that in each of these studies allocation concealment had been ensured (see comments: SN Janssen-Cilag). In Rockwood 2006, allocation concealment was formally ensured by a central randomisation procedure; however, it is conceivable that the unusually small randomisation blocks (blocks of 2 patients), in connection with the typical cholinergic adverse effects, may have led to a partial uncovering of allocation to treatment groups.

In the publications, all studies were described as being double-blind. The blinding of patients as well as treating staff seemed to be adequate in all studies. In Wilcock 2001 and Erkinjuntti 2002, the blinding of CIBIC outcome raters was explicitly mentioned. For Tariot 2000, it could be inferred from additional documents provided by the manufacturer that the CIBIC was assessed by an independent person; therefore the blinding of this outcome was regarded as ensured. The ADAS-cog raters were also supposed to be involved in the treatment of patients as little as possible; however, this was evidently not always possible, so that in these cases the evaluation was performed before the assessment of adverse events (see comments: SN Janssen-Cilag). In Rockwood 2006, it was noted that persons who evaluated both the GAS and the CIBIC were blinded towards other study outcomes and adverse events. In the other publications, the risk that outcome raters may have become unblinded during the study due to knowledge of typical cholinergic adverse effects was not discussed.

All studies included a sample size calculation on the basis of previous efficacy studies. The information provided in this regard was complete in most studies. The planned sample sizes were mostly achieved; only Rockwood 2006 included 130 patients instead of the planned 152. No explanation for this was provided in the publication.

In all studies, a LOCF analysis was performed, which was described as an intention-to-treat analysis (ITT-LOCF), for which a post-baseline value was usually required. A baseline value alone was sufficient for inclusion in the ITT analysis only in Wilcock 2000. Furthermore, an "observed cases" (OC) analysis was performed in all studies. In the publication on the AD-CVD subgroup in Erkinjuntti 2002, no data were provided on the ITT population, but only on the OC. For the present report, previously unpublished data provided by Janssen-Cilag were therefore considered, which also included ITT-LOCF analyses for the relevant subpopulation.

In this study, the difference in the non-consideration rate between groups within the framework of the ITT-LOCF analysis for the primary outcome ADAS-cog was 5 percentage points between groups (galantamine 6%; placebo group 1%). In the comments on the preliminary report, the manufacturer provided additional data on the ITT analysis, in which patients without a post-baseline value were also analysed. The non-consideration rates here were only 3% (galantamine) and 1% (placebo) for ADAS-cog, and 9% and 5% respectively for CIBIC-plus (see comments: SN Janssen-Cilag).[13] In Rockwood 2006, all patients taking placebo were included in the evaluation of the GAS score (the primary outcome), in contrast to only 61 of 64 patients taking galantamine. This difference of 5 percentage points in the non-consideration rate was regarded as a relevant deviation from the ITT principle.

The publications provided sufficient information on the number of study discontinuations and the reasons for discontinuation for 5 of the 6 studies (Brodaty 2005; Raskind 2000; Rockwood 2006; Tariot 2000; Wilcock 2000). This information was provided in Erkinjuntti 2002 for the total population, but not for the subgroup investigated. The corresponding information was provided by Janssen-Cilag (see comments: SN Janssen-Cilag).

The studies did not show relevant data inconsistencies. Inconsistent information on the effects on the ADAS-cog caused by the permutation of an algebraic sign in Raskind 2000 could be clarified by documents provided by the manufacturer.

[13] In the following text, for better comparability with the other galantamine trials, results from the ITT-LOCF analyses are presented for Erkinjuntti 2002. These results were comparable to those of the ITT analysis (see comments: SN Janssen-Cilag).

Table 12. Study and publication quality (galantamine)

Study	Randomisation/ concealment adequate	Blinded outcome evaluation	Sample size planning adequate	Study discontinuations reported/Reasons for discontinuation reported	Relevant deviation from ITT principle	Relevant data inconsistency within publication	Study and publication quality
Brodaty 2005	yes/yes	(yes)[a]	yes[b]	yes/yes	no	no	minor deficiencies
Erkinjuntti 2002	yes/yes[b]	(yes)[c]	yes[b,d]	yes[b]/yes[b]	no[b,e]	no	minor deficiencies
Raskind 2000	yes/yes[b]	(yes)[f]	yes[g]	yes/yes	no	no	minor deficiencies
Rockwood 2006	unclear/yes	(yes)[h]	(yes)[i]	yes/yes	yes[j]	no	major deficiencies
Tariot 2000	yes/yes[b]	(yes)[k]	yes[g]	yes/yes	no[l]	no	minor deficiencies
Wilcock 2000	yes/yes	(yes)[c]	yes[g]	yes/yes	no	no	minor deficiencies

(continued)

Table 12 (continued). Study and publication quality (galantamine)

a: It is reported in the study that all those involved were blinded towards allocation to treatment groups throughout the whole course of the study; however, it was not stated how blinding was maintained.
b: Evaluation based on information provided by the manufacturer Janssen-Cilag in the comments on the preliminary report (see comments: SN Janssen-Cilag).
c: Study is described as being double-blind. Regarding the blinding of the outcome raters, it is merely described that the evaluation of the CIBIC-plus was performed by a rater who was blinded towards other aspects of the study.
d: Sample size planning was performed for the underlying total population of the study, not for the subgroup AD+CVD.
e: Evaluation refers to data from the conventional ITT analysis; these results were comparable to the ITT-LOCF analysis.
f: It is reported in the study that the investigators were blinded towards allocation to treatment groups throughout the whole course of the study; however, it was not stated how blinding was maintained.
g: Sample size planning was only performed for ADAS-cog, even though CIBIC-plus was also a primary outcome. Details on variability are lacking.
h: The person who conducted the interview with patients and relatives to document the achievement of the outcome was blinded with regard to adverse events (AEs) and all other study outcomes (except for CIBIC-plus, which he or she also rated); the treating physician was mostly not blinded with regard to AEs.
i: The planned sample size was not achieved in the study.
j: In total, 2% of the randomised patients were not considered in the ITT-LOCF analysis of the primary outcome GAS; the difference between groups was 5 percentage points (galantamine 5%; placebo 0%).
k: The study was described as double-blind; no information was provided in the publication on blinding of outcome raters. According to information provided by the manufacturer in the comments on the preliminary report, the CIBIC was evaluated in each case by an independent rater. The ADAS-cog rater was not to be involved in the treatment and not to have access to adverse event data. If this was not possible, the rater conducted the ADAS-cog test before documenting adverse events. No information was provided on the evaluation of further outcomes (see comments: SN Janssen-Cilag).
l: 40 patients from one study centre were excluded from the efficacy analysis because of protocol violations of the principal investigator responsible.

5.2.3 Rivastigmine

5.2.3.1 Study design, doses, and study populations

Six relevant studies comparing rivastigmine with placebo were identified, of which 3 published studies (Corey-Bloom 1998, Forette 1999, Rösler 1999), as well as one unpublished study (B304), were included in the evaluation. The data from the unpublished study were provided by the manufacturer Novartis and are marked separately in the report.

Details on study design and general study characteristics of the 4 studies included are presented in Table 13. The main aspects of the studies are summarised in the following text.

All studies had a multicentre, 3-arm design. The study duration was 18 weeks in Forette 1999, and 26 weeks in the other studies.

Corey-Bloom 1998 and Rösler 1999 both investigated low-dose rivastigmine (1 to 4 mg daily) and high-dose rivastigmine (6 to 12 mg daily) compared with placebo. In the first 7 (Corey-Bloom 1998) or 12 weeks (Rösler 1999) the dose was increased weekly until the target dose was reached; no dose reduction was planned in this period. Subsequently, a further increase in dose to the upper limit, or a dose reduction to the lower limit, was possible in the individual treatment groups. In Corey-Bloom 1998, if the lower target dose was not reached in the dose-increase phase in the corresponding treatment group, the affected patients were excluded from the study. In the case of adverse effects, in Rösler 1999, a dose could be missed or an anti-emetic drug could be added. No information in this regard was provided in Corey-Bloom 1998. In the B304 study, the daily rivastigmine dose lay between 2 and 12 mg, depending on the tolerability for the individual patients, in each case the highest possible dose was aimed for. In one group, rivastigmine was administered twice daily, in the other group, 3 times daily. The titration phase lasted between 10 days and 12 weeks, depending on the dose level tolerated by the patient. In Forette 1999, rivastigmine was also administered twice or 3 times daily. However, the daily minimum and maximum dose in this study was 6 mg and 12 mg respectively. The rivastigmine dose was always increased to the highest tolerated dose. If adverse effects occurred, an anti-emetic drug was administered. Patients who could not tolerate at least a 6 mg dose were excluded throughout the course of the study.

The B304, Corey-Bloom 1998 and Rösler 1999 studies included about 700 patients each. Forette 1999, which was described as a phase II study, was considerably smaller and included 114 patients. In total, about 1500 patients took rivastigmine and 700 patients took placebo.

All studies only included patients with probable mild to moderate Alzheimer's disease according to the NINCDS-ADRDA criteria. Disease severity was assessed by means of the MMSE. The B304, Corey-Bloom 1998, and Rösler 1999 studies included patients with an

MMSE score between 10 and 26; in Forette 1999 the MMSE score was 12 to 26. Exclusion criteria were in particular severe or uncontrolled diseases (Table 14).

The populations investigated in the 4 studies were homogeneous with regard to disease symptoms. Details on the characteristics of the patients included in the studies are presented in Table 15. As far as assessable, the treatment groups within the studies were comparable regarding baseline characteristics, even if in Corey-Bloom 1998 the proportion of female patients was slightly higher in the high-dose group, and in Forette 1999 the patients in the placebo group were slightly older than in the test groups. In Rösler 1999, details on baseline characteristics were only available for the total study population, but not for the individual groups.

The discontinuation rates lay between 8% and 15% in the placebo groups and between 14% (Rösler 1999, low-dose group) and 36% (Forette 1999, twice daily administration) in the rivastigmine groups.

In all 3 larger studies (B304, Corey-Bloom 1998, Rösler 1999), the ADAS-cog as well as the CIBIC-plus were assessed. The PDS, MMSE, and GDS were also applied. In Forette 1999, besides the ADAS-cog and CIBIC-plus, the NOSGER was applied. In all 4 studies, the CIBIC-plus was evaluated by means of the proportion of patients with an "at least minimal improvement" (score ≤ 3), instead of the approach mainly used in the studies on other ChEIs, the proportion of patients with "no deterioration" or "improvement" (score ≤ 4).

The 3 larger studies were comparable regarding methodology and the characteristics of study participants.

Table 13. Rivastigmine studies included

Study (additional study ID)	**Study design**	**Study duration (controlled administration of test drug)**	**Intervention groups and number of randomised patients**	**Location and number of centres**	**Main outcomes[a]**
B304 1998[b]	*RCT, parallel, double-blind, multicentre*	*26 weeks*	*1. Rivastigmine 2x/d (2-12 mg): n=229* *2. Rivastigmine 3x/d (2-12 mg): n=227* *3. Placebo: n=222*	*GB, IRL, AUS, CAN, ZA, I* *(total: 37 centres)*	***ADAS-cog, CIBIC-plus*** *PDS, CAS, adverse events*
Corey-Bloom 1998 (B352)	RCT, parallel, double-blind, multicentre	26 weeks	1. Rivastigmine 1-4 mg: n=233 2. Rivastigmine 6-12 mg: n=231 3. Placebo: n=235	USA (22 centres)	**ADAS-cog, CIBIC-plus, PDS** adverse events
Forette 1999 (B104)	RCT, parallel, double-blind, multicentre *Phase II study*	18 weeks	1. Rivastigmine 2x/d (6-12 mg/d): n=45 2. Rivastigmine 3x/d (6-12 mg/d): n=45 3. Placebo: n=24	B, CAN, F, GB, NOR (total: 11 centres)	ADAS-cog, CIBIC-plus, NOSGER, adverse events[c]
Rösler 1999 (B303)	RCT, parallel, double-blind, multicentre	26 weeks	1. Rivastigmine 1-4 mg: n=243 2. Rivastigmine 6-12 mg: n=243 3. Placebo: n=239	Europe and USA (total: 45 centres)	**ADAS-cog, CIBIC-plus, PDS** adverse events

a: Primary and other main outcomes according to Section 4.1.3 (in **bold print** if defined as "primary" in the corresponding study).
b: Information from the clinical study report provided by the manufacturer.
c: In Forette 1999, no primary outcomes were defined.

Table 14. Main inclusion and exclusion criteria (rivastigmine)

Study	Main inclusion criteria	Main exclusion criteria[a]
B304 1998[b]	- *Mild to moderate AD (probable)* - *MMSE: 10-26* - *Hachinski Score[c]: ≤ 4* - *Availability of caregiver* - *CT or MRT*	- *Other possible cause of dementia; cerebrovascular disease* - *Advanced serious or uncontrolled cardiovascular disease; gastrointestinal, hepatic or renal diseases; pulmonary diseases* - *Stomach or intestinal ulcer* - *Epilepsy or substance abuse*
Corey-Bloom 1998	- Mild to moderate AD (probable) - MMSE: 10-26 - CT or MRT - Availability of caregiver	- Serious and uncontrolled diseases Most patients with concomitant diseases were included.
Forette 1999	- Mild to moderate AD (probable) - MMSE: 12-26	- Significant medical, neurological or psychiatric diseases
Rösler 1999	- Mild to moderate AD (probable) - MMSE: 10-26 - Availability of caregiver	- Serious and uncontrolled cardiovascular diseases, serious obstructive pulmonary disease or other life-threatening disease, e.g., rapidly progressing malignant neoplasms Other diseases such as hypertension, non-insulin dependent diabetes or arthritis were permitted.

a: Going beyond the usual contraindications (e.g., drug intolerance) or exclusion criteria (e.g., competing concomitant drug therapy).
b: Information from the clinical study report provided by the manufacturer.
c: The Hachinski scale is used for the differential diagnosis between Alzheimer's disease and vascular dementia.

Table 15. Characteristics of the study population (rivastigmine)

Study	Age (years)[a]	Gender f (%)	MMSE[a]	Comments (e.g., on comparability)	Study discontinuations N (%)
B304 1998[b]					
RIV 2x/d (2-12 mg)	*71 ± 8.2*	*57*	*19 (n.r.)[c]*		*54 (24)*
RIV 3x/d (2-12 mg)	*71 ± 7.9*	*60*	*18 (n.r.)[c]*		*38 (17)*
Placebo	*72 ± 8.7*	*60*	*19 (n.r.)[c]*		*33 (15)*
Corey-Bloom 1998					
RIV 1-4 mg	75 (45-89)	57	20 (n.r.)		34 (15)[d]
RIV 6-12 mg	74 (50-89)	68	20 (n.r.)		82 (35)[d]
Placebo	75 (45-89)	58	20 (n.r.)		39 (17)[d,e]
Forette 1999					
RIV 2x/d (6-12 mg)	70 ± 9.9[f]	n.r.	20 ± 4.2[f]		16 (36)[d]
RIV 3x/d (6-12 mg)	72 ± 6.8[f]	n.r.	19 ± 3.4[f]		11 (24)[d]
Placebo	73 ± 4.8[f]	n.r.	19 ± 3.8[f]		2 (8)[d]
Rösler 1999					
RIV 1-4 mg	72 (45-95)[g]	59[g]	20 (10-29)[g]	"comparable" (according to text)	34 (14)[d]
RIV 6-12 mg					79 (33)[d]
Placebo					31 (13)[d]

a: Mean value with SD (= standard deviation) or range.
b: Data from the clinical study report provided by the manufacturer.
c: Data only available for ITT population (RIV 2x/d: n=227; RIV 3x/d: n=227; placebo: n=220).
d: % calculated from N.
e: In Figure 1 of the publication, 39 study discontinuations of 235 randomised participants of the placebo group are reported. This results in 196 study completers and not 197, as stated in the table.
f: Data only available for the per-protocol publication.
g: Data only available for the total sample. According to the available baseline data on ADAS-cog, the groups seem comparable regarding cognitive function.

f = female, N = number, RIV = rivastigmine, n.r. = not reported
As baseline data on activities of daily living were available only in one study (B304), and no study provided baseline data on NPI, the corresponding data are not presented here.

5.2.3.2 Study and publication quality

In the assessment of biometric quality, 2 studies were assessed as having "minor deficiencies" and 2 as having "major deficiencies". Details on the study and publication quality are presented in Table 16 and are summarised in the following text.

All studies were reported to be randomised, double-blind, and placebo-controlled. Information on the exact randomisation process was missing only in Forette 1999. In 3 studies (B304, Forette 1999, Rösler 1999) it remained unclear whether concealment of allocation of patients to treatment groups was ensured. It is assumed that this is not a major deficiency in actual double-blind studies, even though more detailed information would be desirable.

In the publications, all studies were described as being double-blind. Within the framework of submission of comments on the preliminary report, the manufacturer Novartis reported that the CIBIC-plus rater had had no access to patient data or any other measurement data recorded in the studies (see comments: SN Novartis). However, it was not evident from the publications or comments whether or to what extent the raters of the other outcomes were blinded towards other patient data. In view of the high rate of study discontinuations of up to 36% (mainly due to adverse events), the question arises as to what extent the blinding of patients, relatives, and treating staff could be maintained throughout the study.

In all 3 larger studies (B304, Corey-Bloom 1998, Rösler 1999), adequate sample size planning was reported. The study discontinuations as well as the corresponding reasons for discontinuation were also described appropriately. In contrast, in Forette 1999 no information on sample size planning was provided. The number of study discontinuations can be reproduced; however, the reasons for discontinuation were not fully reported.

Both B304 and Rösler 1999 reported results on the conventional ITT analysis (defined as the population of all randomised patients), the ITT-LOCF population (randomised patients with at least one measurement during drug therapy), and the OC population. In Corey-Bloom 1998, a comparable approach to the statistical analysis was described; however, only the results of the conventional ITT analysis and the OC analysis were reported. In the following text, the data on the conventional ITT population are therefore presented for each study.

In Forette 1999, the analysis was not performed following the ITT, but following the per-protocol principle. In the publication it is explicitly noted that this procedure was determined a priori, as the study was conducted in an early phase of drug development. However, this substantially restricts the evidential value of the study, as up to 50% of the originally randomised patients in the different groups were not considered in the analysis. Therefore, in the following text the efficacy outcomes are not presented, but only adverse event outcomes, as all randomised patients were considered in this analysis.

In Rösler 1999, the difference between groups regarding the non-consideration rate in the ITT-LOCF analysis of the primary outcome (CIBIC-plus) was 6 percentage points (rivastigmine low-dose 4%; rivastigmine high-dose 10%; placebo 4%), which was regarded as a relevant deviation from the ITT principle.

The studies showed only minor inconsistencies; they did not show relevant data inconsistencies that could have had a substantial effect on the studies' conclusions.

Table 16. Study and publication quality (rivastigmine)

Study	Randomisation/ concealment adequate	Blinded outcome evaluation	Sample size planning adequate	Study discontinuations reported / reasons for discontinuation reported	Relevant deviation from the ITT principle	Relevant data inconsistency within the publication	Study and publication quality
B304 1998	*yes/(yes)*	*(yes)*[a]	*yes*	*yes/yes*	*no*	*no*	*minor deficiencies*
Corey-Bloom 1998	unclear/yes	(yes)[a]	yes[b]	yes/yes	no	no	minor deficiencies
Forette 1999	unclear/unclear	(yes)[c]	no	yes/(yes)[d]	yes[e]	no	major deficiencies
Rösler 1999	yes/unclear	(yes)[a]	yes[b]	yes/yes	yes[f]	no	major deficiencies

a: The study is described as being double-blind; no information was provided in the publication on the blinding of the outcome raters. According to information provided by the manufacturer in the comments on the preliminary report, in each case the CIBIC was evaluated by an independent rater who did not have access to patient data or any other measurement data recorded in the study. No information was provided regarding the evaluation of the ADAS-cog or other outcomes (see comments: SN Novartis).
b: Variability estimate not provided for ADAS-cog; unclear information provided for CIBIC-plus.
c: The study is described as being double-blind; regarding the blinding of the outcome raters, only the blinding of the CIBIC-plus rater towards the results of the psychometric tests and the adverse events is mentioned.
d: Incomplete reporting of reasons for discontinuation.
e: Overall, 39% of randomised patients were not considered in the ADAS-cog analysis (rivastigmine 2x/d group: 49%; rivastigmine 3x/d group: 38%; placebo group: 21%).
f: Overall, 6% of randomised patients were not considered in the ITT analysis of the primary outcome CIBIC-plus (rivastigmine low-dose group: 4%; rivastigmine high-dose group: 10%; placebo group: 4%).

5.2.4 Comparisons between different cholinesterase inhibitors

Seven studies were identified that compared different ChEIs with each other; 5 were included in the evaluation. One of these studies compared donepezil and galantamine (Wilcock 2003), 3 studies compared donepezil and rivastigmine (Bullock 2005, Fuschillo 2001, Wang 2001) and a single study compared all 3 drugs with each other (Cumbo 2005). Details on the study designs and study populations are presented in Tables 17 and 19 and are summarised in the following text.

5.2.4.1 Study designs, doses, and study populations

5.2.4.1.1 Galantamine vs. donepezil

Wilcock 2003 (comparing galantamine and donepezil) included 188 patients with MMSE scores between 9 and 18. About 14% of these patients had MMSE scores below 12. The study lasted 52 weeks.

In the galantamine group, between Week 1 and 12, the dose was increased to 16 mg per day. Afterwards, depending on tolerability, the investigator could increase the dose up to 24 mg (distributed in 2 doses per day). In the donepezil group, patients took 5 mg once daily in the first 4 weeks and, depending on tolerability, 5 mg or 10 mg once daily from Week 5 onwards. A total of 71% of patients taking galantamine and 69% of patients taking donepezil received the maximum dose. Medication was open-label. The evaluation of outcomes was performed in a blinded manner.

The Bristol Activities of Daily Living Scale (BADLS), which assesses daily living skills, was the primary outcome. In addition, accessory symptoms and cognitive function were assessed by means of the NPI and MMSE/ADAS-cog respectively. Further parameters (the objective and subjective burden of caregivers) were assessed with the Screen for Caregiver Burden (SCGB).

Patients in both groups were largely comparable, except that the proportion of women was slightly higher in the donepezil group.

5.2.4.1.2 Rivastigmine vs. donepezil

Three studies comparing rivastigmine and donepezil were identified that fulfilled the inclusion criteria (Fuschillo 2001, Wang 2001, Bullock 2005).

Bullock 2005 was characterised by a long observation period and a large sample size. In this double-blind, 2-year study, 998 patients from 94 European and Canadian centres were randomised. The dose was increased over a relatively long period of 16 weeks. Medication was administered in identical capsules (maximum rivastigmine and donepezil doses of 12 mg

and 10 mg respectively). In the maintenance phase, patients received the highest possible tolerated dose up to the maximum permitted dose. The average dose was 9.4 mg in both groups. Compared with other studies, the dose strength of donepezil and rivastigmine was in the upper range. The Severe Impairment Battery (SIB) as a measure of cognitive function was the primary outcome. Furthermore, the GDS, ADCS-ADL, NPI, and MMSE were used to assess the global severity of dementia, activities of daily living, accessory symptoms, and cognitive function respectively.

Participants in Bullock 2005 were outpatients with moderate (MMSE 10-20) possible Alzheimer's disease. The proportion of patients with possible concomitant Lewy body dementia was 3.6% and 4.4 %. The average age was 76 years; 69% of study participants were female, and the mean disease duration was 34 months.

The open study by Fuschillo 2001 lasted 30 weeks. In the first week, rivastigmine was administered in a once-daily dose of 1.5 mg. Subsequently, if tolerated, there was a weekly increase in the daily dose by 1.5 mg up to 6 to 9 mg per day (distributed in 2 doses daily). Donepezil was administered in a once-daily 5 mg dose throughout the whole study period. The efficacy of both drugs was assessed by means of the ADAS-cog and the Physical Self-Maintenance Scale (PSMS), as well as the MMSE.

Fuschillo 2001 only included a small number of patients (11 patients in the rivastigmine group and 16 in the donepezil group). The study was conducted in a neuropsychogeriatric ward in Italy. The patients had mild to moderate Alzheimer's disease (MMSE 10-21). The average age of participants was 68 (donepezil) and 66 years (rivastigmine); the mean disease duration was 21 and 22 months respectively. The proportion of women was 56% in the donepezil group and 55% in the rivastigmine group.

In the Chinese study Wang 2001, which was also an open study, rivastigmine was initially administered in a dose of 1.5 mg twice daily. If no relevant adverse effects occurred, after 4 weeks the dose was increased to 3 mg twice daily. Donepezil was given in a once-daily dose of 5 mg initially for 4 weeks. If possible, the dose was then increased to 10 mg. The efficacy assessment was performed with the MMSE, the Blessed-Roth Dementia Scale (which mainly covers social activities and ADLs), and the GDS (to assess the severity of dementia). The primary efficacy assessment took place after 16 weeks.

In Wang 2001, 62 patients were randomised to each of the 2 treatment groups. The participants had mild to moderate dementia (MMSE 10-26). Sociodemographic data on the total study population was not provided in the population; however, it was noted that there was no statistical significance between groups in this regard.

5.2.4.1.3 Rivastigmine vs. donepezil vs. galantamine

A total of 101 patients participated in the 18-month open study by Cumbo 2005. On average, the 37 patients in the rivastigmine group received 9 mg rivastigmine daily; the 31 patients in the donepezil group received 10 mg donepezil daily, and the 33 patients in the galantamine group received 16 mg galantamine daily. No information was provided on the dose-increase scheme. The primary outcome was the time to the first occurrence of behavioural disorders associated with dementia. Secondary outcomes were the frequency and severity of symptoms at the time of occurrence, measured by means of the NPI and the NPI-D (NPI Caregiver Distress Scale) as well as the Behavioral Pathology in Alzheimer’s Disease Rating Scale (BEHAVE-AD).

Patients with mild to moderate probable Alzheimer's disease (MMSE 10-27) who had suffered from the disease for at least 3 years were included. No detailed information was provided on the study location. The comparability of patients between the 3 treatment groups was not evaluable, as no separate information in this regard was available.

Table 17. Included direct comparative studies on cholinesterase inhibitors

Study	Study design	Study duration (controlled period of administration of test drug)	Intervention groups and number of randomised patients	Study location and number of centres	Main outcomes[(a)]
Galantamine vs. donepezil					
Wilcock 2003	RCT, parallel, open/rater-blinded, multicentre; pilot study	12 months	1. Galantamine 16-24 mg: n=97 2. Donepezil 5-10 mg: n=91	GB (18)	**BADLS** ADAS-cog, NPI, SCGB, adverse events
Rivastigmine vs. donepezil					
Bullock 2005	RCT, parallel, double-blind, multicentre	24 months	1. Rivastigmine 3-12 mg: n=498 2. Donepezil 5-10 mg: n=500	AUS, CAN, F, D, I, E, GB Total (94)	**SIB** ADCS-ADL, GDS, NPI, adverse events
Fuschillo 2001	RCT, parallel, open, single centre	7.5 months	1. Rivastigmine 6-9 mg: n=11 2. Donepezil 5 mg: n=16	Italy, 1 centre	ADAS-cog, PSMS, adverse events [(b)]
Wang 2001	RCT, parallel, open, multicentre	4 months	1. Rivastigmine 3-6 mg: n=62 2. Donepezil 5-10 mg: n=62	China, multicentre	MMSE, Blessed-Roth Dementia Scale, GDS, adverse events [(b)]

(continued)

Table 17 (continued). Included direct comparative studies on cholinesterase inhibitors

Rivastigmine vs. donepezil vs. galantamine					
Cumbo 2005	RCT, parallel, open	18 months	1. Rivastigmine 9 mg: n=37 2. Donepezil 10 mg: n=31 3. Galantamine 16 mg: n=33	No information provided	**Time to first occurrence of behavioural disorders associated with dementia**[c] Frequency and severity of behavioural disorders, adverse events

a: Primary and other main outcomes according to Section 4.1.3 (in **bold print** if defined as "primary" in the corresponding study).
b: No primary outcomes were defined in this study.
c: Assessed by means of NPI, NPI-D, and BEHAVE-AD.

Table 18. Main inclusion and exclusion criteria of the direct comparative studies on cholinesterase inhibitors

Study	Main inclusion criteria	Main exclusion criteria[a]
Galantamine vs. donepezil		
Wilcock 2003	- Moderate Alzheimer's disease (probable) - MMSE: 9-18 - Progressive deterioration of cognitive function for ≥ 12 months - CT or MRT - Availability of a caregiver	- Other neurodegenerative disease, multi-infarct dementia or cerebrovascular disease, cognitive impairment due to a different cause - Other medical conditions that endanger the study completion by the patient
Rivastigmine vs. donepezil		
Bullock 2005	- Moderate[b] AD (probable) - MMSE: 10-20 - Availability of a caregiver	- Other neurodegenerative primary disease (including Parkinson) - Any advanced serious or uncontrolled disease or disability - Episode of major depression, uncontrolled epilepsy, stomach or intestinal ulcer, serious or uncontrolled asthma or cardiovascular disease, cerebrovascular disease
Fuschillo 2001	- Mild to moderate AD (possible or probable)[c] - MMSE: 10-21 - CT or MRT - Availability of a caregiver	Serious and uncontrolled diseases
Wang 2001	- Mild to moderate AD - MMSE: 10-26	- Hachinski Score[d] ≥ 7 - Other possible causes of dementia - Active epilepsy or stomach/duodenal ulcer - Serious cardiovascular disease or asthma

(continued)

Table 18 (continued). Main inclusion and exclusion criteria of the direct comparative studies on cholinesterase inhibitors

Study	Main inclusion criteria	Main exclusion criteria[(a)]
Rivastigmine vs. donepezil vs. galantamine		
Cumbo 2005	- Mild to moderate AD (probable) - MMSE: 10-27 - Duration of disease ≥ 3 years - No behavioural disorders - Availability of a caregiver	- Other (previous) neurological or psychiatric diseases - Substance abuse - Clinically significant medical or surgical disorders (independent of their stability) - Previous dementia therapy

a: Going beyond the usual contraindications (e.g., drug intolerability) or exclusion criteria (e.g., competing concomitant drug therapy).
b: In the publication, the disease stage was referred to as "moderate to moderately-severe".
c: Inconsistent information in the publication (abstract: "probable or possible"; text: only "probable").
d: Die Hachinski-Scale is used for differential diagnosis between Alzheimer's disease and vascular dementia.

Table 19. Characterisation of study populations in the direct comparative studies on cholinesterase inhibitors

Study	Age (years)[a]	Gender f (%)	MMSE[a]	Comment on comparability	Study discontinuations N (%)
Galantamine vs. donepezil					
Wilcock 2003					
GAL 16-24 mg	74 (53-88)	56	15 (14.5; 15.7)[b]		19 (20)
DON 5-10 mg	73 (54-88)	68	15 (14.2; 15.3)[b]		20 (22)
Rivastigmine vs. donepezil					
Bullock 2005					
RIV 3-12 mg	76 (6.6)	69	15 (3.0)		237 (48)
DON 5-10 mg	76 (6.8)	69	15 (2.9)		183 (37)
Fuschillo 2001					
RIV 6-9 mg	66 (9.2)	55	13 (3.3)		unclear[c]
DON 5 mg	68 (5.6)	56	14 (3.4)		
Wang 2001				Not assessable, as essential information is missing	
RIV 3-6 mg	n.r.	n.r.	17 (4.1)		2 (3)
DON 5-10 mg	n.r.	n.r.	18 (4.7)		1 (2)
Rivastigmine vs. donepezil vs. galantamine					
Cumbo 2005[d]				Not assessable, as no separate data available	
DON 10 mg		58			
RIV 9 mg	76 (66-83)	57	17 (n.r.)		unclear[c]
GAL 16 mg		58			

a: Mean value with SD (standard deviation) or range.
b: Confidence interval.
c: Not reported explicitly in the publication whether study discontinuations occurred.
d: Mean dose reported in each case.

DON = donepezil, f = female, GAL = galantamine, n.r. = not reported, RIV = rivastigmine

Baseline data on NPI were only available in one study (Bullock 2005); the available data on activities of daily living refer to 3 different scales, so that they are only of limited help in assessing the comparability of the study populations. These data are therefore not presented.

5.2.4.2 Study and publication quality

Table 20 summarises the study and publication quality of studies comparing different ChEIs with each other.

5.2.4.2.1 Galantamine vs. donepezil

In Wilcock 2003 the randomisation plan was prepared adequately. However, no information was provided as to what extent allocation to treatment groups was concealed. Unlike in actual double-blind studies, in an open study this is a relevant deficiency of quality. The non-blinding of patients and treating staff (for practical reasons) also clearly decreases the methodological quality of the study. Although it was reported that the clinical measurements were conducted by blinded raters, it was not described how the blinding of raters was actually maintained. Comments by patients or caregivers on medication were presumably not always preventable. Furthermore, it is not described whether the raters were blinded towards the occurrence of adverse events.

It is unclear from the description on sample size planning whether the study had sufficient statistical power, nor was it recognisably designed as an equivalence or non-inferiority study. The number of study discontinuations was reported in the publication; however, the information on the reasons for discontinuation was incomplete. More detailed information on the reasons for discontinuation was provided by Janssen-Cilag within the framework of the submission of comments on the preliminary report. In the statistical analysis, the differences between end of study and baseline were considered in the LOCF analysis (called ITT-LOCF), after controlling for age and baseline MMSE, but without controlling for the corresponding baseline values of the scales.

5.2.4.2.2 Rivastigmine vs. donepezil

All 3 studies were described as being randomised. One study (Bullock 2005) was reported to be double-blind and both the other studies (Fuschillo 2001, Wang 2001) were reported to be open. In Bullock 2005, randomisation was adequate, and concealment of allocation to treatment groups was also ensured. In Wang 2001, randomisation was also adequate; however, information was not provided on the concealment of allocation to treatment groups. In Fuschillo 2001, both aspects were unclear. In both of these open studies, the lack of clarity regarding allocation concealment is a relevant deficiency of quality. Furthermore, none of the studies reported whether the outcome evaluation was performed in a blinded manner. In contrast, it was reported in Bullock 2005 that all persons involved in the study were blinded throughout the study towards the corresponding treatment group.

In Bullock 2005, sample size planning was suitable to detect a difference between treatment groups; overall, 998 patients were randomised. In contrast, no information on sample size

planning was available in Fuschillo 2001 and Wang 2001. Particularly in Fuschillo 2001 the patient group investigated (27 randomised patients) was too small to detect even moderate differences between groups. All 3 studies were not recognisably designed as equivalence or non-inferiority studies.

In Bullock 2005 and Wang 2001, both the number of study discontinuations and the corresponding reasons were reported. No such information was provided in Fuschillo 2001.

In Bullock 2005, the ITT-LOCF analysis was the primary analysis. A relatively large number of patients (48% in the rivastigmine group and 37% in the donepezil group) discontinued the study over the 2-year period, which was long compared with the other studies. In Fuschillo 2001, it was unclear whether all 27 participants were considered in all analyses.

Furthermore, relevant data inconsistencies were noticeable regarding adverse events in the publication of Fuschillo 2001 (see Table 20).

5.2.4.2.3 Rivastigmine vs. donepezil vs. galantamine

One direct open comparative study investigating rivastigmine, donepezil, and galantamine, which was reported to be randomised, was available (Cumbo 2005). No detailed information on the randomisation process was provided in the publication. It was also unclear whether allocation to treatment groups was concealed. It was not reported whether the evaluation of outcomes was blinded. The publication did not explicitly report whether sample size planning was performed. Also, this study was evidently not designed as an equivalence or non-inferiority study. Information on possible study discontinuations was also missing. However, it was reported that all patients took part in the examinations as planned, so one may assume that there were no study discontinuations and that the ITT principle was not violated. However, due to the lack of clarity regarding allocation concealment and the lack of blinding, the study had major deficiencies overall.

Table 20. Study and publication quality: Comparative studies

Study	Randomisation/ concealment adequate	Blinded evaluation of outcomes	Sample size planning adequate	Study discontinuations reported / reasons for discontinuation reported	Relevant deviation from the ITT principle	Relevant data inconsistency within the publication	Study and publication quality
Galantamine vs. donepezil							
Wilcock 2003	yes/unclear	yes[a]	unclear	yes/yes[b]	no	no	major deficiencies
Rivastigmine vs. donepezil							
Bullock 2005	unclear/yes	yes[c]	yes	yes/yes	(no)[d]	no	minor deficiencies
Fuschillo 2001	unclear/unclear	no[e]	no	unclear/unclear	unclear	yes[f]	major deficiencies
Wang 2001	yes/unclear	no[e]	no	yes/yes	no	no	major deficiencies
Rivastigmine vs. donepezil vs. galantamine							
Cumbo 2005	unclear/unclear	no[e]	no	unclear/unclear	no	no	major deficiencies

a: Only the outcome raters were blinded in the study.
b: The evaluation is based on information provided by Janssen-Cilag in the comments on the preliminary report (see comments: SN Janssen-Cilag).
c: The study was described as double-blind. It was reported that the staff involved in the study were blinded towards the allocation to treatment groups throughout the whole study. However, it was not described how the blinding was maintained.
d: Analysis was conducted according to the LOCF principle; however, 5.4% (rivastigmine) and 3.4% of patients were not considered in the primary outcome analysis. Furthermore, the relatively large and in particular the different proportion of study discontinuations in the 2 treatment groups during the study is problematical.
e: Open study.
f: The reported rates on single adverse events are not compatible with the number of patients.

5.3 Results on therapy goals

5.3.1 Donepezil

In the donepezil studies, different scales were often used as assessment instruments, for example in the assessment of activities of daily living. Due to the lack of information in the text on mean values and measures of dispersion, information was in part obtained from the figures, which means the data are not absolutely certain. Values estimated from figures are marked accordingly.

5.3.1.1 Activities of daily living

The daily living skills were assessed as an outcome in 6 studies by means of different assessment tools (Burns 1999, Gauthier 2002, Homma 2000, Mohs 2001, Tariot 2001, Winblad 2001). Furthermore, in Mohs 2001, a different type of operationalisation was used (time to reaching a defined deterioration).

In Burns 1999, at the end of study, small (statistically significant) effects were shown with the 10 mg dose (but not with the 5 mg dose) compared with placebo in the IDDD subscale "complex tasks" (instrumental activities). In contrast, there was no effect on the progression of basic activities (subscale: "self care"); otherwise no detailed information was provided in the publication in this regard. No results on the overall scale (instrumental and basic activities) were reported. Due to the seemingly selective way of presentation, these results are only interpretable to a very limited extent.

In Gauthier 2002, scales on both basic activities of daily living (PSMS-plus) and instrumental activities (IADL-plus) were applied, as well as a combined scale (DAD) which was dependent on the 2 separate scales. In this study, donepezil had a statistically significant effect, both on instrumental activities (IADL-plus), as well as (to a slightly lesser extent) on basic activities and on the combined scale DAD.

A modified version of the Crichton Scale (Caregiver-rated Modified Crichton Scale – CMCS), which measures various aspects of activities of daily living, was assessed in Homma 2000. Significantly less deterioration was reported in the donepezil group. However, at the same time, it was noted that the psychometric quality of this scale has not yet been investigated.

Table 21. Donepezil: Results on daily living skills

Study (duration)		**Out-come**	**N**[a]	**Mean difference from baseline (SD)**	**Difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Burns 1999 (24 weeks)	DON 5 mg	IDDD Overall scale	(271)[b]	n.r.	n.r.	?[c]	n.r.
	DON 10 mg		(273)[b]	n.r.	n.r.	(↗)[d]	n.r.
	Placebo		(274)[b]	n.r.			
Gauthier 2002 (24 weeks)	DON (5-) 10 mg	DAD	92	0[e] (13.4[f])	- 9.25 (n.r.)	↗	<0.001
	Placebo		101	-9.25[e] (14.3[f])			
Homma 2000 (24 weeks)	DON 5 mg	CMCS	103[g]	1.03 (6.7)	-2.42	↗	0.010
	Placebo		99[g]	3.45 (7.1)			
Tariot 2001[h] (24 weeks)	DON (5-) 10 mg	PSMS	(103)[b,h]	1	n.r.	?[c]	"n.s."
	Placebo		(105)[b,h]	1			
Winblad 2001 (52 weeks)	DON (5-) 10 mg	PDS	89[i]	-11[e]	4[f]	↗	"<0.05"
	Placebo		94[i]	-15[e]			

a: Number of patients in the analysis, unless otherwise stated.
b: Number of randomised patients, as no exact information was provided on the number of patients in the analysis.
c: As no information was provided in the publication on the observed difference between groups, the direction of change remains unclear.
d: As a statistically significant advantage for the subscale "complex tasks" was shown for placebo, the direction of the effect is presumably the same in the overall scale, but ultimately this presumption is not totally certain.
e: Values estimated from the figure.
f: Own calculation.
g: Detailed data for the analysis are only available for the per-protocol population; ITT analysis: p = 0.019.
h: The patient population presented also included patients with severe Alzheimer's disease (MMSE 5-26).
i: Data are only presented for the "observed cases"; the results were also statistically significant for the LOCF analysis. The number of patients in the analysis was inferred from patient numbers for the single items of the scale (89 to 93 for donepezil, 94 to 97 for placebo, without consideration of the item "safe driving").

CI = confidence interval, DON = donepezil, N = number, n.r. = not reported, n.s. = not statistically significant, SD = standard deviation

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect.

In Tariot 2001, no statistically significant effect of donepezil was shown at the end of study with regard to a change in the Physical Self-Maintenance Scale (PSMS), which strongly reflects basic activities of daily living. More detailed data were not provided in the study. This analysis referred to the total study population, which also included severely impaired patients. A subgroup analysis for mild to moderately impaired patients was not available.

In Winblad 2001, it was reported that patients taking donepezil showed less deterioration in activities (measured by means of the PDS) than patients taking placebo at all times of measurement. These differences were statistically significant at the end of study (LOCF); however, no detailed information was provided.

In Mohs 2001, the time to reaching a clinically manifest functional deterioration was assessed, defined by a specific degree of deterioration in basic and instrumental ADL (in each case measured with the ADFACS) or by the increase in the CDR score by at least one point. The median time to reaching the outcome "functional deterioration" was 357 days (lower limit 95% CI: 280 days) for the test group and 208 days (upper limit 95% CI: 252 days) for the placebo group (statistically significant difference; $p = 0.005$[14]). Furthermore, Mohs 2001 included additional analyses of the differences in the ADFACS between the placebo and test group at the last measurement performed, as well as of group differences regarding changes throughout the course of the study. However, due to the study design, results beyond the (primary) survival time analysis cannot be interpreted with sufficient certainty, as patients were either successively lost for the corresponding analyses (OC analysis), or the values of patients at the time of reaching the outcome were used (resulting in a violation of the principle of "missing at random").

The differences in the instruments applied and in part the varying methods of operationalisation, as well as the mostly insufficient description of results (see Table 21), only allowed a very limited quantitive summary of results. Only 3 of the 6 studies could be included in a meta-analysis. Furthermore, for 2 of these 3 studies, detailed data were only available from OC analyses, with a loss of data of randomised patients of 25% (Homma 2000) and 36% (Winblad 2001). However, on the other hand, in the publications of both of these studies, statements were made that the results of these OC analyses did not essentially differ from the results of a LOCF analysis, so they were used for exploratory reasons in this meta-analysis. The meta-analysis showed a statistically significant superiority of donepezil versus placebo (Figure 2; standardised mean difference: -0.44 [95% CI: -0.21 to -0.66], random effects model). Heterogeneity was modest ($I^2 = 46.3\%$). The determined difference of nearly half a standard deviation must be seen as an overestimation of the effect, as on the one hand the clearly negative result in Tariot 2001 could not be considered here, and on the other, the difference noted in Gauthier 2002 of more than 9 points on the DAD scale was unusually

[14] This refers to the higher of 2 reported p-values (for 2 different statistical tests).

large compared with the other ChEIs (see Sections 5.3.2.1 and 5.3.3.1). In summary, considering the poor reporting in this regard, one can at best conclude an indication of a favourable effect on daily living skills by donepezil (with an uncertain estimate of the effect strength). This assessment is supported by the additional meta-analysis provided by the manufacturer Eisai in the comments submitted on the preliminary report. Under consideration of Burns 1999 and Tariot 2001, a slightly smaller common effect was shown (d = -0.28 [95% CI: -0.44 to -0.12]; see comments: SN Eisai)

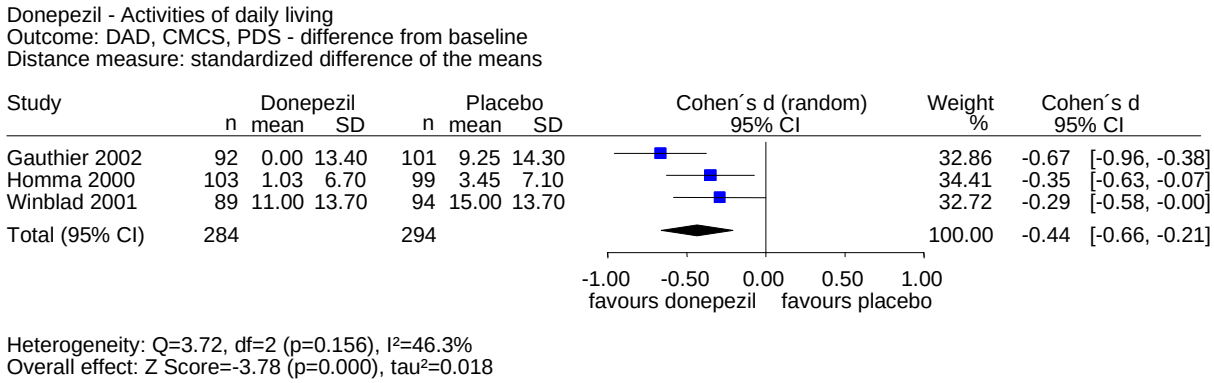


Figure 2. Donepezil: Meta-analysis of activities of daily living

5.3.1.2 Accompanying psychopathology

Three larger studies used the NPI (Winblad 2001, Gauthier 2002) or the NPI-NH (Neuropsychiatric Interview – Nursing Home, Tariot 2001) to assess the effects on accompanying psychopathology. Whereas a statistically significant difference between treatment groups in favour of donepezil was shown in Gauthier 2002, no such difference was shown in Winblad 2001 and Tariot 2001. In Winblad 2001, only a cursory note was made in this regard, stating that from Week 12, a beneficial effect in favour of donepezil was shown. In contrast, an opposite effect was shown in Tariot 2001 (Table 22). However, the analysis by Tariot 2001 refers to the total population of patients investigated, which also included severely impaired patients (MMSE 5-26). No separate analysis was reported for the subgroup of patients with mild to moderate disease regarding the NPI-NH.

The NPI was also used in both of the small studies by Prasher 2002 and Tune 2003 (in each case ≤ 30 patients). In Prasher 2002, which only included patients with Down syndrome, a stronger deterioration was shown under donepezil than under placebo (p = 0.03); however, the basis of the calculation for the reported p-value is unclear. In Tune 2003, the changes in the NPI in both groups were not statistically significant; however, the trend was also in disfavour of donepezil. Regarding the NPI subscales, in most studies, no data were reported (Prasher

2002, Tune 2003, Winblad 2001) or the data provided were not sufficiently interpretable (Gauthier 2002, Tariot 2001).

In summary, the studies do not provide a clear indication of a favourable or unfavourable effect on psychopathology with donepezil. A meta-analysis (Figure 3) confirms this assessment. A strong heterogeneity is noticeable (I^2 = 74.1%), which is caused by the differences between the results of Gauthier 2002 and Tariot 2001. This difference may be explained by the specific population included in Tariot 2001 (patients from nursing homes). Otherwise, no differences in study design or patient characteristics were found that could have explained this discrepancy. Due to this heterogeneity, a random effects model was chosen. When a fixed effects model was used, a slightly more (non-statistically significant) beneficial effect in favour of donepezil was shown (data not presented). The results of Prasher 2002 could not be included in the meta-analysis, as no variability measure was provided for the relevant time point (Week 24) and such a measure could not be clearly estimated from the figures in the publication.

Table 22. Donepezil: Results on accompanying psychopathology

Study (duration)		**Out-come**	**N**[a]	**Mean difference from baseline (SD)**	**Group difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Gauthier 2002 (24 weeks)	DON (5-) 10 mg	NPI	97	-5.0 (15.8[b])	-5.9 (n.r.)	↗	0.002
	Placebo		104	1.0 (14.3[b])			
Prasher 2002[c] (24 weeks)	DON 10 mg	NPI	27[d]	-2.2 (n.r.)	+2.2 (n.r.)	↘	n.r.[e]
	Placebo			-4.4 (n.r.)			
Tariot 2001[f] (24 weeks)	DON (5-) 10 mg	NPI-NH	*103*[g]	-2.3 (19.3[b])	+2.6 (n.r.)	↘	"n.s."
	Placebo		*103*[g]	-4.9 (19.3[b])			
Tune 2003[c] (24 weeks)	DON 10 mg	NPI	14	5.4 (17.8)	+2.8 (-9.9; 15.4)	↘	0.688
	Placebo		13	2.7 (14.0)			
Winblad 2001 (52 weeks)	DON (5-) 10 mg	NPI	(142)[h]	n.r.	n.r.	↗	"n.s."
	Placebo		(144)[h]	n.r.			

a: Number of patients in the analysis, unless otherwise stated.
b: Own calculations.
c: Unclear whether reported results represent the ITT-LOCF analysis.
d: Number of patients in the analysis inferred from data provided in the publication on degrees of freedom. However, the allocation to treatment groups is unclear.
e: In the publication, a p-value is only reported for the difference between groups over the whole study period.
f: Data refer to the total population of the patients investigated (MMSE 5-26), as no subgroup analysis for mild to moderately impaired patients was available.
g: Data obtained directly from the manufacturer.
h: Number of randomised patients, as no exact data were available on the number of analysed patients.

CI = confidence interval, DON = donepezil, N = number, n.r. = not reported, n.s. = not statistically significant, SD = standard deviation

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect.

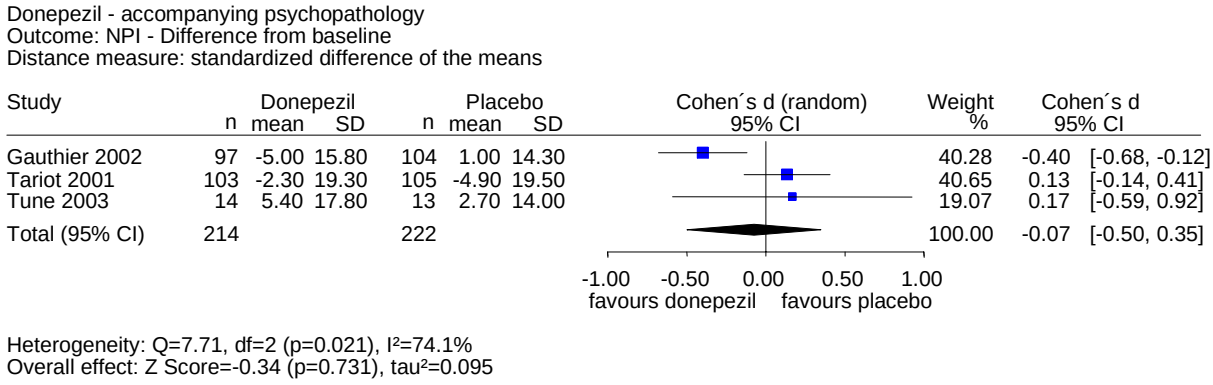


Figure 3. Donepezil: Meta-analysis of accompanying psychopathology

5.3.1.3 Cognitive function

In 7 studies (Burns 1999, Homma 2000, Krishnan 2003, Moraes 2006, Rogers 1998, Seltzer 2004, Tune 2003), the progression of cognitive deficits was investigated with the ADAS-cog. Data on the MMSE was available in 3 studies (Gauthier 2002, Tariot 2001, Winblad 2001). At the end of study, the differences from baseline between the donepezil and placebo groups regarding ADAS-cog lay between 1.5 (donepezil 5 mg) and 3.1 points (donepezil 10 mg) in favour of donepezil. Only in Moraes 2006 was the observed effect substantially greater. In this study, the baseline scores in both groups were also substantially higher than those in other studies; furthermore, the baseline difference between groups at study inception was not considered in the analysis. It ultimately remains unclear as to what caused this difference in comparison with the other studies. The effects on the MMSE lay between 1.0 (donepezil [5-] 10 mg) and 2.1 points (donepezil 10 mg) and were therefore consistent with the ADAS-cog outcomes.

In Prasher 2002 on Alzheimer's disease in people with Down syndrome, only the SIB was used to assess cognitive function. The difference in favour of donepezil was not statistically significant (p = 0.06); however, this may be due to the small sample size.

Mohs 2001, whose primary outcome was the time to reaching a specific outcome, also reported changes in cognitive function (MMSE), and reported that at the end of study, the donepezil group had significantly better MMSE scores. However, the interpretability of results is greatly limited due to the particularities of the study design (see above).

In summary, in the scales applied, consistently positive results were available with regard to the improvement of cognitive function. A meta-analysis (Figure 4) did not show a heterogeneity of effects and showed a moderate, statistically significant, effect strength of the dimension of half a standard deviation (Cohen's d = -0.51; 95% CI: -0.60 to -0.42). This

corresponds to about 2.5 to 3 points on the ADAS-cog. Moraes 2006 and Prasher 2002 could not be included in the meta-analysis, as no variability measure was reported for the estimated difference between groups (measured as the change between baseline and end of study), nor could this measure be estimated from the reported p-values.

Table 23. Donepezil: Results on cognitive function

Study (duration)		**Out-come**	**N[a]**	**Mean difference from baseline (SD)**	**Treatment difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Burns 1999 (24 weeks)	DON 5 mg	ADAS-cog	(271)[b]	0.3 (4.9)[c]	-1.5 (n.r.)	↗	< 0.001
	DON 10 mg		(273)[b]	-1.3 (5.0)[c]	- 2.9 (n.r.)	↗	0.002
	Placebo		(274)[b]	1.8 (5.0)[c]			
Gauthier 2002 (24 weeks)	DON (5-) 10 mg	sMMSE	91	1.5 (4.8)[c]	2.1 (n.r.)	↗	< 0.001
	Placebo		100	-0.5 (4.0)[c]			
Homma 2000 (24 weeks)	DON 5 mg	ADAS-J-cog	126	-2.4 (5.1)	-2.5 (n.r.)	↗	< 0.001
	Placebo		113	0.1 (5.2)			
Krishnan 2003 (24 weeks)	DON 10 mg	ADAS-cog	34	0.1[c] (n.r.)	-3.1[c] (n.r.)	↗	< 0.04
	Placebo		32	3.2[c] (n.r.)			
Moraes 2006 (24 weeks)	DON 10 mg	ADAS-cog	17	-7.4[d] (n.r.)	-11.2[d] (n.r.)	↗	<0.01[e]
	Placebo		18	3.8[d] (n.r.)			
Prasher 2002[f] (24 weeks)	DON 10 mg	SIB	27[g]	-5.2 (n.r.)	10.8 (n.r.)	↗	n.r.[h]
	Placebo			-16.0 (n.r.)			
Rogers 1998 (24 weeks)	DON 5 mg	ADAS-cog	152	-0.7 (6.3)	-2.5 (n.r.)	↗	< 0.001
	DON 10 mg		150	-1.1 (6.3)	-2.9 (n.r.)	↗	< 0.001
	Placebo		153	1.8 (6.1)			
Seltzer 2004 (24 weeks)	DON 10 mg	ADAS-cog**13**	91	-1.6 (3.3)[c]	-2.3 (n.r.)	↗	0.001
	Placebo		55	0.7 (3.2)[c]			

(continued)

Table 23 (continued). Donepezil: Results on cognitive function

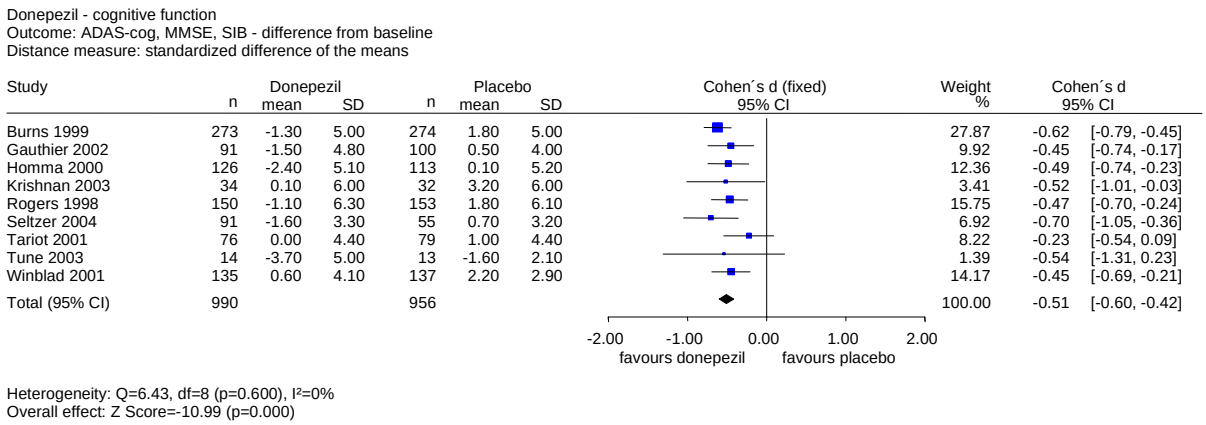
Study (duration)		**Out-come**	**N[a]**	**Mean difference from baseline (SD)**	**Treatment difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Tariot 2001[i] (24 weeks)	DON (5-) 10 mg	MMSE	76	0.0 (4.4)[c]	1.0[c] (n.r.)	↗	"n.s."
	Placebo		79	-1.0 (4.4)[c]			
Tune 2003[f] (24 weeks)	DON 10 mg	ADAS-cog	14	-3.7 (5.0)	-2.1 (-5.2; 1.0)	↗	0.186
	Placebo		13	-1.6 (2.1)			
Winblad 2001 (52 weeks)	DON (5-) 10 mg	MMSE	135	-0.6 (4.1)[c]	1.6[c] (n.r.)	↗	< 0.001
	Placebo		137	-2.2 (2.9)[c]			

a: Number of patients in the analysis, unless otherwise stated.
b: As no exact case numbers were reported, the number of patients in the ITT population was assumed.
c: Values estimated from the figure; standard deviations based on own calculations.
d: Own calculation.
e: P-value refers to the interaction factor "treatment/time" in the bi-factorial ANOVA.
f: Unclear whether reported results represent the ITT-LOCF analysis.
g: Number of patients in the analysis inferred from the degrees of freedom in the publication. However, the allocation to groups in unclear.
h: In the publication, only a single p-value for the whole study period is provided for the difference between groups at different measurement time points.
i: Data for the subgroup MMSE (10-26); see also total population (MMSE): 5-26 (not significant).

CI = confidence interval, DON = donepezil, N = number, n.r. = not reported, n.s. = not statistically significant, SD = standard deviation

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect.

A separate analysis of the studies according to the corresponding dose used (low dose [5 mg], flexible dose [5-10 mg], high dose [10 mg]) showed that the effect observed was higher in the higher dose range (Cohen's d = -0.58; 95% CI: -0.70 to -0.46) compared with a low or flexible dose (Figures 5 to 7).



Note: Algebraic signs changed in MMSE and SIB, i.e., low values correspond to positive effects.
Krishnan 2003: Standard deviations calculated from p-value = 0.04.

Figure 4. Donepezil: Meta-analysis of cognitive function

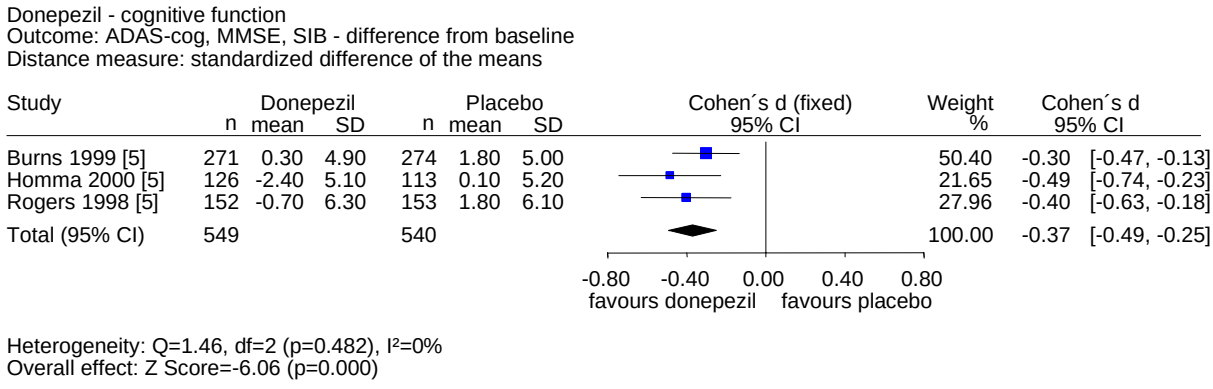


Figure 5. Donepezil: Meta-analysis of cognitive function – low dose

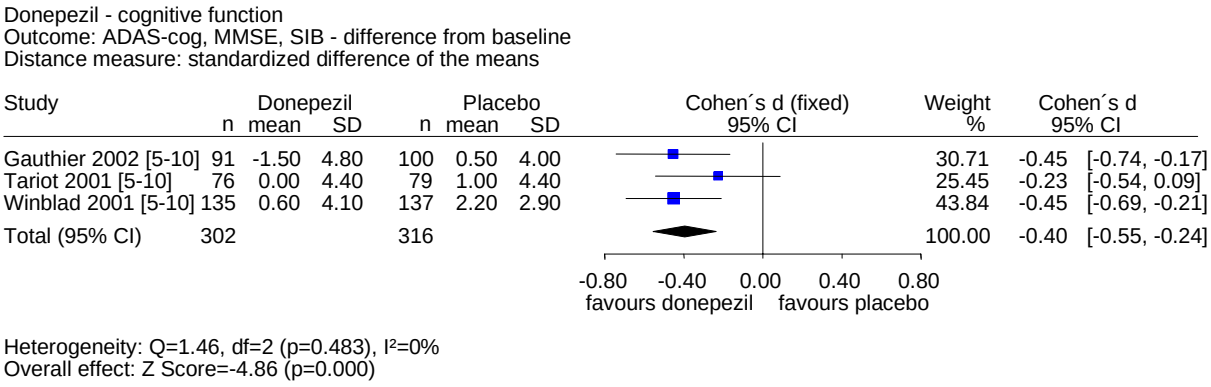


Figure 6. Donepezil: Meta-analysis of cognitive function – flexible dose

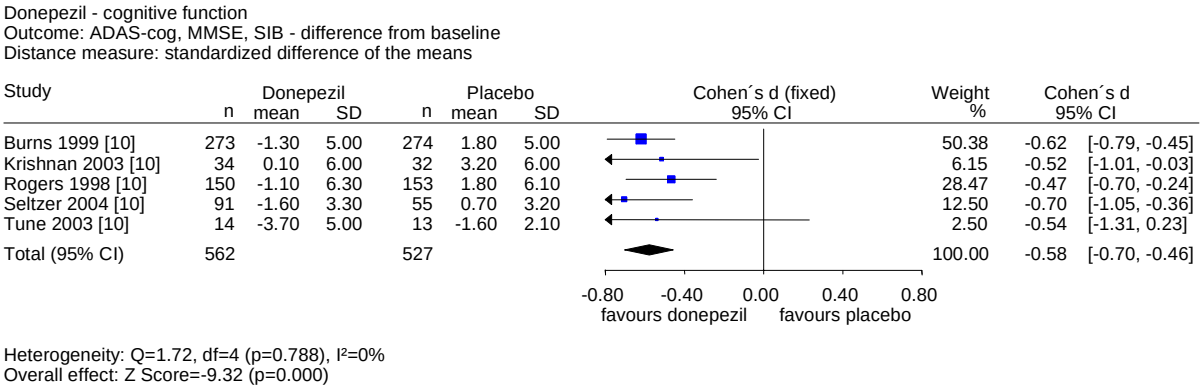


Figure 7. Donepezil: Meta-analysis of cognitive function – high dose

5.3.1.4 Health-related quality of life

Quality of life instruments were used in the Rogers 1998 and Burns 1999 studies. In both studies, the QoL scale by Blau 1977 [104] was used, which however is not validated for use in patients with dementia [105]. In Rogers 1998, in both donepezil groups (5 mg and 10 mg) a trend in the improvement of quality of life was shown compared with placebo. However, the difference compared with placebo was only statistically significant in the 5 mg group in Week 24 ($p = 0.05$). In the LOCF analysis at the end of study, no differences between groups were shown. In Burns 1999, no data were presented. However, it was noted that there was a lack of statistically significant differences in quality of life between the donepezil 5 mg, donepezil 10 mg and placebo groups (response variability was high).

In summary, no evidence of a beneficial effect of donepezil on health-related quality of life can be inferred from the available results.

5.3.1.5 Placement in a nursing home (institutionalisation)

Data on the outcome "Placement in a nursing home (institutionalisation)" were only available in a publication by Winblad 2001 [67]. A total of 132 (93%) and 133 (92%) of the 142 and 144 patients in the donepezil and placebo groups respectively lived at home at study inception. Of these patients, 9 and 10 patients respectively moved to another more expensive abode (residence providing nursing care, old people's home, living group, nursing home, or different type of residence). It was reported that fewer patients moved to a nursing home in the donepezil group than in the placebo group; however, this difference was not statistically significant (3 patients vs. 8 patients; $p = 0.13$). Moreover, no further information was provided on the different types of residence; therefore, the interpretation of this analysis is limited.

5.3.1.6 Mortality

Overall, the number of deaths in the studies was low and no noticeable difference between groups was shown (Table 24).

The reported data did not provide a clear indication of a favourable or unfavourable effect on mortality.

5.3.1.7 Adverse events

Discontinuations due to adverse events in patients taking donepezil 10 mg were more common in 5 out of 6 studies compared with placebo (odds ratio 2.02 [95% CI: 1.44 to 2.84]; $p < 0.001$; $I^2 = 0\%$; Figure 10); in patients taking the flexible dose this was the case in 2 out of 3 studies (odds ratio 0.98 [95% CI: 0.47 to 2.02]; $p = 0.950$; $I^2 = 44\%$; Figure 9). No higher discontinuation rates due to adverse events were reported in patients taking the 5 mg dose. Similar results were shown for the occurrence of serious adverse events. The pooled estimate for these events was slightly lower and differences were no longer statistically significant, even in the high-dose range (Table 24 and Figures 11 to 13). A moderate to high heterogeneity was noticeable in the studies using flexible doses. This was evidently caused by the Tariot 2001 and Winblad 2001 studies; the specific patient population in Tariot 2001 (nursing home inhabitants) should be noted here.

In 3 studies, no detailed information on adverse events was provided (Krishnan 2003, Moraes 2006 and Tune 2003). In Prasher 2002, the data were inconsistent and are therefore not presented here. Typical adverse effects associated with the mode of action of ChEIs (nausea, vomiting, and diarrhoea) occurred 3-4 times more often in the 10 mg test group compared with the placebo group (Table 25). In contrast, in the 5 mg group, adverse events were only slightly more common than in the placebo group. Lack of appetite and weight loss were 3 times and about twice as common respectively in the 10 mg group than under placebo.

Further adverse events that were more common in the test groups were dizziness, headache, and abdominal symptoms.

Meta-analyses confirm the dose-effect relationship for the adverse events stated above, with a statistically significant risk increase in the 10 mg groups (Figures 8 to 27). There was only a statistically significant risk increase in the 5 mg groups for the adverse event "diarrhoea". Except for the aspect mentioned above, no noticeable heterogeneity of results was shown.

Table 24. Donepezil: Study discontinuations, deaths, and adverse events

Study (duration)		**Increase in dose within the first month**	**N[a]**	**Study discontinuations N (%)**	**Deaths N**	**Serious adverse events N (%)**	**Discontinuations due to serious adverse events N (%)**	**Total adverse events N (%)**
Burns 1999 (24 weeks)	DON 5 mg	5 mg	271	60 (22)	1	19 (7)	24 (9)	213 (79)
	DON 10 mg	10 mg	273	72 (26)	2	29 (11)	50 (18)	234 (86)
	Placebo		274	55 (20)	2	25 (9)	27 (10)	207 (76)
Gauthier 2002 (24 weeks)	DON (5-) 10 mg	10 mg	102	19[b] (19)	1[b]	14[c] (14)	9 (9)[b]	84 (82)
	Placebo		105	12[b] (11)	0[b]	13[c] (12)	5 (5)[b]	84 (80)
Homma 2000 (24 weeks)	DON 5 mg	5 mg	136	17 (13)[b]	n.r.	n.r.	2 (1)	54 (40)
	Placebo		131[d]	22 (17)[b]	n.r.	n.r.	6 (5)	33 (25)
Krishnan 2003 (24 weeks)	DON 10 mg	5 mg	34	6 (18)	n.r.	n.r.	0	32[c] (94)
	Placebo		33	10 (30)	n.r.	n.r.	1 (3[e])	28[c] (85)
Mohs 2001 (54 weeks)	DON 10 mg	5 mg	214	60 (28)	3	29[f] (14)	20 (9)	n.r.
	Placebo		217	56 (26)	4	23[f] (11)	12 (6)	n.r.
Prasher 2002 (24 weeks)	DON 10 mg	5 mg	16	2 (13)	n.r.	Inconsistencies[g]	n.r.	n.r.
	Placebo		15	2 (13)	n.r.	Inconsistencies[g]	n.r.	n.r.
Rogers 1998 (24 weeks)	DON 5 mg	5mg	154	23[c] (15)	0	7 (5)	9[c] (6)	n.r.
	DON 10 mg	10 mg	157	50[c] (32)	1	15 (10)	25[c] (16)	n.r.
	Placebo		162	32[c] (20)	1	9 (6)	11[c] (7)	n.r.

(continued)

Table 24 (continued). Donepezil: Study discontinuations, deaths, and adverse events

Study (duration)		**Increase in dose within the first month**	**N[(a)]**	**Study discontinuations N (%)**	**Deaths N**	**Serious adverse events N (%)**	**Discontinuations due to serious adverse events N (%)**	**Total adverse events N (%)**
Seltzer 2004 (24 weeks)	DON 10 mg	5 mg to Week 6, then 10 mg	96	26 (27)	n.r.	5 (5)	15 (16)	67 (70)
	Placebo		57	11 (19)	n.r.	3 (5)	5 (9)	37 (65)
Tariot 2001[(h)] (24 weeks)	DON (5-) 10 mg	5 mg	103	19 (18)	3	10[(c)] (10)	11 (11)	99 (96)
	Placebo		105	27 (26)	7	17[(c)] (16)	19 (18)	102 (97)
Tune 2003 (24 weeks)	DON 10 mg	5 mg	14	0	n.r.	n.r.	n.r.	n.r.
	Placebo		14	2 (14[(e)])	n.r.	n.r.	n.r.	n.r.
Winblad 2001 (24 weeks)	DON (5-) 10 mg	5 mg	142	47 (33)	4	35 (25)	10 (7)	116 (82)
	Placebo		144	47 (33)	3	20 (14)	9 (6)	109 (76)

a: Number of randomised patients.
b: Information provided by the manufacturer Eisai in the comments on the preliminary report (see comments: SN Eisai).
c: Calculated from percentage.
d: In the safety analysis, one patient in the placebo group was excluded who, after randomisation, had not come to any further examinations.
e: Calculated from N.
f: Including deaths (were reported separately in the publication).
g: In the publication, inconsistent information is provided on the number of patients with serious adverse events. Donepezil group: 0, 8, and 12 patients; placebo group: 0, 3, and 7 patients.
h: Data refer to the total population of investigated patients (MMSE 5-26), as corresponding data are not available for mild to moderately impaired patients.

DON = donepezil, N = number, n.r. = not reported

Table 25. Donepezil: Adverse events

Study (duration)		**Increase in dose in first month**	**N[a]**	**Nausea**	**Vomiting**	**Diarrhoea**	**Dizziness**	**Lack of appetite**	**Weight loss**	**Agitation**	**Headache**	**Abdominal symptoms**	**Fatigue**	**Feeling of unwellness**
				Proportion (%) with AEs										
Burns 1999 (24 weeks)	DON 5 mg	5 mg	271	7	4	10	5	4	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	DON 10 mg	10 mg	273	24	16	16	9	8	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	Placebo		274	7	4	4	5	1	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Gauthier 2002 (24 weeks)	DON (5-) 10 mg	10 mg	102	8	7	13	8	n.r.	8	n.r.	11	7	n.r.	n.r.
	Placebo		105	4	3	6	4	n.r.	4	n.r.	4	8	n.r.	n.r.
Homma 2000 (24 weeks)	DON 5 mg	5 mg	136	4	1	4	n.r.	1	n.r.	0[c]	3	1	n.r.	n.r.
	Placebo		131[b]	1	2	3	n.r.	2	n.r.	2[c]	1	2	n.r.	n.r.
Mohs 2001 (54 weeks)	DON 10 mg	5 mg	214	9	n.r.	17	n.r.	6	4	13	9	6[d]	n.r.	n.r.
	Placebo		217	4	n.r.	5	n.r.	2	6	10	3	1[d]	n.r.	n.r.
Rogers 1998 (24 weeks)	DON 5 mg	5 mg	154	4	3	9	10	2	n.r.	n.r.	n.r.	n.r.	5	n.r.
	DON 10 mg	10 mg	157	17	10	17	8	7	n.r.	n.r.	n.r.	n.r.	8	n.r.
	Placebo		162	4	2	7	4	2	n.r.	n.r.	n.r.	n.r.	2	n.r.

(continued)

Table 25 (continued). Donepezil: Adverse events

Study (duration)		**Increase in dose in first month**	**N[(a)]**	**Nausea**	**Vomiting**	**Diarrhoea**	**Dizziness**	**Lack of appetite**	**Weight loss**	**Agitation**	**Headache**	**Abdominal symptoms**	**Fatigue**	**Feeling of unwellness**
				Proportion (%) with AEs										
Seltzer 2004 (24 weeks)	DON 10 mg	5 mg to Week 6, then 10 mg	96	10	n.r.	20	8	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	Placebo		57	4	n.r.	9	2	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Tariot 2001[(e)] (24 weeks)	DON (5-) 10 mg	5 mg	103	9	15	15	8	9	19	10	15	10	n.r.	n.r.
	Placebo		105	4	14	10	8	5	10	8	16	5	n.r.	n.r.
Winblad 2001 (52 weeks)	DON (5-) 10 mg	5 mg	142	11	n.r.	7	6	n.r.	n.r.	n.r.	8	2	n.r.	n.r.
	Placebo		144	9	n.r.	7	4	n.r.	n.r.	n.r.	6	6	n.r.	n.r.

a: Number of randomised patients.
b: In the safety analysis, one patient in the placebo group was excluded, who, after randomisation, had not come to any further examinations.
c: "Restlessness".
d: "Dyspepsia".
e: Data refer to the total population of patients investigated (MMSE 5-26), as the corresponding data were not available for the mild to moderately impaired patients.

AE = adverse event, DON = donepezil, N = number, n.r. = not reported

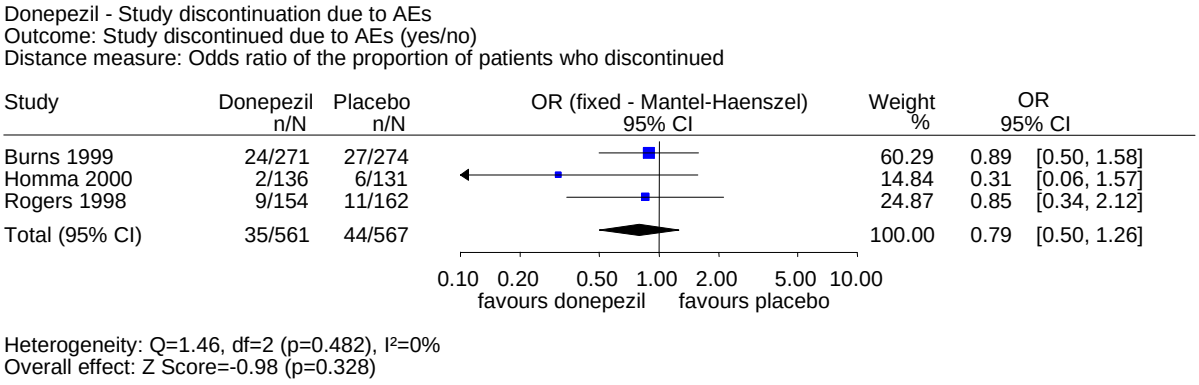
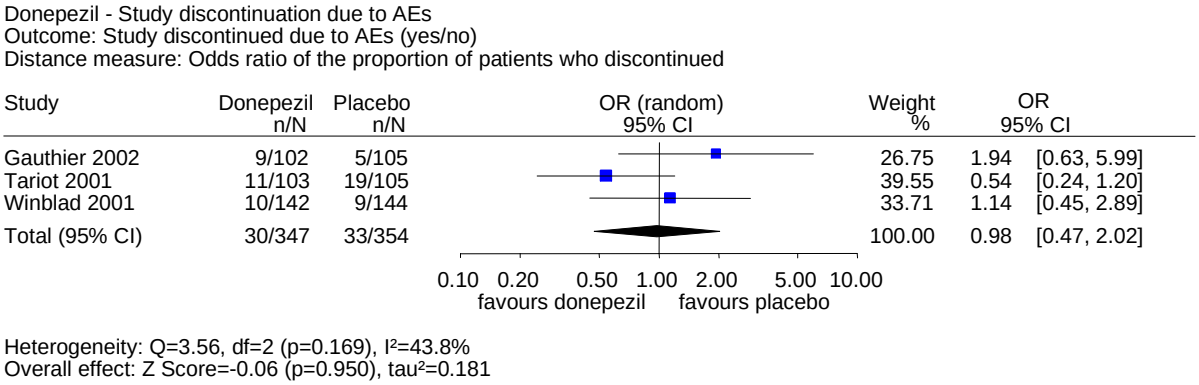


Figure 8. Donepezil: Meta-analysis of study discontinuations due to adverse events – low dose



Note: Due to the heterogeneity, a random effects model was chosen. A fixed effects model showed similar results.

Figure 9. Donepezil: Meta-analysis of study discontinuations due to adverse events – flexible dose

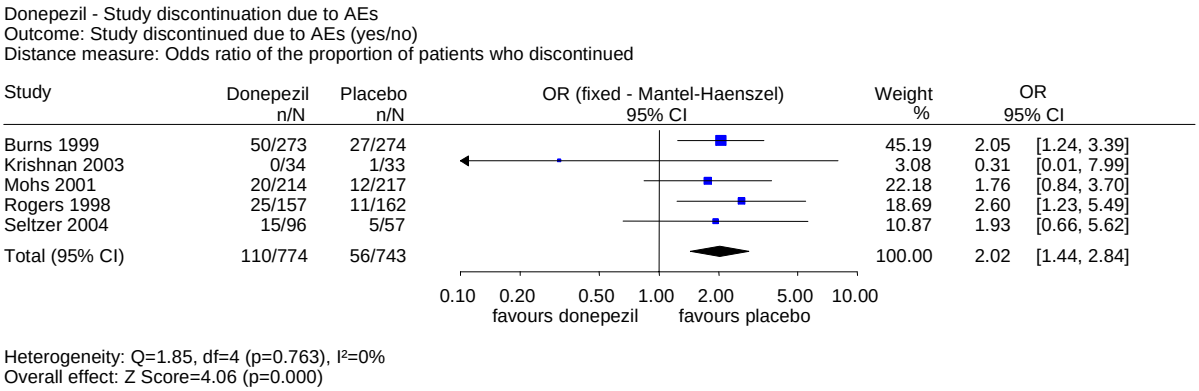


Figure 10. Donepezil: Meta-analysis of study discontinuations due to adverse events – high dose

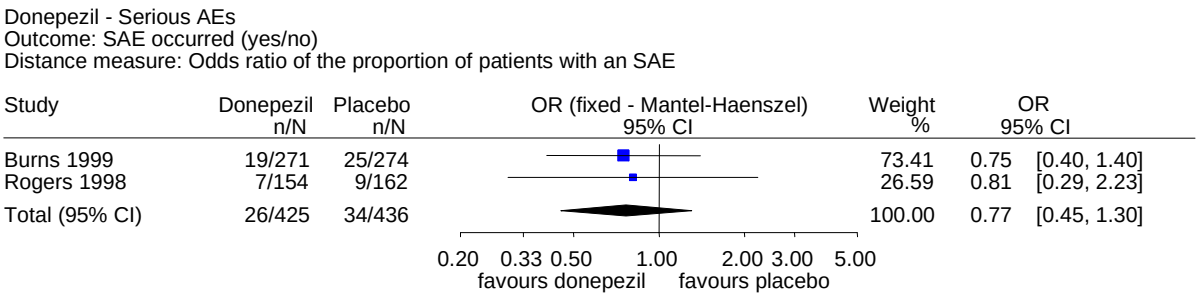
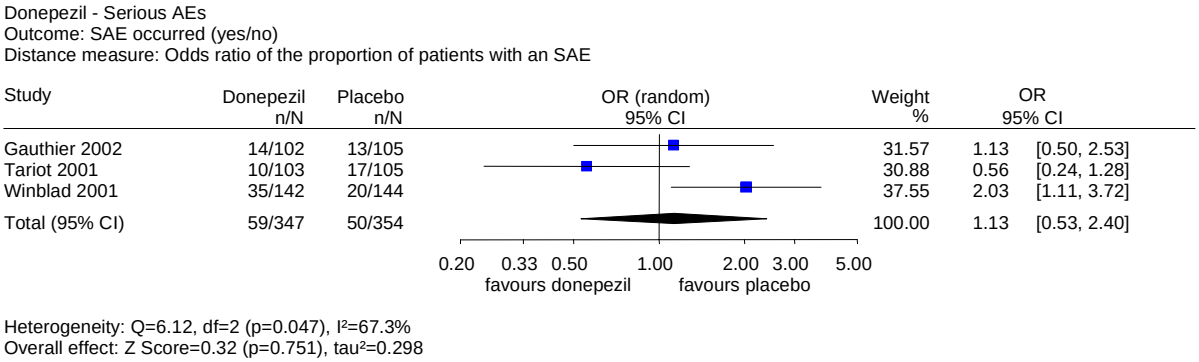


Figure 11. Donepezil: Meta-analysis of serious adverse events – low dose



Note: Due to the heterogeneity, a random effects model was chosen. A fixed effects model showed similar results.

Figure 12. Donepezil: Meta-analysis of serious adverse events – flexible dose

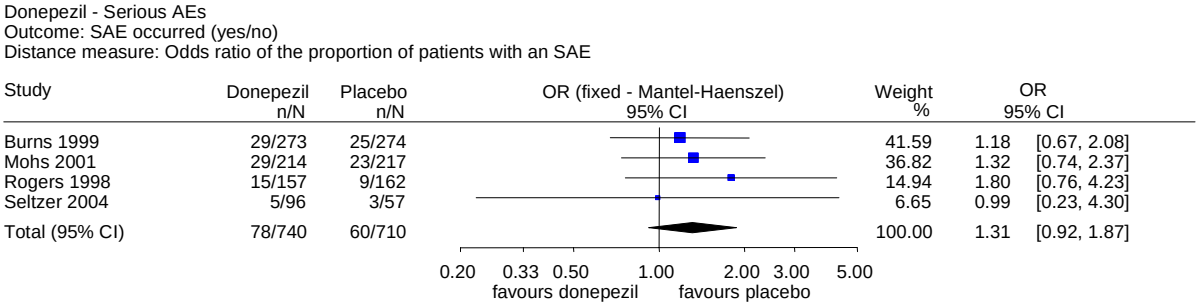


Figure 13. Meta-analysis of serious adverse events – high dose

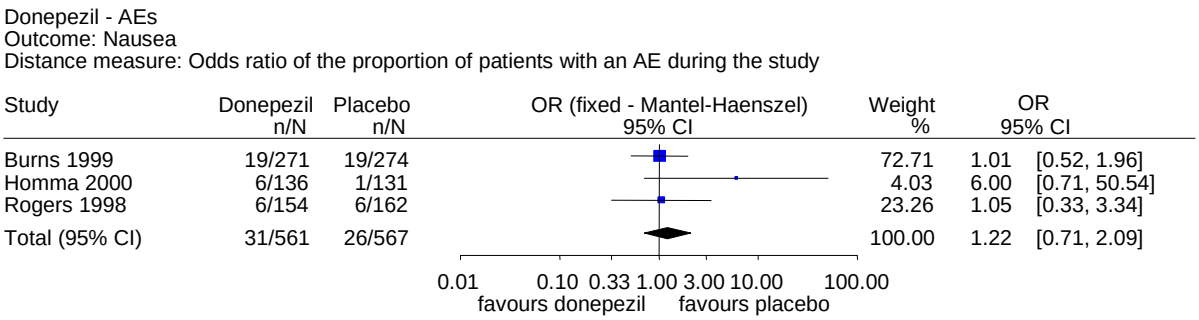


Figure 14. Donepezil: Meta-analysis of the outcome "nausea" – low dose

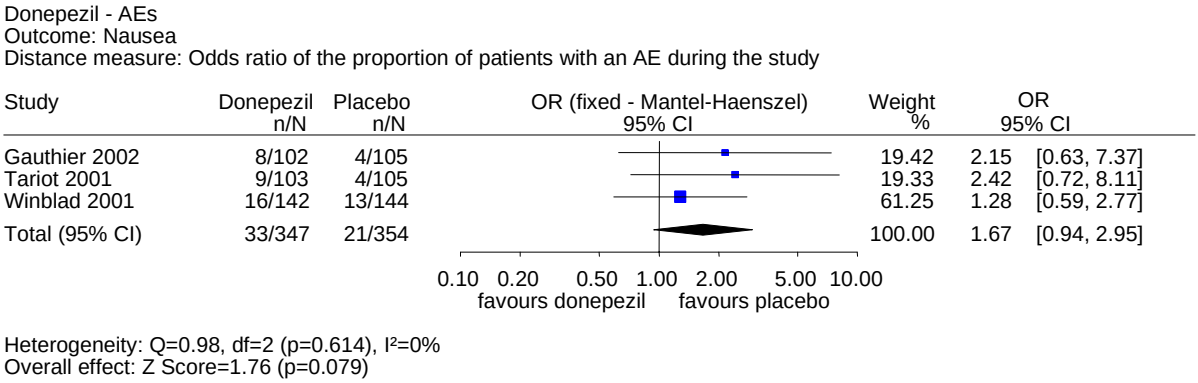


Figure 15. Donepezil: Meta-analysis of the outcome "nausea" – flexible dose

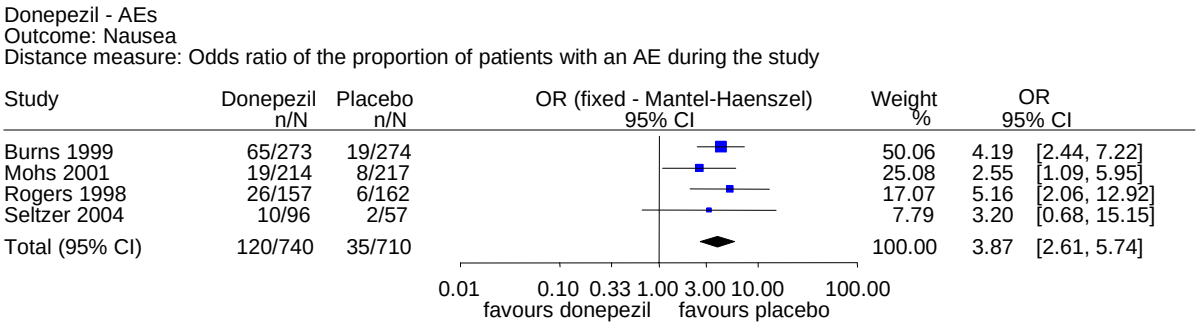


Figure 16. Donepezil: Meta-analysis of the outcome "nausea" – high dose

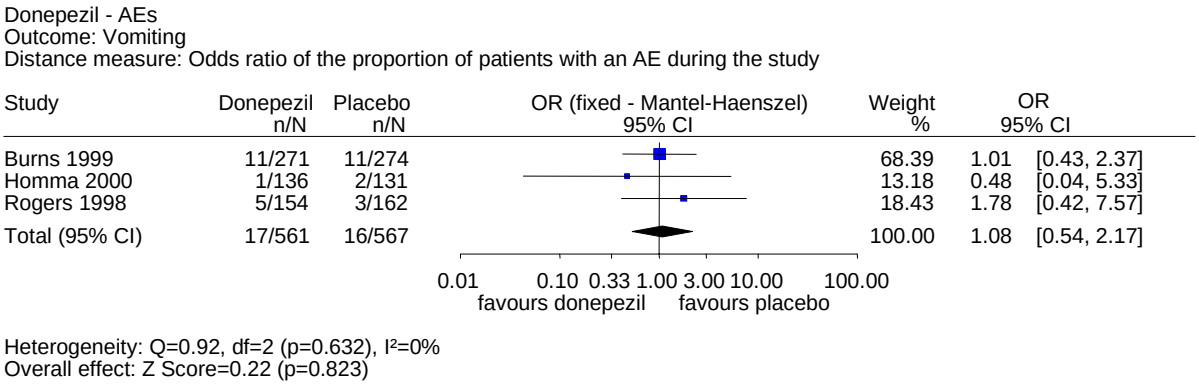


Figure 17. Donepezil: Meta-analysis of the outcome "vomiting" – low dose

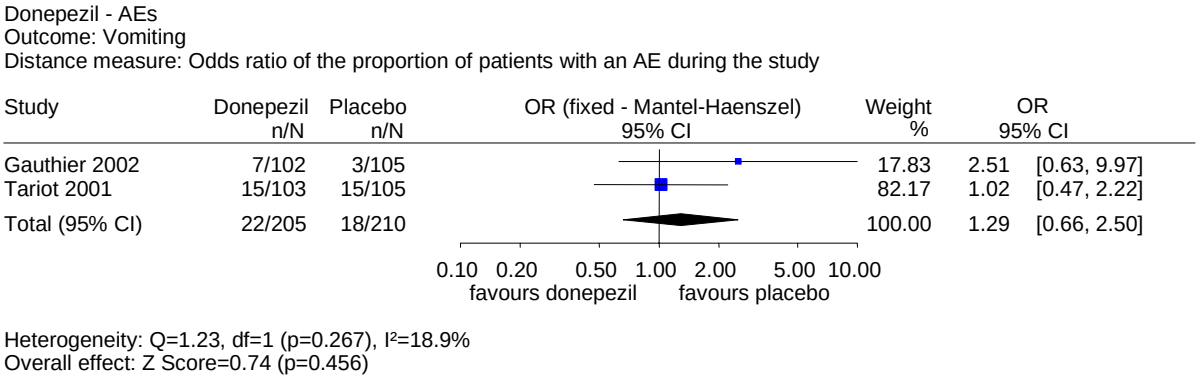


Figure 18. Donepezil: Meta-analysis of the outcome "vomiting" – flexible dose

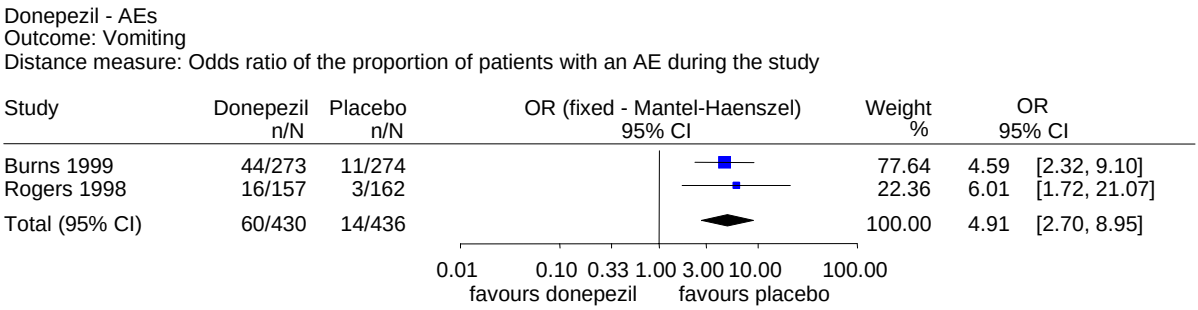


Figure 19. Donepezil: Meta-analysis of the outcome "vomiting" – high dose

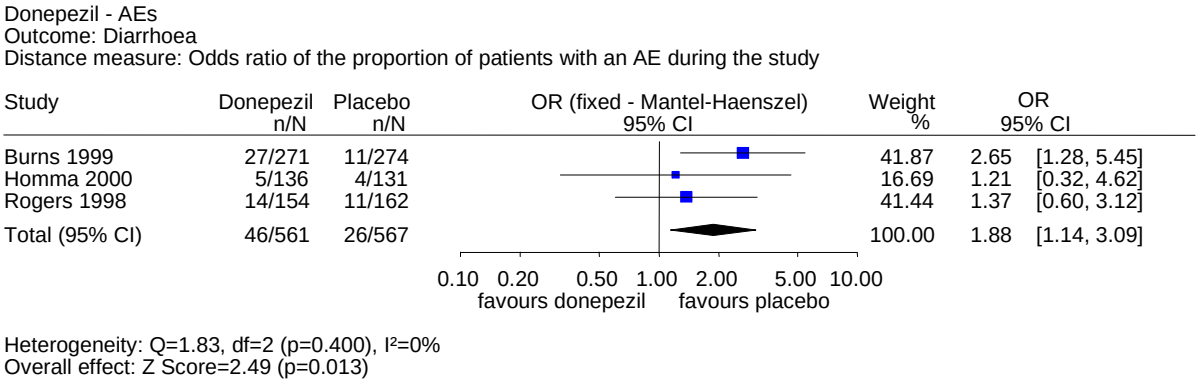


Figure 20. Donepezil: Meta-analysis of the outcome "diarrhoea" – low dose

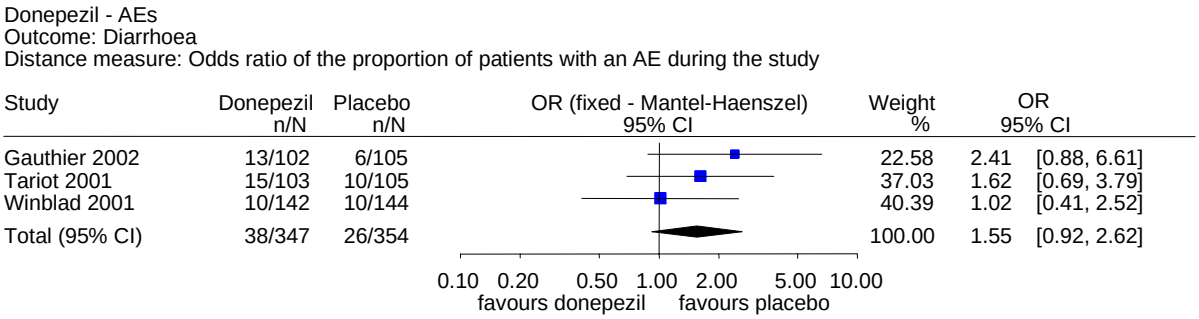


Figure 21. Donepezil: Meta-analysis of the outcome "diarrhoea" – flexible dose

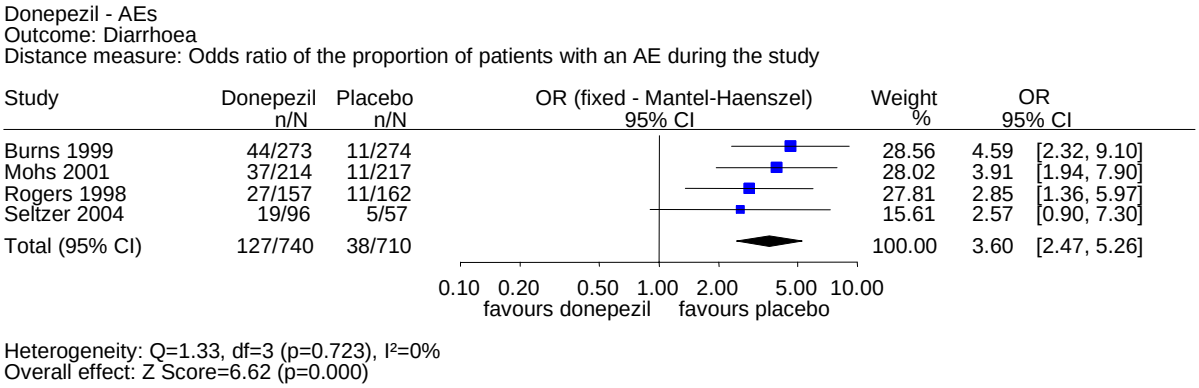


Figure 22. Donepezil: Meta-analysis of the outcome "diarrhoea" – high dose

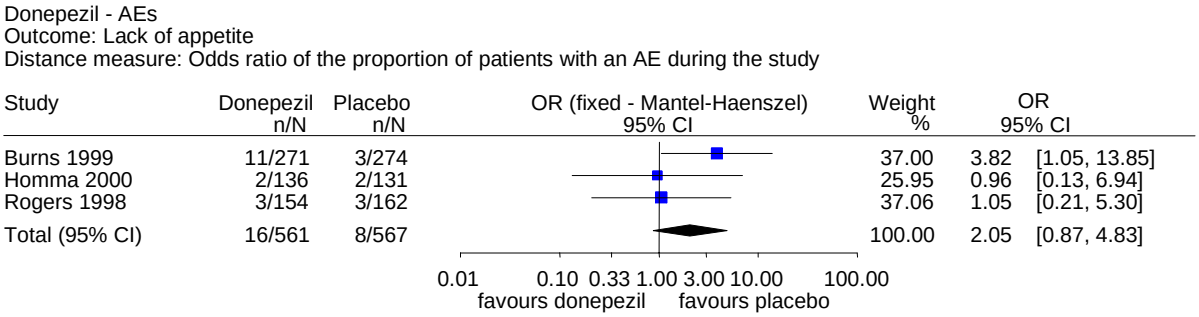


Figure 23. Donepezil: Meta-analysis of the outcome "lack of appetite" – low dose

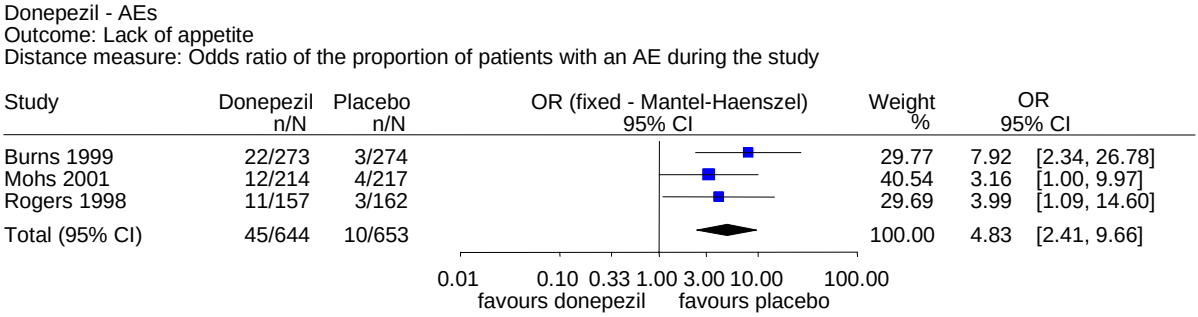
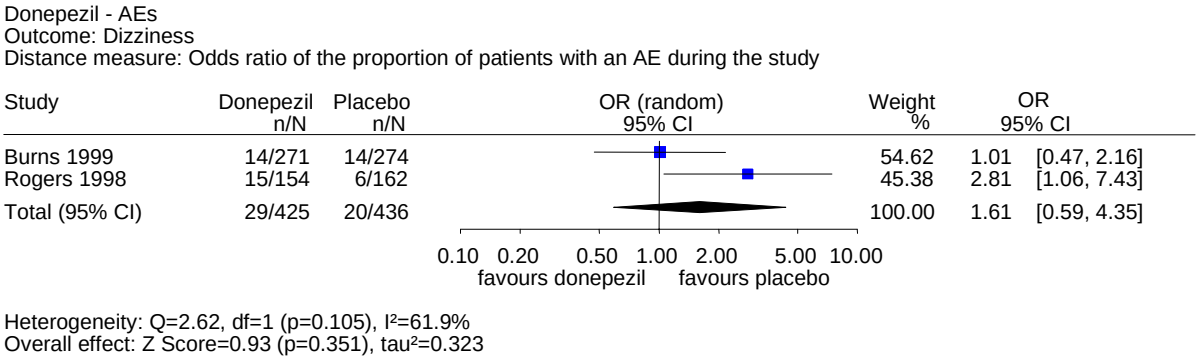


Figure 24. Donepezil: Meta-analysis of the outcome "lack of appetite" – high dose



Note: due to the heterogeneity, a random effects model was chosen. A fixed effects model shows similar results.

Figure 25. Donepezil: Meta-analysis of the outcome "dizziness" – low dose

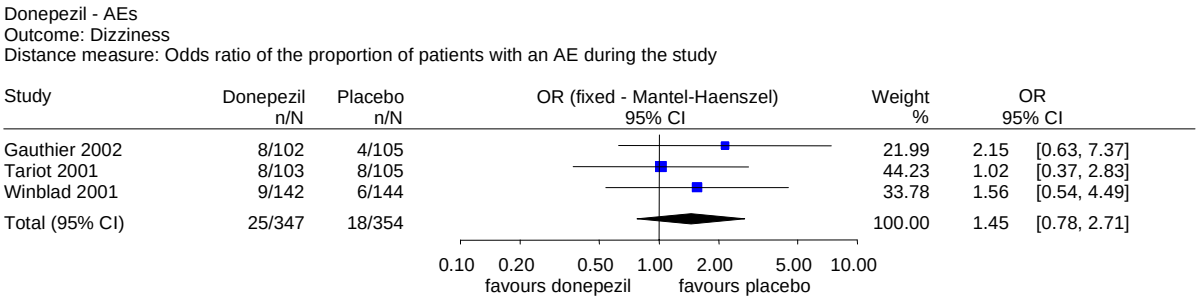


Figure 26. Donepezil: Meta-analysis of the outcome "dizziness" – flexible dose

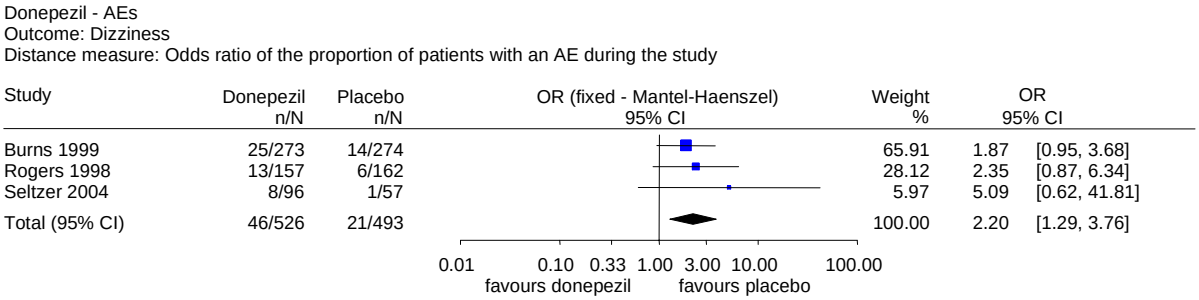


Figure 27. Donepezil: Meta-analysis of the outcome "dizziness" – high dose

5.3.1.8 Quality of life of (caregiving) relatives

An additional publication [54] of the study by Gauthier 2002 assessed stress caused to relatives by caring for patients as an outcome and used a version of the Caregiver Stress Scale (CSS), which was modified for Alzheimer's disease. The inclusion criterion for patients in this study was that a caregiving relative (caregiver) had to be caring for the patient at least 24 hours per week. Analyses were only available for the total group of patients with moderate and severe dementia (MMSE 5-17). At end of study (ITT-LOCF), practically no change was noticeable in the donepezil group in the total score, whereas there was a slight increase (in stress) in the placebo group. The difference between groups was not statistically significant. Similar results applied to the analysis of the 11 subdomain scores. In 6 subdomains, donepezil had a favourable effect (in 1 subdomain, with statistical significance). In 2 subdomains, no noticeable difference was shown. In 3 subdomains, the placebo group showed (non-statistically significant) better results.

In summary, no favourable effect on the quality of life of caregiving relatives by donepezil can be inferred from the results.

5.3.1.9 Degree of care provided by one or more caregivers or institutions

In the additional publication [54] of the study by Gauthier 2002, the caregiver time provided by caregiving relatives was also assessed as an outcome. The caregivers reported how many minutes per day they helped patients with their basic and instrumental activities (assessed by means of the IADL-plus and the PSMS-plus). Analyses were again only available for the total group of patients with moderate to severe dementia (MMSE 5-17). The baseline caregiver time for assisting with basic and instrumental activities was substantially longer (49 minutes) in the test group than in the placebo group; however, this was considered in the statistical analysis. At the end of study (ITT-LOCF), the difference between groups regarding the change in caregiver time was 50 minutes ($p = 0.004$). Whereas in the donepezil group the caregiver time was reduced from about 325 minutes to about 300 minutes, it increased in the placebo group from about 275 to about 300 minutes. The absolute duration of caregiver time within both groups had therefore evidently become similar at the end of study. As these results may possibly be explained by a regression to the mean, the validity of the data is unclear.

Winblad 2001 also published data on caregiver time [66]. Caregiver time was assessed as an outcome with the "Resource Utilization in Dementia" (RUD) scale. After 52 weeks, a statistically significant difference in the increase in caregiver time was shown in favour of donepezil (difference about 60 minutes; $p = 0.03$): However, this analysis was only based on about 50% of the patients originally randomised, so that the results cannot be interpreted with sufficient certainty.

The interpretation of the results presented is further limited beyond the specific aspects described above. In Winblad 2001, if patients were staying in a hospital, the caregiver time for the hospitalisation period was apparently rated as "0". This procedure seems inappropriate, as an adverse event (hospitalisation) had a favourable impact on the estimation of caregiver time. It was not reported in the publication how often or to what extent such a procedure was required. Within the framework of the submission of comments on the preliminary report, Pfizer reported that during the study, 9 out of 96 patients taking donepezil and 12 out of 94 patients taking placebo changed their type of residence. A total of 5 of the 9 patients in the donepezil group and 7 of the 12 placebo patients subsequently discontinued the study, so that the caregiver time in the placebo group was therefore more frequently rated as "0" (see comments: SN Pfizer). However, this information does not solve the problem that, for example, during hospitalisation periods, the caregiver time was rated as "0" in the analysis.

The underlying problem was not discussed at all in the Gauthier 2002 publication. In their comments on the preliminary report, Pfizer reported that the LOCF approach was used for patients for whom no caregiver time had been noted (e.g., due to hospitalisation) (see comments, SN Pfizer). This does not affect the uncertainty described above regarding the reported results.

In summary, no certain indication of a favourable effect on the degree of care (caregiver time) provided by caregivers can be inferred for donepezil.

5.3.1.10 Additional information: clinical disease stage

In 4 studies, the global clinical impression was assessed by means of the CIBIC-plus and the J-CGIC (Japanese-Clinical Global Impression of Change), and was the primary outcome in each study (Burns 1999, Gauthier 2002, Homma 2000 and Rogers 1998; Table 26). The difference in the proportion of patients assessed as being "unchanged" or "improved" between the test and placebo groups in favour of donepezil lay between 8% (donepezil 5 mg, Burns 1999), 24% (donepezil 5 mg, Homma 2000), and 23% (donepezil 10 mg, Gauthier 2002) (absolute values). Rogers 1998 only reported changes regarding the number of improved patients (not of unchanged and improved patients).

In Winblad 2001, the Gottfries-Bråne-Steen Scale (GBS) was used to assess the global impression, and was also the primary outcome. Whereas there was a statistically significant difference in the mean change on the scale between treatment groups at Weeks 24, 36 and 52 in favour of the donepezil group ($p < 0.05$), the difference at the end of study in the ITT-LOCF analysis was no longer statistically significant ($p = 0.054$). Furthermore, the proportion of patients with an improvement of the global impression at Weeks 12, 24 and 52 was reported. The difference between groups lay between 6% at Week 24 and 10% at Week 52 (absolute values).

Seltzer 2004 and Tariot 2001 also did not use the CIBIC, but used the CDR as a global measure. In Seltzer 2004, which only included mildly impaired patients (MMSE 21-26), it was merely reported that regarding the CDR-SB, no differences existed between treatment groups. In contrast, in Tariot 2001, a statistically significant difference was shown in the ITT-LOCF analysis after 24 weeks ($p < 0.05$) in the CDR-SB (Nursing Home Version); this applied to both the total population investigated as well as to the subgroup of patients with mild to moderate Alzheimer's disease (MMSE 10-26).

Mohs 2001 reported that the donepezil group showed statistically significantly better scores in the CDR-SB at several measurement points (but not at the end of study). However, the design of the study does not allow the certain interpretation of results outside the (primary) survival time analysis (see Section 5.2.2.1)

In summary, it was shown donepezil improves the global clinical impression compared with placebo. A meta-analysis did not seem meaningful due to the lack of uniform instruments and partially different methods of operationalisation. Furthermore, the validity of this surrogate with regard to the relevance for patients is unclear (see Section 4.5).

Table 26. Donepezil: Results on the global clinical impression

Study (duration)		**Out-come**	**N**[a]	**Proportion (%) with a score ≤ 4**[b]	**Treatment difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Burns 1999 (24 weeks)	DON 5 mg	CIBIC-plus	*271*[c]	57	8% (n.r.)	↗	0.007[d]
	DON 10 mg		*273*[c]	63	14% (n.r.)	↗	< 0.001[d]
	Placebo		*274*[c]	49			
Gauthier 2002 (24 weeks)	DON (5-) 10 mg	CIBIC-plus	98	70	23% (n.r.)	↗	< 0.001[d]
	Placebo		105	47			
Homma 2000 (24 weeks)	DON 5 mg	J-CGIC	133	81	23% (n.r.)	↗	< 0.001[d]
	Placebo		128	58			
Rogers 1998 (24 weeks)	DON 5 mg	CIBIC-plus	149	26[e]	15% (n.r.)	↗	0.005[d]
	DON 10 mg		149	25[e]	14% (n.r.)	↗	< 0.001[d]
	Placebo		152	11[e]			
				Mean difference from baseline (SD)			
Seltzer 2004 (24 weeks)	DON 10 mg	CDR-SB	*96*[c]	n.r.	n.r. (n.r.)		"n.s."
	Placebo		*57*[c]	n.r.			
Tariot 2001 (24 weeks)	DON (5-) 10 mg	CDR-SB	76	-0.2 (2.8)[f]	-1.0[f] (n.r.)	↗	< 0.05
	Placebo		79	0.8 (2.6)[f]			
Winblad 2001 (52 weeks)	DON (5-) 10 mg	GBS	138	8 (18)[f]	-4[f] (n.r.)	↗	0.054
	Placebo		144	12 (18)[f]			

a: Number of patients analysed, unless otherwise stated.
b: Stabilisation or improvement.
c: Number of randomised patients; number of analysed patients not reported in the publication.
d: P-values not based on the analysis of dichotomised data.
e: Criterion CIBIC ≤ 3 (improvement only).
f: Values estimated from figure.

CI = confidence interval, DON = donepezil, N = number, n.r. = not reported, n.s. = not statistically significant, SD = standard deviation.

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect.

5.3.2 Galantamine

5.3.2.1 Activities of daily living

In all 6 studies comparing galantamine and placebo, activities of daily living were secondary outcomes (Table 27). In 4 studies, the change in the score achieved in the Disability Assessment for Dementia Scale (DAD) was the outcome measure investigated (Erkinjuntti 2002, Raskind 2000, Rockwood 2006, Wilcock 2000). In 2 studies (Brodaty 2005, Tariot 2000), the AD Cooperative Study Activities of Daily Living Scale (ADCS-ADL) [106] was used. In Erkinjuntti 2002, according to previously unpublished data by Janssen-Cilag, a statistically significant advantage of galantamine 24 mg vs. placebo was shown in the subgroup of patients with Alzheimer's and cerebrovascular disease (AD-CVD subgroup) on the DAD scale after 6 months. As for Erkinjuntti 2002, Janssen-Cilag provided data beyond the data reported in the Raskind 2000 publication. At the end of study, no statistically significant differences between the placebo group and the galantamine 24 mg group were shown regarding the change in the DAD score. In Rockwood 2006, it was also reported that the groups investigated (placebo vs. 16–24 mg galantamine) did not show statistically significant differences in the primary analysis (ANOVA) after 4 months ($p = 0.13$). In a mixed-effects analysis, which considered the baseline differences between groups regarding disease severity, the p-value lay close to the statistical significance level ($p = 0.051$). In Wilcock 2000, no statistically significant difference was shown between the galantamine 24 mg group and the placebo group, either.

In the ADCS-ADL scale in Brodaty 2005, treatment with both galantamine prolonged release and conventional galantamine (16-24 mg) was superior to treatment with placebo in the LOCF analysis. In Tariot 2000, the results for ADCS-ADL in the 16 mg and 24 mg group were statistically significantly better than in the placebo group (the 16 mg showed a slightly higher difference compared with placebo). No statistically significant effect was shown in the 8 mg group.

In Rockwood 2006, the degree of reaching therapy goals was the primary outcome. For this purpose, treatment goals were defined by clinicians on the one hand and patients or relatives on the other by means of the Goal Attainment Scale (GAS) for the areas cognition, function, behaviour, free time and social activities. The changes were later compared to the baseline scores. The GAS is therefore an individualised outcome measure which, depending on which goals are defined, covers different areas.[15] In this study, patients/relatives as well as clinicians defined most goals in the areas cognition and function (67% and 60%) and the least goals in the areas free time and social activities (14% and 19%). After 4 months, the ITT analysis

[15] As the Goal Attainment Scale differs noticeably from other psychometric instruments to assess activities of daily living, for Rockwood 2006 both the results from the DAD and from the GAS are presented here.

showed an increased GAS score in the galantamine group (both according to the assessment by patients/relatives and by clinicians), which corresponded to an improvement in the defined goals compared with baseline. The GAS scores in the galantamine group for the goals defined and assessed by the clinicians were statistically significantly higher than in the placebo group (Cohen's d = 0.451; p = 0.02); this did not apply to the goals assessed by patients or relatives (Cohen's d = 0,20; p = 0.27). In particular with regard to the assessment of goal achievement by patients or relatives, the placebo group also improved in this period – this is discussed as a possible explanation for the above difference. Even if the differences in disease severity between groups at baseline were considered, no statistically significant difference was shown regarding goals defined by patients and relatives.

In summary, the studies largely (but not consistently) provided indications that galantamine can delay the deterioration in activities of daily living compared with placebo. The meta-analysis of all studies including conventional (non-prolonged release) galantamine (16-)24 mg (Figure 28) confirmed the only minor heterogeneity of results (I^2 = 0.5%) and shows a small but statistically significant pooled effect in the dimension of a fifth of the standard deviation (Cohen's d = -0.18; 95% CI: -0.26 to -0.10). This corresponds to about 3 points on the DAD scale.

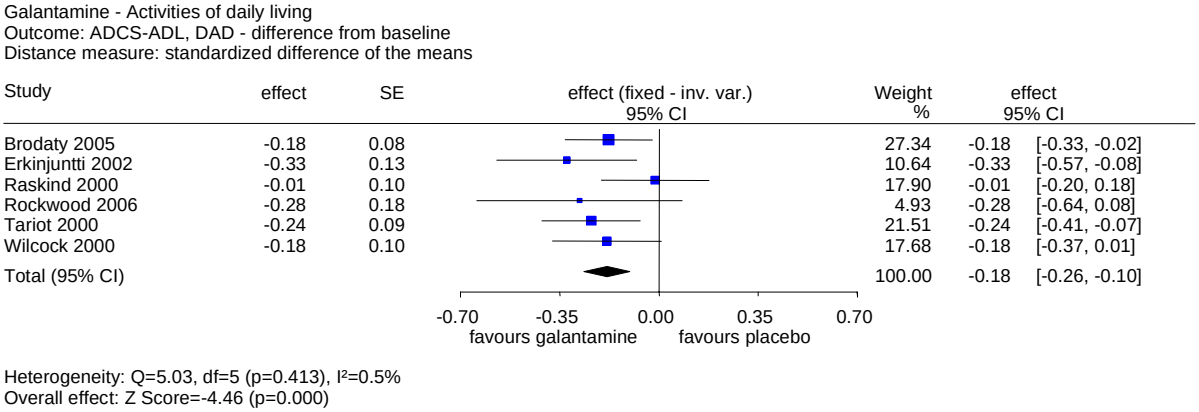
Table 27. Galantamine: Results on daily living skills

Study (duration)		**Out-come**	**N**[a]	**Mean difference from baseline (SD)**	**Treatment difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Brodaty 2005 (6 months)	GAL-PRC 16-24 mg	ADCS -ADL	(320)[b]	0.0 (8.6)[c]	2.7 (1.1; 3.9)	↗	< 0.001
	GAL 16-24 mg		(327)[b]	-1.0 (9.0)[c,d]	1.7 (0.2; 3.0)	↗	0.018
	Placebo		(324)[b]	-2.7 (10.1)[c]			
Erkinjuntti 2002[e,f] (6 months)	GAL 24 mg	DAD	*172*	*-1.0 (15.8)[c]*	*5.5 (n.r.)[g]*	↗	*<0.01*
	Placebo		*93*	*-6.0 (14.5)[c]*			
Raskind 2000[f] (6 months)	GAL 24 mg	DAD	(212)[b]	*-2.7 (14.9)[c]*	*0.2 (n.r.)*	↗	*"n.s."*
	Placebo		(213)[b]	*-2.9 (15.8)[c]*			
Rockwood 2006 (4 months)	GAL 16-24 mg	DAD	(64)[b]	n.r.	Cohen's d=0.28 (n.r.)	↗	0.13[h]
	Placebo		(66)[b]	n.r.			
Tariot 2000 (5 months)	GAL 8 mg	ADCS -ADL	129	-3.2 (9.1)[c]	0.6 (n.r.)	↗	"n.s."
	GAL 16 mg		255	-0.7 (8.0)[c]	3.1 (n.r.)	↗	< 0.001
	GAL 24 mg		253	-1.5 (9.5)[c]	2.3 (n.r.)	↗	< 0.01
	Placebo		262	-3.8 (9.7)[c]			
Wilcock 2000 (6 months)	GAL 24 mg	DAD	212	-3.2 (14.9)[c]	2.8 (-0.6; 6.1)	↗	0.1
	Placebo		210	-6.0 (15.7)[c]			

a: Number of analysed patients, unless otherwise stated.
b: Number of randomised patients, number of analysed patients not reported in the publication.
c: Own calculation.
d: Data inconsistency regarding SD and SE; the reported value in Table 2 (SE = 0.05) is not consistent with the value in the figure and probably should be SE = 0.5.
e: Subgroup of patients with Alzheimer's and cerebrovascular disease.
f: Information obtained directly from the manufacturer Janssen-Cilag.
g: The discrepancy between the reported difference and the reported group-internal estimates can presumably be ascribed to adjustments.
h: In an additional analysis that considered the differences in disease severity, as well as the study discontinuations, the p-value was p = 0.051.

CI = confidence interval, GAL = galantamine, GAL-PRC = galantamine prolonged release, N = number, n.r. = not reported, n.s. = not statistically significant, SD = standard deviation

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect.



Rockwood 2006: SE calculated from p-value = 0.13
Algebraic sign of the scores changed, i.e. negative values correspond to positive effects.
Presentation of the group difference including the SE, as group-internal data were not published in Rockwood.

Figure 28. Galantamine: Meta-analysis of activities of daily living

5.3.2.2 Accompanying psychopathology

In 3 of 6 studies on galantamine, accompanying psychopathology was assessed by means of the Neuropsychiatric Inventory (NPI) as an outcome parameter (Brodaty 2005, Erkinjuntti 2002, Tariot 2000). The average baseline values in the NPI in the 3 studies lay in the narrow range of 10-13 points, with high variability between individual patients (Table 11). In Brodaty 2005, no statistically significant effect was shown for galantamine. The same applies to the subgroup of AD-CVD patients in Erkinjuntti 2002. In contrast, Tariot 2000 reported statistically significant effects in favour of the galantamine 16 and 24 mg groups, but not in the 8 mg group (Table 28). Data on the NPI subscales were not available for Brodaty 2005 and Tariot 2000, nor were they available for the subgroup of patients with Alzheimer's and cerebrovascular disease in Erkinjuntti 2002.

In summary, indications exist of an effect of galantamine regarding the impact on neuropsychiatric symptoms.

The meta-analysis (Figure 29) confirms this and shows only a slight, even though statistically significant pooled effect in the dimension of a seventh of the standard deviation (Cohen's d = -0.14; 95% CI: -0.24 to -0.03). Converted to the NPI scale, this corresponds to about 1 to 2 points.

Table 28. Galantamine: Results on accompanying psychopathology

Study (duration)		**Out-come**	**N[(a)]**	**Mean difference from baseline (SD)**	**Treatment difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Brodaty 2005 (6 months)	GAL-PRC 16-24 mg	NPI	*299[(b)]*	0.6[(c)] (11.4[(d)])	0[(d)] (-1.9; 1.8)	⇔	0.941
	GAL 16-24 mg		*303[(b)]*	-0.9 (12.7[(d)])	-1.5[(d)] (-3.4; 0.2)	↗	0.102
	Placebo		*304[(b)]*	0.6 (11.4[(d)])			
Erkinjuntti 2002[(b,e)] (6 months)	GAL 24 mg	NPI	*167*	*-0.2 (9.8[(d)])*	*-1.0 (n.r.)*	↗	*"n.s."*
	Placebo		*90*	*0.8 (10.8[(d)])*			
Tariot 2000 (5 months)	GAL 8 mg	NPI	129	2.3 (11.4)[(f)]	0.3[(d)] (n.r.)	↘	"n.s."
	GAL 16 mg		255	-0.1 (11.4)[(f)]	-2.1[(d)] (n.r.)	↗	< 0.05
	GAL 24 mg		253	0.0 (11.1)[(f)]	-2.0[(d)] (n.r.)	↗	< 0.05
	Placebo		262	2.0 (11.0)[(f)]			

a: Number of patients in the analysis.
b: Information obtained directly from the manufacturer Janssen-Cilag.
c: In the original publication, an algebraic sign was permuted.
d: Own calculation.
e: Subgroup of patients with Alzheimer's disease plus cerebrovascular disease.
f: Information from Cummings et al, 2004 [73].

CI = confidence interval, GAL = galantamine, GAL-PRC = galantamine prolonged release, N = number, n.r. = not reported, n.s. = not statistically significant, SD = standard deviation

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect.

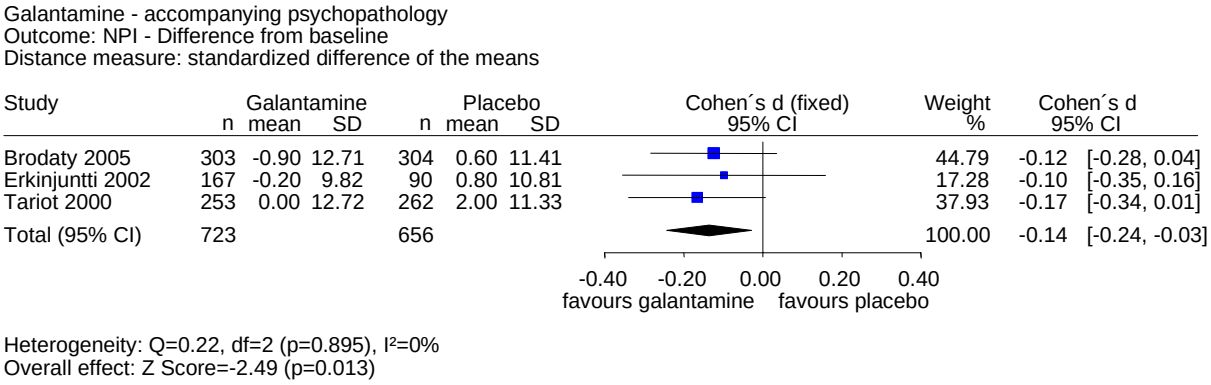


Figure 29. Galantamine: Meta-analysis of accompanying psychopathology

5.3.2.3 Cognitive function

In all 6 studies, the efficacy of galantamine regarding cognitive function was measured with the cognitive subscale of the ADAS (ADAS-cog) (Brodaty 2005, Erkinjuntti 2002, Raskind 2000, Rockwood 2006, Tariot 2000, Wilcock 2000). In all studies, statistically significant advantages of galantamine 16 mg and 24 mg versus placebo were shown. In contrast, the 8 mg group in Tariot 2000 did not show a statistically significant effect (Table 29).

Overall, the studies consistently showed an advantage of galantamine in respect of a favourable impact on cognitive function, measured with the ADAS-cog. No heterogeneity of results was shown between the studies. In the meta-analysis of 6 studies (Figure 30), which in each case included patients treated with 24 mg or 16–24 mg, the average difference in the improvement in the ADAS-cog was about half a standard deviation (Cohen's d = -0.51; 95% CI: -0.59 to -0.43), which corresponds to about 3 points on the ADAS-cog scale.

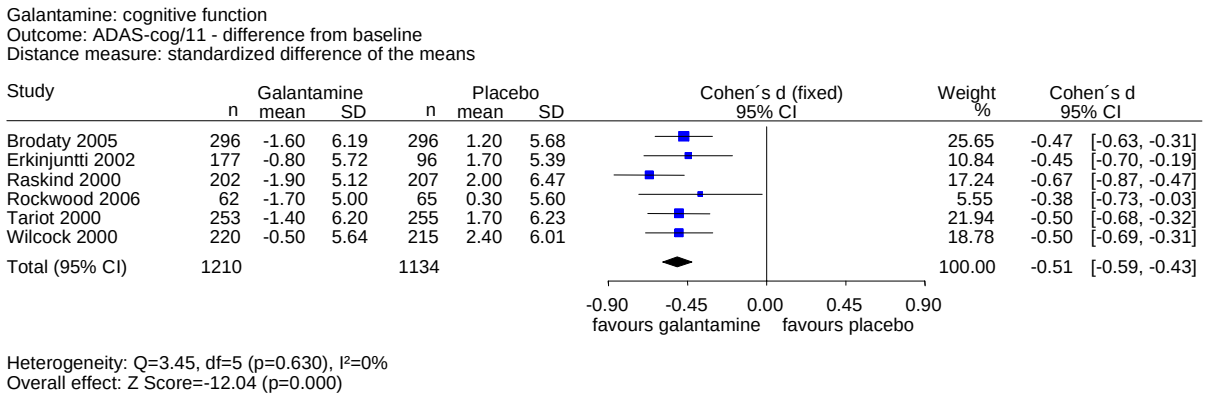
Table 29. Galantamine: Results on cognitive function

Study (duration)		**Outcome**	**N**[(a)]	**Mean difference from baseline (SD)**	**Treatment difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Brodaty 2005 (6 months)	GAL-PRC 16-24 mg	ADAS-cog	291	-1.3 (5.3[(b)])	-2.5[(b)] (-3.3; -1.5)	↗	< 0.001
	GAL 16-24 mg		296	-1.6 (6.2[(b)])	-2.8[(b)] (-3.7; -1.9)	↗	< 0.01
	Placebo		296	1.2 (5.7[(b)])			
Erkinjuntti 2002 [(c,d)] (6 months)	GAL 24 mg	ADAS-cog	*177*	*-0.8 (5.7[(b)])*	*-2.5 (n.r.)*	↗	*< 0.001*
	Placebo		*96*	*1.7 (5.4[(b)])*			
Raskind 2000[(d)] (6 months)	GAL 24 mg	ADAS-cog	202	*-1.9[(e)]* (5.1[(b)])	*-3.8 (n.r.)*	↗	< 0.001
	Placebo		207	2.0 (6.5[(b)])			
Rockwood 2006 (4 months)	GAL 16-24 mg	ADAS-cog	62	-1.7 (5.0)[(f)]	-2.0[(b)] (n.r.)	↗	0.04[(g)]
	Placebo		65	0.3 (5.6)[(f)]			
Tariot 2000 (5 months)	GAL 8 mg	ADAS-cog	126	0.4 (5.8[(b)])	-1.3[(b)] (n.r.)	↗	"n.s."
	GAL 16 mg		253	-1.4 (5.6[(b)])	-3.1[(b)] (n.r.)	↗	< 0.001
	GAL 24 mg		253	-1.4 (6.2[(b)])	-3.1[(b)] (n.r.)	↗	< 0.001
	Placebo		255	1.7 (6.2[(b)])			
Wilcock 2000 (6 months)	GAL 24 mg	ADAS-cog	220	-0.5 (5.6[(b)])	-2.9[(h)] (-4.1; -1.6)	↗	< 0.001
	Placebo		215	2.4 (6.0[(b)])			

a: Number of patients in the analysis.
b: Own calculation.
c: Subgroup of patients with Alzheimer's disease plus cerebrovascular disease.
d: Information obtained directly from the manufacturer Janssen-Cilag.
e: A value of +1.9 was (seemingly mistakenly) reported in the publication; however, in the data provided by the manufacturer Janssen-Cilag, the value was –1.9.
f: Values estimated from figure.
g: Result also remains statistically significant if the differences between groups in disease severity, as well as study discontinuations, are considered.
h: Algebraic signs permuted in the original publication.

CI = confidence interval, GAL = galantamine, GAL-PRC = galantamine prolonged release, N = number, n.r. = not reported, n.s. = not statistically significant, SD = standard deviation

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect.



Note: For Rockwood 2006, the standard deviations were estimated from the figure.

Figure 30: Galantamine: Meta-analysis of cognitive function

5.3.2.4 Health-related quality of life

No data on the outcome "health-related quality of life" were reported in the studies.

5.3.2.5 Placement in a nursing home (institutionalisation)

No data on the outcome "placement in a nursing home (institutionalisation)" were reported in the controlled phases of the studies included.

5.3.2.6 Mortality

Only few deaths within the reporting period were noted in the studies included. No noticeable increase was shown in any of the treatment groups (Table 30).

Overall, the data did not indicate a positive or detrimental effect of galantamine regarding mortality.

5.3.2.7 Adverse events

Except for Tariot 2000, in all studies noticeably higher discontinuation rates due to adverse events were observed with galantamine, especially in studies with a faster increase in dose (24 mg or 16 mg within the first month) (Erkinjuntti 2002, Raskind 2000, Wilcock 2000). Data on serious adverse events were only reported in the publications of Rockwood 2006 and Tariot 2000; for the other studies (expect for the relevant subgroup in Erkinjuntti 2002), the manufacturer Janssen-Cilag provided the corresponding data. Overall, no difference was shown in the meta-analysis between the test and placebo groups regarding serious adverse events (Figure 32).

Typical cholinergic adverse effects occurred noticeably more often in the test group, especially in the dose-increase phase. In studies in which the dose was increased by 8 mg per week (Raskind 2000, Wilcock 2000), about a third of the patients in the test group suffered from nausea and a fifth from vomiting (Table 31). Overall (except for the 8 mg group in Tariot 2000), nausea occurred 3 to 4 times more often in the test group; the absolute differences lay between 8% and 25%. Vomiting (absolute values) was between 5% and 16% more common (in the 8 mg group in Tariot 2000: 3%). The corresponding sensitivity analysis including studies with an increase in dose according to the Summary of Product Characteristics [107] and studies with a faster increase in dose showed neither consistent nor clear advantages for the slower increase in dose. About twice as many patients suffered from dizziness and lack of appetite in the test groups. Weight loss was particularly noticeable in the 24 mg group in Raskind 2000.

In summary, the studies showed an increase in the adverse event rate in patients taking galantamine compared with placebo. The meta-analyses presented below (Figures 31 to 37) did not show noticeable heterogeneity between results.

Table 30. Galantamine: Study discontinuations, deaths, and number of patients with adverse events

Study (duration)		**Increase in dose within the first month**	**N[a]**	**Study discontinuations N (%)**	**Deaths N**	**Serious adverse events N (%)**	**Discontinuations due to adverse events N (%)**	**Overall adverse event rate N (%)**
Brodaty 2005 (6 months)	GAL-PRC 16-24 mg	8 mg	(319)[b]	68 (21)	3	35[c] (11)[d]	28 (9)	253 (79)
	GAL 16-24 mg	8 mg	(326)[b]	75 (23)	1	39[c] (12)[d]	24 (7)	235 (72)
	Placebo		(320)[b]	54 (17)	1	35[c] (11)[d]	15 (5)	224 (70)
Erkinjuntti 2002 (6 months)	GAL 24 mg	16 mg	188[d]	34 (18)[d]	2[d]	n.r.	25 (13)[d]	330[d] (83)[e]
	Placebo		97[d]	10 (10)[d]	1[d]	n.r.	5 (5)[d]	133[d] (68)[e]
Raskind 2000 (6 months)	GAL 24 mg	24 mg	212	68 (32)	1	29 (14)[d]	49 (23)	195 (92)
	Placebo		213	41 (19)	1	27 (13)[d]	16 (8)	168 (79)
Rockwood 2006 (4 months)	GAL 16-24 mg	8 mg	64	11 (17)	0	5 (8)[f,g]	5 (8)	54 (84)
	Placebo		66	10 (15)	1	10 (15)[f,g]	2 (3)	41 (62)
Tariot 2000 (5 months)	GAL 8 mg	8 mg	140	32 (23)	1	14 (10)	9 (6)	106 (76)
	GAL 16 mg	8 mg	279	60 (22)	3	28 (10)	19 (7)	206 (74)
	GAL 24 mg	8 mg	273	61 (22)	3	35 (13)	27 (10)	219 (80)
	Placebo		286	46 (16)	4	31 (11)	20 (7)	206 (72)
Wilcock 2000 (6 months)	GAL 24 mg	24 mg	220	44 (20)	2[d]	31 (14)[d,h]	31 (14)	182 (83)
	Placebo		215	29 (13)	2[d]	27 (13)[d,h]	19 (9)	165 (77)

(continued)

Table 30 (continued). Galantamine: Study discontinuations, deaths, and number of patients with adverse events

a: Number of randomised patients.
b: Number of randomised and treated patients.
c: Calculated from the reported percentage.
d: Information provided by the manufacturer Janssen-Cilag in the comments on the preliminary report (see comments: SN Janssen-Cilag).
e: Data refer to the total population of patients investigated (galantamine: n=396, placebo: n=196), including those with only cerebrovascular dementia, as no separate data were available for the subgroup of patients with Alzheimer's disease plus cerebrovascular disease.
f: Percentages calculated from N.
g: Allocation of numbers to both groups is not fully clear in the publication; the most probable version is presented here.
h: Deaths were reported separately in the comments on the preliminary report and are included here.

GAL = galantamine, GAL-PRC = galantamine prolonged release, N = number, n.r. = not reported

Table 31. Galantamine: Adverse events

Study (duration)		**Increase in dose within the first month**	**N[a]**	**Nausea**	**Vomiting**	**Diarrhoea**	**Dizziness**	**Lack of appetite**	**Weight loss**	**Agitation**	**Headache**	**Abdominal symptoms**	**Fatigue**	**Feeling of unwellness**
				Proportion (%) with AEs										
Brodaty 2005 (6 months)	GAL PRC 16-24 mg	8 mg	(319)[b]	17	7	5	10	6	4	7	8	*2[d]*	*4[d]*	n.r.
	GAL 16-24 mg	8 mg	(326)[b]	14	9	7	7	7	5	6	6	*3[d]*	*4[d]*	n.r.
	Placebo		(320)[b]	5	2	7	4	3	1	7	6	*2[d]*	*1[d]*	n.r.
Erkinjuntti 2002[c, d] (6 months)	GAL 24 mg	16 mg	396[c]	*24[d]*	*13[d]*	*8[d]*	*9[d]*	*5[d]*	*4[d]*	*3[d]*	*6[d]*	*5[d]*	*4[d]*	n.r.
	Placebo		196[c]	*7[d]*	*6[d]*	*5[d]*	*5[d]*	*2[d]*	*2[d]*	*4[d]*	*6[d]*	*6[d]*	*5[d]*	n.r.
Raskind 2000 (6 months)	GAL 24 mg	24 mg	212	37	21	12	14	14	12	*11[d]*	*9[d]*	7	*6[d]*	n.r.
	Placebo		213	13	8	10	11	6	5	*16[d]*	*8[d]*	4	*4[d]*	n.r.
Rockwood 2006 (4 months)	GAL 16-24 mg	8 mg	64	23	17	n.r.	n.r.	11	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	Placebo		66	6	3	n.r.	n.r.	2	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

(continued)

Table 31 (continued). Galantamine: Adverse events

Study (duration)		**Increase in dose within the first month**	**N[(a)]**	**Nausea**	**Vomiting**	**Diarrhoea**	**Dizziness**	**Lack of appetite**	**Weight loss**	**Agitation**	**Headache**	**Abdominal symptoms**	**Fatigue**	**Feeling of unwellness**
				Proportion (%) with AEs										
Tariot 2000 (5 months)	GAL 8 mg	8 mg	140	6	4	5	5[(e)]	6	n.r.	15	4[(e)]	n.r.	n.r.	n.r.
	GAL 16 mg	8 mg	279	13	6	12	*5[(d)]*	7	*5[(d)]*	10	*7[(d)]*	*4[(d)]*	*4[(d)]*	n.r.
	GAL 24 mg	8 mg	273	17	10	6	*7[(d)]*	9	*5[(d)]*	8	*5[(d)]*	*3[(d)]*	*5[(d)]*	n.r.
	Placebo		286	5	1	6	*4[(d)]*	3	*1[(d)]*	9	*5[(d)]*	*4[(d)]*	*2[(d)]*	n.r.
Wilcock 2000 (6 months)	GAL 24 mg	24 mg	220	37	20	7	11	10	8	*4[(d)]*	10	*8[(d)]*	*6[(d)]*	n.r.
	Placebo		215	12	4	7	5	0	1	*8[(d)]*	3	*5[(d)]*	*5[(d)]*	n.r.

a: Number of randomised patients, unless otherwise stated.
b: Number of randomised and treated patients.
c: Data refer to the total population of patients investigated, including those with only cerebrovascular dementia, as no separate data were available for the subgroup of patients with Alzheimer's disease plus cerebrovascular disease.
d: Information obtained directly from the manufacturer Janssen-Cilag.
e: Information provided by the manufacturer Janssen-Cilag in the comments on the preliminary report (see comments; SN Janssen-Cilag).

AE = adverse event, GAL = galantamine, GAL-PRC = galantamine prolonged release, N = number, n.r. = not reported

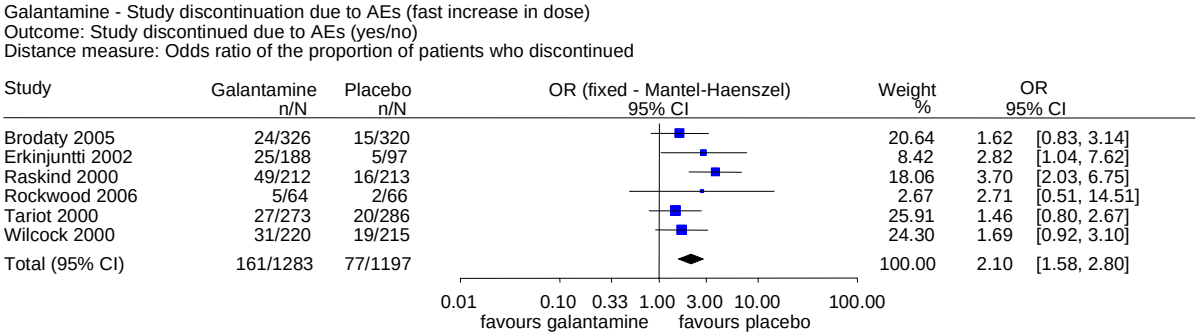


Figure 31. Galantamine: Meta-analysis of study discontinuations due to adverse events

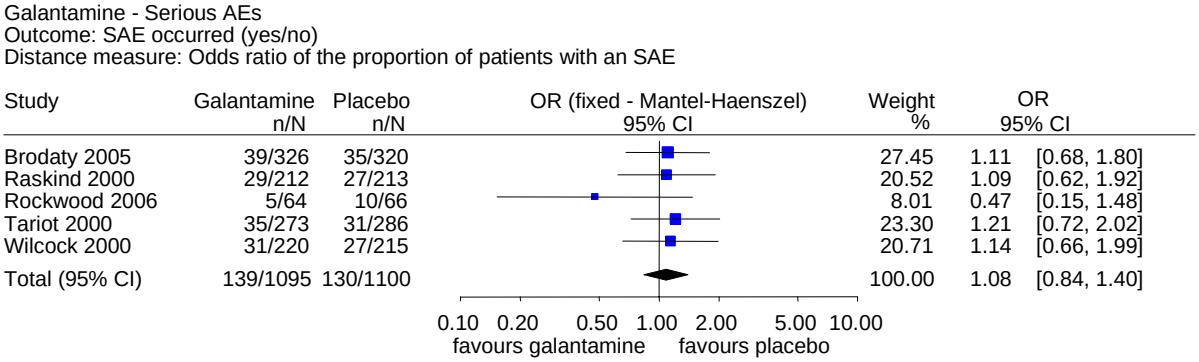


Figure 32. Galantamine: Meta-analysis of serious adverse events

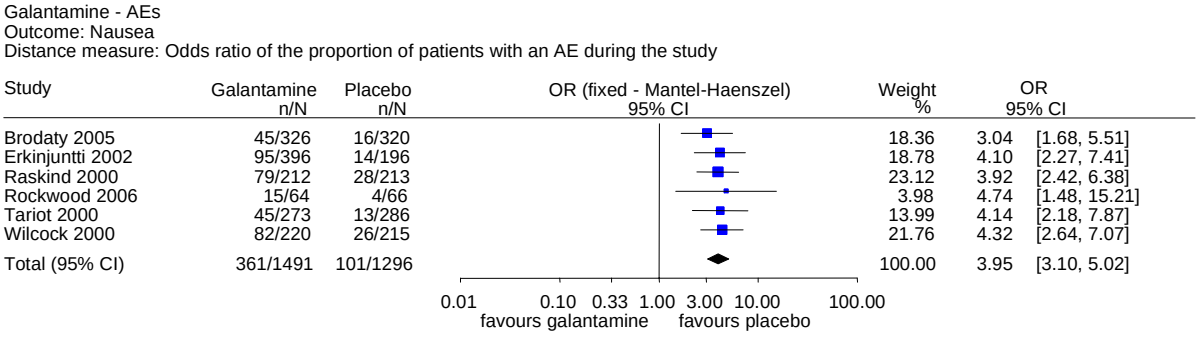


Figure 33. Galantamine: Meta-analysis of the outcome "nausea"

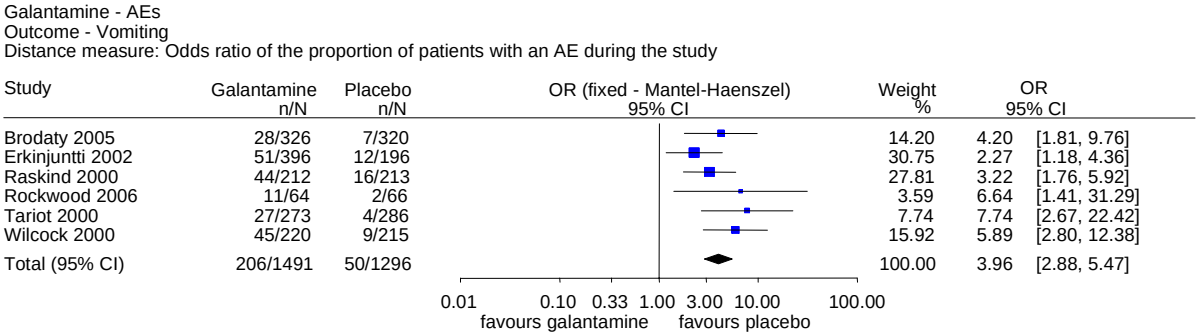


Figure 34. Galantamine: Meta-analysis of the outcome "vomiting"

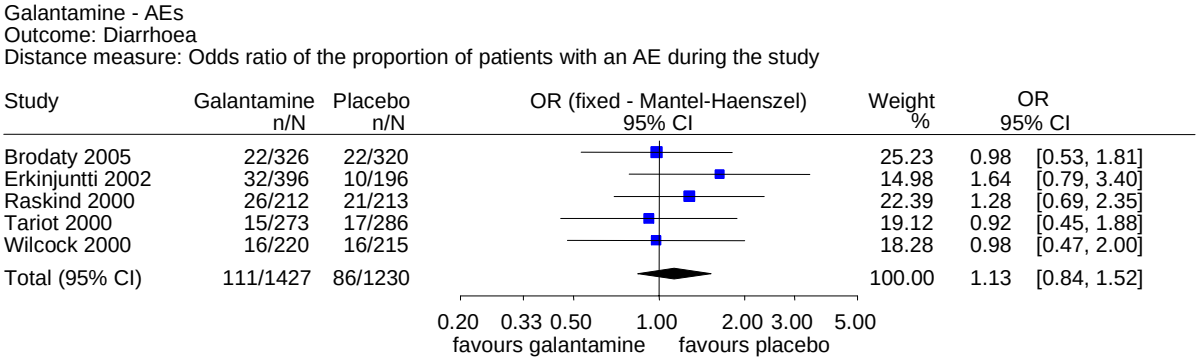


Figure 35. Galantamine: Meta-analysis of the outcome "diarrhoea"

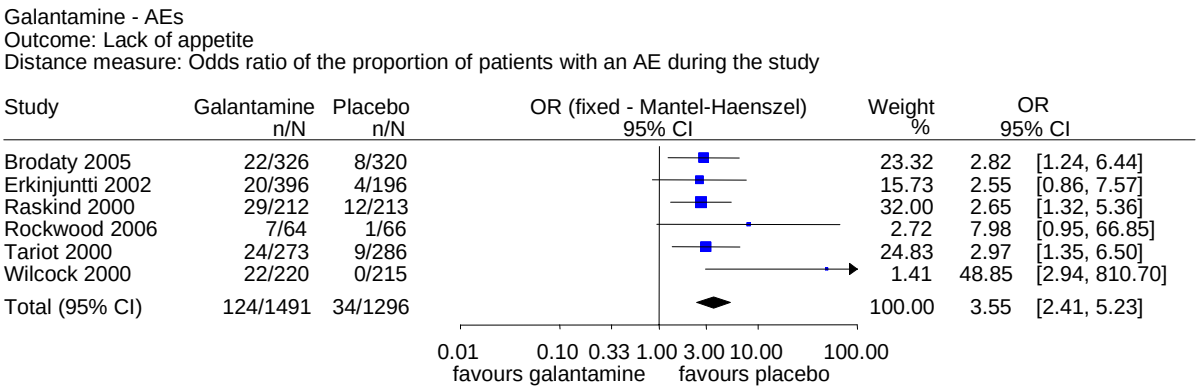


Figure 36. Galantamine: Meta-analysis of the outcome "lack of appetite"

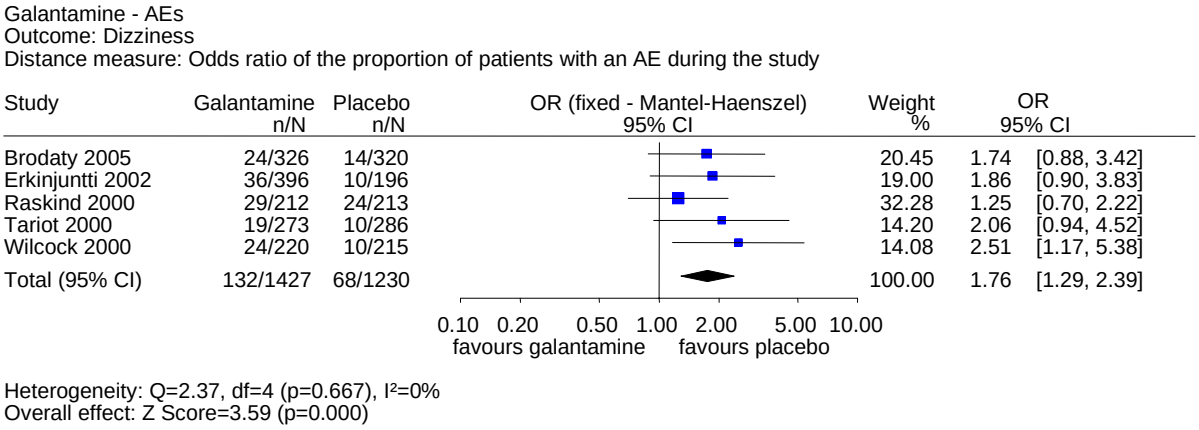


Figure 37. Galantamine: Meta-analysis of the outcome "dizziness"

5.3.2.8 Quality of life of (caregiving) relatives

In Rockwood 2006, the burden on caregiving relatives was investigated by means of the Caregiving Burden Scale (CBS). After 4 months, the difference between the galantamine and the placebo group was not statistically significantly different (standardised mean difference = -0.17; p = 0.38).

The publication by Cummings 2004 [73] reported results from the Tariot 2000 study regarding the Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D), which assesses the emotional stress experienced by relatives in connection with the psychopathological symptoms of Alzheimer's disease. In addition, data were provided by the manufacturer Janssen-Cilag regarding this scale for the Brodaty 2005 and Erkinjuntti 2002 studies, as well as for the 16 and 24 mg galantamine groups in Tariot 2000. No statistically significant differences were shown between treatment groups in any of the studies.

The summarisation by means of meta-analysis (Figure 38), with a small (even though statistically significant) pooled effect of about one tenth of a standard deviation (Cohen's d = -0.11; 95% CI: -0.21 to -0.00) provided an indication of a favourable effect on the quality of life of caregiving relatives.

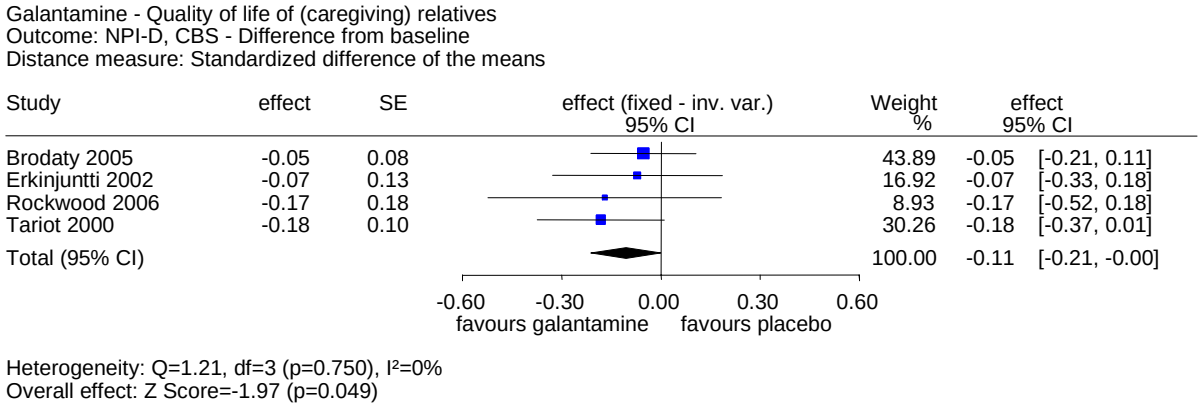
Table 32. Galantamine: Results on quality of life of (caregiving) relatives

Study (duration)		**Out-come**	**N[a]**	**Mean difference from baseline (SD)**	**Treatment difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Brodaty 2005[b] (6 months)	GAL-PRC 16-24 mg	NPI-D	*299*	*0.1 (5.7[c])*	*0.0[d] (n.r.)*	⇔	*"n.s."*
	GAL 16-24 mg		*303*	*-0.4 (6.1[c])*	*-0.3[d] (n.r.)*	↗	*"n.s."*
	Placebo		*304*	*0.3 (5.1[c])*			
Erkinjuntti 2002 [b,e] (6 months)	GAL 24 mg	NPI-D	*167*	*-0.1 (5.4[c])*	*-0.4 (n.r.)*	↗	*"n.s."*
	Placebo		*90*	*0.3 (5.9[c])*			
Rockwood 2006 (4 months)	GAL 16-24 mg	CBS	(64)[f]	n.r.	Cohen's d = -0.17	↗	0.38
	Placebo		(66)[f]	n.r.			
Tariot 2000[b] (5 months)	GAL 8 mg	NPI-D	116 [g]	1.2 (5.9)[g]	0.3[c] (n.r.)	↘	"n.s." [g]
	GAL 16 mg		*215*	*-0.1 (5.9[c])*	*-1.1 (n.r.)*	↗	*"n.s."*
	GAL 24 mg		*206*	*-0.2 (7.2[c])*	*-1.2 (n.r.)*	↗	*"n.s."*
	Placebo		*214*	*0.9 (5.9[c])*			

a: Number of patients in the analysis, unless otherwise stated.
b: Information obtained directly from the manufacturer Janssen-Cilag.
c: Own calculation.
d: Discrepancies between the reported differences and the reported group-internal estimates can presumably be ascribed to adjustments.
e: Subgroup of patients with Alzheimer's disease plus cerebrovascular disease.
f: Number of randomised patients; number of analysed patients not reported in the publication.
g: Data from Cummings et al, 2004 [73].

CI = confidence interval, GAL = galantamine, GAL-PRC = galantamine prolonged release, N = number, n.r. = not reported, n.s. = not statistically significant, SD = standard deviation

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect



Note: Rockwood 2006: SE calculated from p-value (p = 0.38).

Figure 38. Galantamine: Meta-analysis of quality of life of (caregiving) relatives

5.3.2.9 Degree of care provided by one or several caregivers or institutions

A pooled analysis of the degree of care provided by caregivers (caregiver time) for patients with Alzheimer's disease was published by Sano 2003 [98] on the basis of data from Wilcock 2000 and Raskind 2000. The original data were not reported in the original publications. The caregiver time was assessed by means of the Allocation of Caregiver Time Survey (ACTS); in addition, caregivers were asked how much time the patients could spend per day without needing care. Overall, 411 patients in the test group and 414 patients in the placebo group were analysed (97% and 98% of randomised patients), whereby the patient flow was unclear. In the reported population, the test and placebo group seemed comparable. It was reported that after 6 months, caregivers of patients taking galantamine 24 mg on average invested 32 minutes less per day in supporting patients in their activities of daily living than caregivers of patients in the placebo group ($p = 0.011$). In patients with moderate Alzheimer's disease (MMSE ≤ 18), the difference between the test and placebo group was noticeably higher (53 minutes; $p = 0.021$). The result for the criterion "time without care" was similar. Different analyses (categorical versus continuous assessment of outcomes; adjustment for degree of care at baseline) by means of a sensitivity analysis showed consistent results.

The ACTS was also used in Rockwood 2006; however, the publication did not report the corresponding results.

In summary, the data available only provide an indication of a favourable effect of galantamine on the degree of care provided.

5.3.2.10 Additional information: clinical stage of disease

All studies investigated changes in the global clinical impression using the CIBIC-plus. In 5 studies, it was a primary outcome and in each case assessed in a categorical manner under consideration of all 7 stages. Table 33 shows the proportion of responders, i.e. the proportion of patients with a score ≤ 4 ("no deterioration" or "improvement"). After 5 to 6 months, the proportion of responders in the test groups (except for the 8 mg group) lay between 62% and 75%. The proportion of patients in the placebo group who were assessed as being unchanged or improved lay between 49% and 58%. In 4 of the 5 studies, the distribution of the CIBIC-plus scores between the galantamine and placebo groups was statistically significantly different.

In Rockwood 2006, the CIBIC-plus was a secondary outcome and was only analysed within the framework of a comparison of mean values. After 4 months, in the LOCF analysis, the CIBIC-plus was also statistically significantly lower in the galantamine group than in the placebo group.

Overall, the studies showed that galantamine improves the global clinical impression compared with placebo.

Table 33. Galantamine: Results of the CIBIC-plus ≤ 4 ("no change" or "improvement")

Study (duration)		**Out-come**	**N[a]**	**Proportion (%) with score ≤ 4**	**Treatment difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Brodaty 2005 (6 months)	GAL-PRC 16-24 mg	CIBIC -plus	291	62	+ 5% (n.r.)	↗	"n.s."[b]
	GAL 16-24 mg		302	63	+ 6% (n.r.)	↗	"n.s."[b]
	Placebo		301	57			
Erkinjuntti 2002[c] (6 months)	GAL 24 mg	CIBIC -plus	172	75	+ 21% (n.r.)	↗	0.001[b]
	Placebo		92	54			
Raskind 2000 (6 months)	GAL 24 mg	CIBIC -plus	186	73	+ 16% (n.r.)	↗	< 0.01[b]
	Placebo		196	57			
Tariot 2000 (5 months)	GAL 8 mg	CIBIC -plus	128	53	+ 4% (n.r.)	↗	"n.s"[b]
	GAL 16 mg		256	66	+ 17% (n.r.)	↗	< 0.001[b]
	GAL 24 mg		253	64	+ 15% (n.r.)	↗	< 0.001[b]
	Placebo		261	49			
Wilcock 2000 (6 months)	GAL 24 mg	CIBIC -plus	206	62	+ 12% (n.r.)	↗	< 0.05[b]
	Placebo		203	50			
				Mean difference from baseline (SD)			
Rockwood 2006 (4 months)	GAL 16-24 mg	CIBIC -plus	61	n.r.	-1.0[d] (n.r.)	↗	0.03
	Placebo		65	n.r.			

a: Number of patients in the analysis.
b: The p-values are based on a comparison of the distribution of patients over 7 categories (van Elteren test).
c: Subgroup of patients with Alzheimer's disease plus cerebrovascular disease.
d: Estimated from figure.

CI = confidence interval, GAL = galantamine, GAL-PRC = galantamine prolonged release, N = number, n.r. = not reported, n.s. = not statistically significant, SD = standard deviation

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect.

5.3.3 Rivastigmine

5.3.3.1 Activities of daily living

In 3 studies (B304, Corey-Bloom 1998, Rösler 1999), the activities of daily living were measured by means of the Progressive Deterioration Scale (PDS). The scores are based on information provided by relatives or other caregivers. In the B304 study, which allowed a flexible dose up to 12 mg, statistically significant improvements compared with placebo were noted both for the twice or 3 times daily administration. The observed difference was slightly larger in the group taking rivastigmine 3 times per day. In Corey-Bloom 1998, statistically significant effects were shown for the high-dose group in the PDS (6 to 12 mg), but not for the low-dose group. In Rösler 1999, only the high-dose group showed a (statistically non-significant) trend in favour of rivastigmine ($p = 0.07$); an opposite trend was shown in the low-dose group (1–4 mg).

In summary, the studies provided an indication of a favourable effect of high-dose rivastigmine or rivastigmine administered 3 times daily on activities of daily living. A meta-analysis (Figure 39) did not show a heterogeneity of effects and showed a small statistically significant effect strength in the dimension of a quarter of a standard deviation (Cohen's $d = -0.27$; 95% CI: -0.37 to -0.16). This corresponds to about 3 points in the PDS. The consideration of the results from the B351 study (which so far has not been published and for which the manufacturer Novartis did not provide the study report) within the framework of a sensitivity analysis showed statistically marked heterogeneity and slightly reduced the effect estimate. However, the statistical significance remained, both in the fixed effects model ($p < 0.001$) and in the random effects model ($p < 0.001$) (data presented in Appendix G).

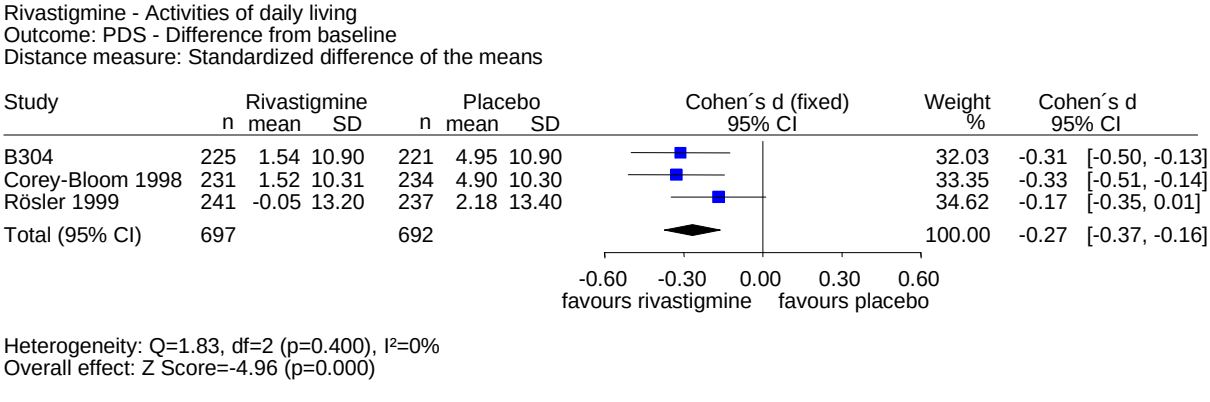
Table 34. Rivastigmine: Results on daily living skills

Study (duration)		**Out-come**	**N[a]**	**Mean difference from baseline (95% CI)**	**Group difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
B304 1998[b] (26 weeks)	*RIV 2-12 mg (2x/d)*	*PDS*	*227*	*-2.7 (n.r.)*	*2.3[c] (n.r.)*	↗	*0.030*
	RIV 2-12 mg (3x/d)		*225*	*-1.5 (n.r.)*	*3.4[c] (n.r.)*	↗	*0.001*
	Placebo		*221*	*-5.0 (n.r.)*			
Corey-Bloom 1998 (26 weeks)	RIV low dose (1-4 mg)	PDS	233	-5.2 [-6.5; -3.9]	-0.3[c] (n.r.)	↘	n.r.[d]
	RIV high dose (6-12 mg)		231	-1.5 [-2.9; -0.2]	3.4 (1.5; 5.3)	↗	< 0.001
	Placebo		234	-4.9 [-6.2; -3.6]			
Rösler 1999 (26 weeks)	RIV low dose (1-4 mg)	PDS	241	-3.4 [-5.0; -1.6]	-1.2[c] (n.r.)	↘	"n.s."
	RIV high dose (6-12 mg)		241	0.1 [-1.6; 1.8]	2.2[c] (n.r.)	↗	0.07[e]
	Placebo		237	-2.2 [-3.9; -0.5]			

a: Number of patients included in the analysis.
b: Data from the study report provided by the manufacturer.
c: Own calculation.
d: One can infer non-significance from the information in the text (p. 61: "This same effect was not seen for the low dose ENA 713 group").
e: Information from the erratum in BMJ 2001; 322:1456.

CI = confidence interval, N = number, n.r. = not reported, n.s. = not statistically significant,
RIV = rivastigmine, SD = standard deviation

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect.



Note:
Algebraic signs changed; i.e. negative values correspond to positive effects.
B304: standard deviations calculated from the p-value = 0.001.
Corey-Bloom 1998, Rösler 1999: standard deviations calculated from confidence intervals.

Figure 39. Rivastigmine: Meta-analysis of daily living skills

5.3.3.2 Accompanying psychopathology

In Forette 1998, patients' observable behaviour and individual psychopathological aspects were assessed by means of the Nurses' Observation Scale for Geriatric Patients (NOSGER). The results are not presented here due to the high proportion of patients not considered in the analysis (20-50 % in the treatment groups) (see Section 5.2.3.2). In Corey-Bloom 1998 and Rösler 1999, the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) was applied [92]; however, the results were not reported in the original publication. Novartis stated that the BEHAVE-AD was not evaluated in these studies but was only used to calculate the domain "behaviour" in the CIBIC.

Therefore, there are no indications of a favourable effect of rivastigmine on accompanying psychopathology.

5.3.3.3 Cognitive function

In all 4 available studies, the ADAS-cog was used to assess cognitive deficits.

ITT analyses were reported in 3 studies (B304, Corey-Bloom 1998, Rösler 1999). Statistically significant advantages were shown in both treatment groups in the B304 study (2–12 mg with twice or 3 times daily administration) versus placebo. The same applies to the high-dose groups (6-12 mg) in Corey-Bloom 1998 and Rösler 1999. In contrast, no statistically significant difference versus placebo was shown for the low-dose group (1–4 mg) in Rösler

1999. In Corey-Bloom 1998, the advantage versus placebo in the low-dose group was also substantially lower than in the high-dose group. In this context, no p-value was reported; however, the noted difference indicated statistical significance.

Table 35. Rivastigmine: Results on cognitive function

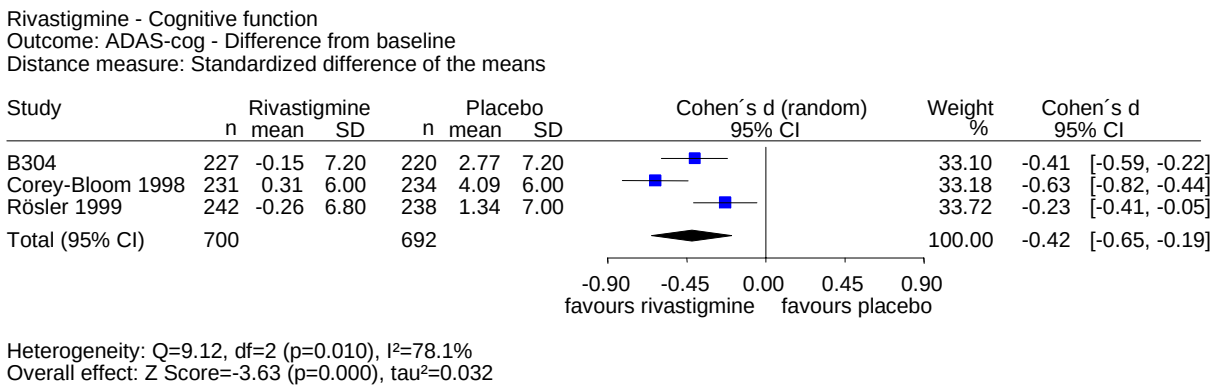
Study (duration)		**Out-come**	**N[a]**	**Mean difference from baseline (95% CI)**	**Treatment difference compared with placebo**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
B304 1998 [b] (26 weeks)	*RIV 2-12 mg (2x/d)*	*ADAS-cog*	*228*	*1.2[c] (n.r.)*	*-1.61[d] (n.r.)*	↗	*0.019*
	RIV 2-12 mg (3x/d)		*227*	*-0.2[c] (n.r.)*	*-2.9[d] (n.r.)*	↗	*< 0.001*
	Placebo		*220*	*2.8[c] (n.r.)*			
Corey-Bloom 1998 (26 weeks)	RIV low dose (1-4 mg)	ADAS-cog	233	2.4[c] (1.6; 3.1)	-1.7[d] (n.r.)	↗	n.r.
	RIV high dose (6-12 mg)		231	0.3[c] (-0.5; 1.1)	-3.8 (-4.9; -2.7)	↗	< 0.001
	Placebo		234	4.1[c] (3.3; 4.9)			
Rösler 1999 (26 weeks)	RIV low dose (1-4 mg)	ADAS-cog	242	1.4[c] (0.5; 2.3)	0.1[d] (n.r.)	↘	"n.s."
	RIV high dose (6-12 mg)		242	-0.3[c] (-1.1; 0.7)	-1.6[d] (n.r.)	↗	0.011[e]
	Placebo		238	1.3[c] (0.4; 2.2)			

a: Number of patients in the analysis
b: Data from the study report provided by the manufacturer.
c: Algebraic signs permuted in the publication.
d: Own calculation.
e: Information provided in the erratum in BMJ 2001; 322:1456.

CI = confidence interval, N = number, n.r. = not reported, n.s. = not statistically significant, RIV = rivastigmine

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect.

The studies available demonstrate the benefit of rivastigmine in respect of cognitive function. They also indicate the existence of a dose-effect relationship. The meta-analysis (Figure 40) for the highest dose level or the group with the more frequently administered dose showed a strong heterogeneity of results, which cannot be clearly explained by the differences in design or patient characteristics between studies. The estimated effects ranged between one to two thirds of the standard deviation. This corresponds to about 3 points on the ADAS-cog scale. The inclusion of the results of the B351 study only has a minor effect on the overall result (data presented in Appendix G).



Note:
B304: Data on the standard deviation for the placebo group from [49] was used for both groups.
Corey-Bloom 1998, Rösler 1999: Standard deviations calculated from confidence intervals.

Figure 40. Rivastigmine: Meta-analysis of cognitive function

5.3.3.4 Health-related quality of life

No data on the outcome "health-related quality of life" were reported in the studies.

5.3.3.5 Placement in a nursing home (institutionalisation)

No data on the outcome "placement in a nursing home (institutionalisation)" were reported in the studies.

5.3.3.6 Mortality

Only single cases of death were reported in the studies (see Table 36).

No indication of a favourable or unfavourable effect of rivastigmine on mortality can be inferred from these data.

5.3.3.7 Adverse events

In the studies, the adverse event rates and discontinuation rates due to adverse events were high in patients taking rivastigmine, especially in the high-dose group. For example, in Corey-Bloom 1998, 48% of patients in the high-dose group suffered from nausea (low-dose: 14%, placebo: 11%); 27% suffered from vomiting (vs. 7% and 3%); 20% had a lack of appetite (vs. 8% and 3%), and 24% suffered from dizziness (vs. 15% and 13%. in the placebo group). Furthermore, in Rösler 1999, 24% of patients in the high-dose group lost more than 7% of their body weight (vs. 9% and 7%). In the B304 study, the adverse event rate was comparable to that in the high-dose groups, independently of the frequency of drug administration.

In summary, the studies demonstrated an increased rate of adverse events in patients taking high-dose rivastigmine compared with placebo. The meta-analyses (Figures 41 to 47) for the highest dose level group or the group taking the more frequently administered dose in each case showed an odds ratio of about 8 in respect of the occurrence of nausea, vomiting, and lack of appetite, and therefore showed a considerably increased risk versus placebo. The marked heterogeneity in the meta-analysis of study discontinuations due to adverse events can evidently be ascribed to the B304 study, in which, compared with the other studies, a lower minimum dose (using a flexible dose regimen) was administered. The direction of the effect of all 4 studies was however identical, and the overall result was statistically significant. The consideration of the adverse events observed in the B351 study only slightly changed these results (data presented in Appendix G).

In the low-dose range, the results from the 2 available studies (Corey-Bloom 1998 and Rösler 1999) indicated a clearly lower potential to cause harm. However, in this dose range, no benefit was demonstrated.

Table 36. Rivastigmine: Study discontinuations, deaths, and number of patients with adverse events

Study (duration)		**Increase in dose within the first month**	**N[(a)]**	**Study discontinuations N (%)**	**Deaths N**	**Serious adverse events N (%)**	**Discontinuations due to adverse events N (%)**	**Overall adverse event rate N (%)**
B304 1998[(b)] (26 weeks)	*RIV 2-12 mg (2x/d)*	*2 to 6 mg*	*228[(c)]*	*54 (24)*	*1*	*40 (18)*	*38 (17)*	*208 (91)*
	RIV 2-12 mg (3x/d)	*2 to 6 mg*	*227*	*38 (17)*	*0*	*40 (18)*	*24 (11)*	*208 (92)*
	Placebo		*222*	*33 (15)*	*1*	*33 (15)*	*20 (9)*	*169 (76)*
Corey-Bloom 1998 (26 weeks)	RIV low dose (1-4 mg)	n.r.	233	34 (15)[(d)]	0	n.r.	19 (8)[(d)]	"> 85 %"
	RIV high dose (6-12 mg)	n.r.	231	82 (35)[(d)]	1	n.r.	66 (29)[(d)]	"> 85 %"
	Placebo		235	39 (17)[(d)]	0	n.r.	17 (7)[(d)]	"> 85 %"
Forette 1999 (18 weeks)	RIV 6-12 mg (2x/d)	6 mg[(e)]	45	16 (36)[(d)]	n.r.		14 (31)[(d)]	n.r.
	RIV 6-12 mg (3x/d)	6 mg[(e)]	45	11 (24)[(d	n.r.	total: 13 (11)[(d)]	10 (22)[(d)]	n.r.
	Placebo		24	2 (8)[(d)]	n.r.		1 (4)[(d)]	n.r.
Rösler 1999 (26 weeks)	RIV low dose (1-4 mg)	up to 4 mg	243	34 (14)	0	"≈ 18 %"	18 (7)	172 (71)
	RIV high dose (6-12 mg)	up to 6 mg	243	79 (33)	1	"≈ 18 %"	55 (23)	220 (91)
	Placebo		239	31 (13)	0	"≈ 18 %"	16 (7)	172 (72)

(continued)

Table 36 (continued). Rivastigmine: Study discontinuations, deaths, and number of patients with adverse events

a: Number of randomised patients, unless otherwise stated.
b: Data from the study report provided by the manufacturer.
c: One person in the twice-daily group refused to take the study medication and was therefore excluded from the safety analysis.
d: % calculated from N.
e: 2 mg initially, on Day 4 + 1 mg, every 4 days + 0.5 mg.

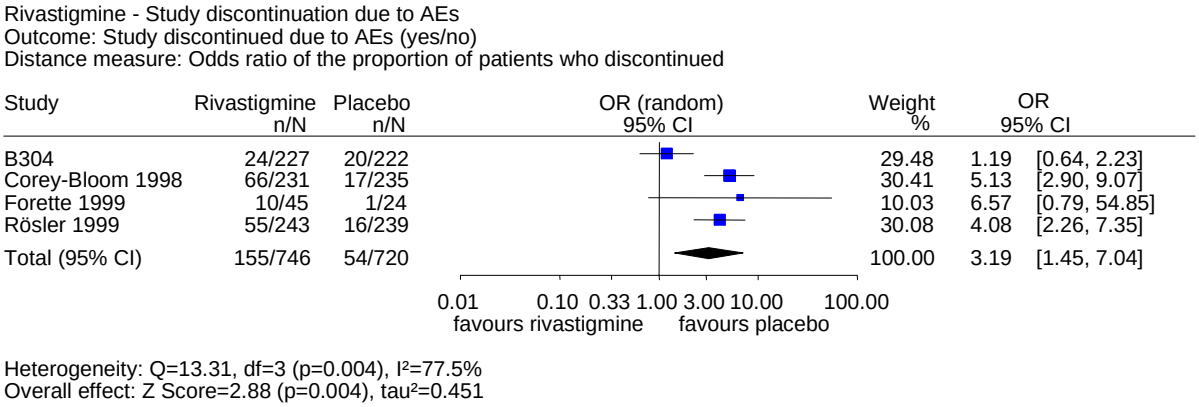
N = number, n.r. = not reported, RIV = rivastigmine

Table 37. Rivastigmine: Adverse events

Study (duration)		**Dose increase within the first month**	**N[a]**	**Nausea**	**Vomiting**	**Diarrhoea**	**Dizziness**	**Lack of appetite**	**Weight loss**	**Agitation**	**Headache**	**Abdominal symptoms**	**Fatigue**	**Feeling of unwellness**
				Proportion (%) with AE										
B304[b] (26 weeks)	*RIV 2-12 mg (2x/d)*	*2 to 6 mg*	*228[c]*	*54*	*39*	*18*	*18*	*21*	*n.r.*	*9*	*18*	*15*	*5*	*6*
	RIV 2-12 mg (3x/d)	*2 to 6 mg*	*227*	*48*	*30*	*17*	*17*	*19*	*n.r.*	*6*	*16*	*11*	*6*	*7*
	Placebo		*222*	*14*	*6*	*9*	*7*	*3*	*n.r.*	*12*	*10*	*5*	*5*	*3*
Corey-Bloom 1998 (26 weeks) Dose adjustment phase	RIV low dose (1-4 mg)	n.r.	233	14	7	n.r.	15	8	1	n.r.	n.r.	n.r.	5	1
	RIV high dose (6-12 mg)	n.r.	231	48	27	n.r.	24	20	4	n.r.	n.r.	n.r.	10	3
	Placebo		235	11	3	n.r.	13	3	1	n.r.	n.r.	n.r.	4	1
Forette 1999 (18 weeks)	RIV 6-12 mg (2x/d)	6 mg[d]	45	58	38	n.r.	27	18	n.r.	n.r.	16	n.r.	n.r.	n.r.
	RIV 6-12 mg (3x/d)	6 mg[d]	45	58	31	n.r.	9	16	n.r.	n.r.	20	n.r.	n.r.	n.r.
	Placebo		24	8	4	n.r.	0	0	n.r.	n.r.	4	n.r.	n.r.	n.r.
Rösler 1999 (26 weeks)	RIV low dose (1-4 mg)	up to 4 mg	242[e]	17	8	10	10	3	9[f]	n.r.	7	5	2	1
	RIV high dose (6-12 mg)	up to 6 mg	242[e]	50	34	17	20	14	24[f]	n.r.	19	12	10	10
	Placebo		239	10	6	9	7	2	7[f]	n.r.	8	3	3	2

a: Number of randomised patients, unless otherwise stated.
b: Data from the study report provided by the manufacturer.
c: One person from the twice-daily group refused to take the study medication and was therefore excluded from the safety analysis.
d: 2 mg initially, on Day 4 + 1 mg, every 4 days + 0.5 mg.
e: The safety data were collected for 242 patients in both test groups (instead of the randomised 243).
f: Weight loss: > 7% body weight.

AE = adverse events, N = number, n.r. = not reported, RIV = rivastigmine



Note: due to heterogeneity, a random effects model was chosen. A fixed effects model showed similar results.

Figure 41. Rivastigmine: Meta-analysis of study discontinuations due to adverse events

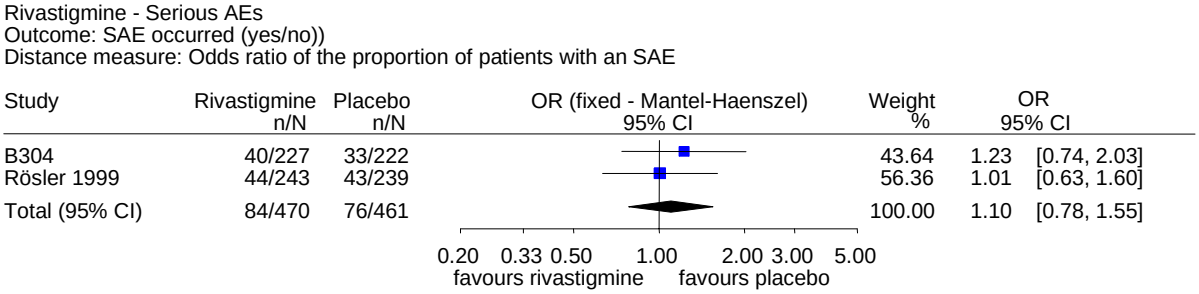


Figure 42. Rivastigmine: Meta-analysis of serious adverse events

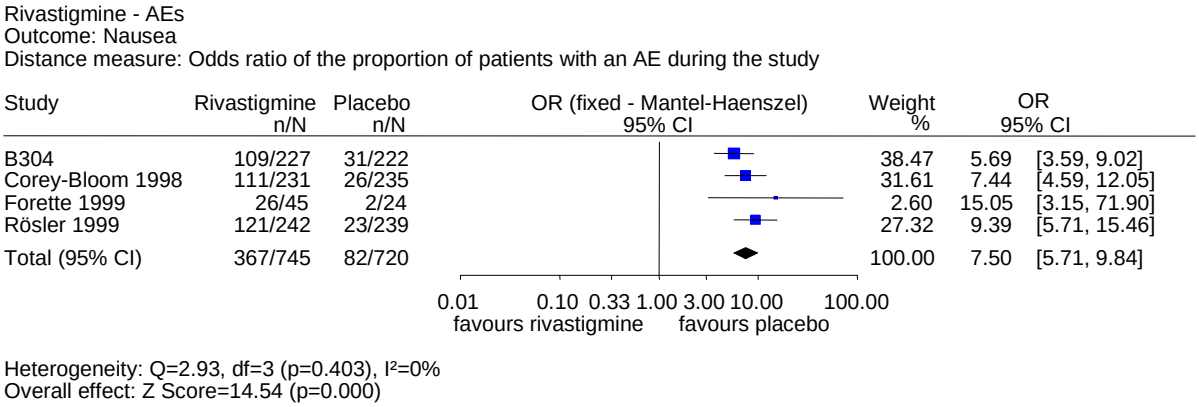


Figure 43. Rivastigmine: Meta-analysis of the outcome "nausea"

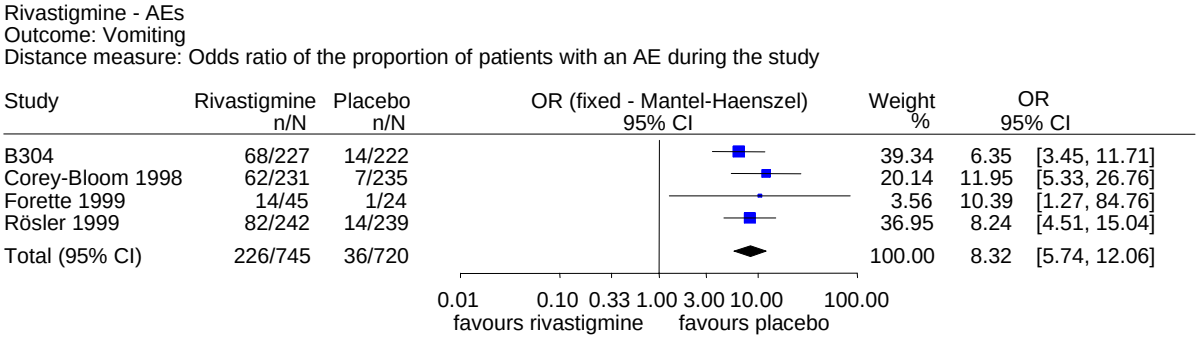


Figure 44. Rivastigmine: Meta-analysis of the outcome "vomiting"

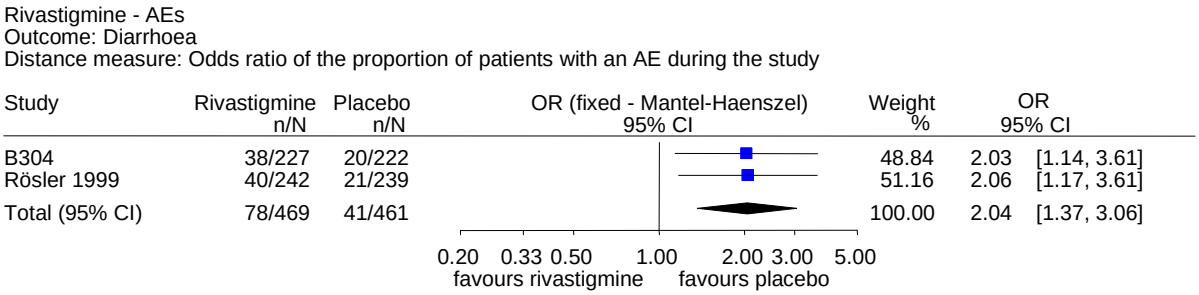


Figure 45. Rivastigmine: Meta-analysis of the outcome "diarrhoea"

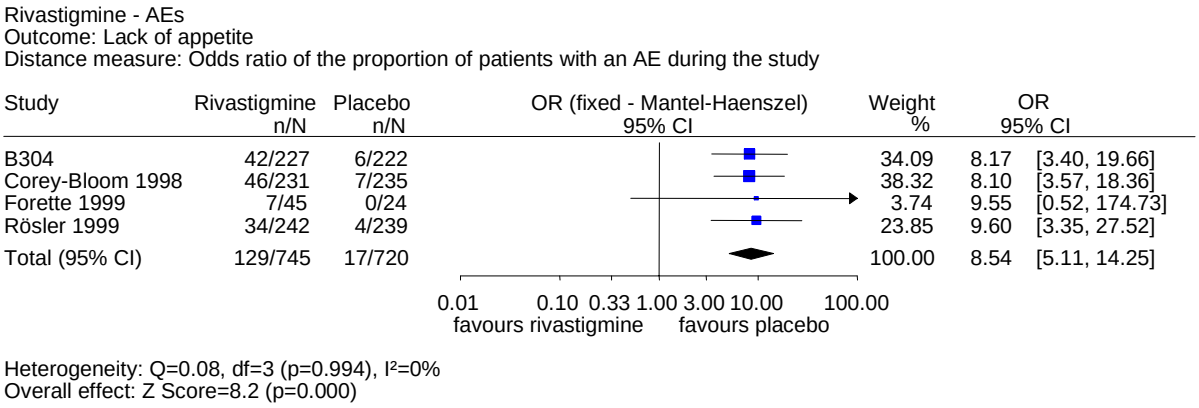


Figure 46. Rivastigmine: Meta-analysis of the outcome "loss of appetite"

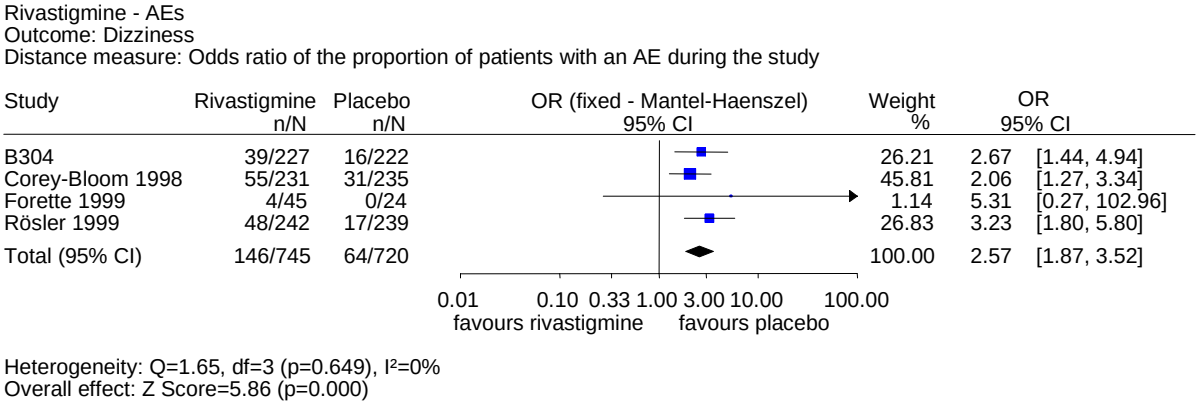


Figure 47. Rivastigmine: Meta-analysis of the outcome "dizziness"

5.3.3.8 Quality of life of (caregiving) relatives

No data were reported in the studies regarding the outcome "quality of life of (caregiving) relatives".

5.3.3.9 Degree of care provided by one or more caregiver(s) or institution(s)

In the study report on the B304 study, it was reported in Amendment 6 of the study protocol (May 1995) that the Caregiver Activity Survey (CAS) was introduced as a further efficacy measure to assess the association between the administration of rivastigmine and caregiver times. However, on page 56 of the last amendment of the study protocol (March 1997) it was "..stated that the analysis of the CAS was only to be performed on data pooled from all four phase III studies." It remains unclear whether this decision was made before or after the unblinding regarding patient data – the last patient completed the study in September 1996.

Furthermore, this note indicates that the CAS was also used in the other phase III studies (B351, Corey-Bloom 1998, Rösler 1999). However, in the publications by Corey-Bloom 1998 and Rösler 1999, no information was provided in this regard. Moreover, no publications on the pooled analyses of the CAS from these 4 studies were identified. Novartis stated that no analyses of these CAS data were available.

Therefore there are no indications of a favourable effect of rivastigmine on the degree of care. The fact that the analysis of data evidently collected for this purpose has not been published rather indicates that a favourable effect of rivastigmine on this outcome is unlikely.

5.3.3.10 Additional information: clinical disease stage

In all 4 studies, the global clinical impression was assessed using the CIBIC-plus.

The difference in the proportion of patients assessed as "improved" (Score ≤ 3) was assessed in 2 studies by means of an ITT analysis (Table 38). In the B304 study, a statistically significant advantage was only shown for the group taking rivastigmine 3 times daily (31%), but not for the group taking rivastigmine twice daily (23%; placebo: 19%). In Rösler 1999, after 26 weeks a statistically significantly higher proportion of patients, both in the high-dose and low-dose group, showed an improvement in the clinical global impression (37% and 30%) than in the placebo group (20%). In the ITT analysis in Corey-Bloom 1998, only the continuous evaluation of the CIBIC scale was reported, but not the proportion of patients assessed as "improved". A reduction in the CIBIC score was shown both in the high-dose and low-dose group (i.e. an improvement) compared with placebo. A p-value was only reported for the high-dose group ($p < 0.01$).

In summary, indications are available showing that rivastigmine can improve the global clinical impression.

Table 38. Rivastigmine: Results for CIBIC-plus ≤ 3 (improvement)

Study (duration)	**Dose**	**Out-come**	**N**[a]	**Proportion (%) with score ≤ 3**	**Treatment difference compared with placebo** **Difference 95% CI**	**Direction of the effect**	**P-value**
B304[b] (26 weeks)	*RIV 2-12 mg (2x/d)*	*CIBIC-plus*	*222*	*23*	*4%[c] (n.r.)*	↗	*0.260*
	RIV 2-12 mg (3x/d)		*222*	*31*	*12%[c] (n.r.)*	↗	*0.002*
	Placebo		*216*	*19*			
Rösler 1999 (26 weeks)	RIV low dose (1-4 mg)	CIBIC-plus	233	30	10%[c] (n.r.)	↗	< 0.05
	RIV high dose (6-12 mg)		219	37	17%[c] (n.r.)	↗	< 0.001
	Placebo		230	20			
				Mean difference from baseline (CI)			
Corey-Bloom 1998 (26 weeks)	RIV low dose (1-4 mg)	CIBIC-plus	233	0.2 (0.1; 0.4)	-0.3[c] (n.r.)	↗	n.r.
	RIV high dose (6-12 mg)		231	0.2 (0.0; 0.4)	-0.3 (-0.5; -0.1)	↗	< 0.01
	Placebo		234	0.5 (0.3; 0.7)			

a: Number of patients in the analysis, unless otherwise stated.
b: Data from the study report provided by the manufacturer.
c: Values calculated.

CI = confidence interval, N = number, n.r. = not reported, RIV = rivastigmine

The arrow indicates whether the numerical change on the relevant scale is an improvement (↗) or deterioration (↘). It does not indicate the size of the effect.

5.3.4 Comparisons between different cholinesterase inhibitors

5.3.4.1 Galantamine vs. donepezil

5.3.4.1.1 Activities of daily living

In Wilcock 2003, activities of daily living (measured with the BADLS) were the primary outcome. It was reported that the BADLS scores remained constant in both groups until Month 9 and then deteriorated. An analysis of covariance, including age and MMSE scores as covariables at the time of screening, did not show a statistically significant difference between patients taking galantamine and patients taking donepezil ($p > 0.5$). A similar result was shown in a subgroup analysis of patients with an MMSE score between 12 and 18.

5.3.4.1.2 Accompanying psychopathology

In Wilcock 2003, no differences between the galantamine and donepezil group were shown regarding changes in the NPI. Exact data were not reported in the publication.

5.3.4.1.3 Cognitive function

In Wilcock 2003, the effects of galantamine and donepezil on cognitive function were assessed by means of the MMSE and ADAS-cog. As for the other comparisons presented in the present report, the results for the ADAS-cog are primarily presented here. After an initial improvement in the ADAS-cog in both groups, at the end of study (after 52 weeks), both groups showed a deterioration compared with baseline, which was slightly less pronounced in the galantamine group. However, at the end of study the difference between both groups was not statistically significant.

Although, regarding the ADAS-cog, explorative analyses indicated a stronger effect of galantamine in the subgroup of patients with moderate dementia (MMSE: 12–18), it could not be inferred from the publication whether this subgroup analysis was planned a priori. Furthermore, no results of a statistical interaction test were available. The tendency of the MMSE results corresponded to the ADAS-cog results.

5.3.4.1.4 Health-related quality of life

No data on the outcome "health-related quality of life" were reported in the study.

5.3.4.1.5 Placement in a nursing home (institutionalisation)

No data on the outcome "placement of patients in a nursing home (institutionalisation)" were reported in the study.

5.3.4.1.6 Mortality

In Wilcock 2003, 2 patients (2.1%) died in the galantamine group and 3 (3.3%) in the donepezil group.

5.3.4.1.7 Adverse events

In Wilcock 2003, in the galantamine and donepezil groups, similar rates were shown for study discontinuations due to adverse events (11% vs. 12%) and overall discontinuation rates (20% vs. 22%). The overall adverse event rate was also similar in both groups (91% in the galantamine group versus 93% in the donepezil group). Similar rates for nausea (galantamine 20%, donepezil 18%) and vomiting (galantamine 18%, donepezil 14%) were shown in both groups. Minor differences between groups to the disadvantage of galantamine were shown for agitation (19% vs. 12%), falling (17% vs. 9%), and headache (17% vs. 12%).

The serious adverse event rate was 19% in the galantamine group and 20% in the donepezil group.

5.3.4.1.8 Quality of life of (caregiving) relatives

In Wilcock 2003, the objective and subjective burdens of caregivers were assessed with the Screen for Caregiver Burden (SCGB). In the galantamine group, an improvement or maintenance of objective burdens was reported by 67% of caregivers (of n = 57); regarding subjective burdens, this rate was 68% (of n = 85). The corresponding rates in the donepezil group were 51% (of n = 41) for objective burdens and 49% (of n = 79) for subjective burdens. It was not reported whether these differences were statistically significant. However, the interpretation of this analysis is greatly limited, as no data were available for up to half of the caregivers. It was also unclear to what extent the data on subjective burdens were based on (noticeably) larger case numbers than the data on objective burdens (after all, the scores for the subjective burdens were calculated from those of the objective burdens).

5.3.4.1.9 Degree of care provided by one or several caregiver(s) or institution(s)

No data were reported in the study on the outcome relevant to relatives "degree of care provided by one or several caregiver(s) or institution(s)".

5.3.4.1.10 Additional information: clinical disease stage

No data were reported in the study on the outcome "clinical disease stage".

5.3.4.2 Rivastigmine versus donepezil

5.3.4.2.1 Activities of daily living

In Bullock 2005, a statistically significant advantage in favour of rivastigmine was shown in the ADCS-ADL scale (ITT-LOCF analysis) after 2 years; patients in the rivastigmine group had deteriorated 2.1 points less than those in the donepezil group ($p = 0.047$). However, the results are of limited evidential value, as the rate of study discontinuations was high in both groups and differed between groups. At the end of study, nearly 50% and 37% of patients in the rivastigmine and donepezil groups respectively had already prematurely discontinued the study. The publication only reported the Least Squares (LS) Means, including the standard error for the change per group. If the t-test was applied, the p-value was more than twice as high ($p = 0.103$; own calculation). This is noticeable, as this was a randomised study including many patients, and a big difference between the 2 analyses was not to be expected. A query to Novartis resulted in the provision of unadjusted mean values and standard deviations from which the p-value for the t-test was calculated ($p = 0.016$), which, in turn, was substantially smaller than the p-value calculated from the ANCOVA. It can be assumed that these discrepancies were due to the discontinuation rates; however, this could not be ultimately clarified. Finally, it was noted in the publication that the differences in the per-protocol analyses were no longer statistically significant. Whether this was due to a change in the effect estimate and/or a lack of power remains unclear.

In Fuschillo 2001, regarding the PSMS scale only the results for the intra-group comparisons were presented. In both the rivastigmine and in the donepezil group, practically no changes on the PSMS scale were shown after 30 weeks compared to baseline.

In Wang 2001, no changes in scores on the Blessed Roth Dementia Scale were shown between rivastigmine and donepezil after 16 weeks ($p = 0.472$).

In summary, in respect of daily living skills, the data were insufficient to provide evidence of a superiority or inferiority of either drug, but may at best only be interpreted as an indication in this regard.

Table 39. Rivastigmine vs. donepezil: Results on daily living skills

Study (duration)		**Out-come**	**N[(a)]**	**Mean difference from baseline (SD)**	**Treatment difference (RIV vs. DON)**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Bullock 2005 (24 months)	RIV 3-12 mg	ADCS /ADL	454	-12.8 (19.2[(b)])	2.1 (n.r.)	RIV > DON	0.047
	DON 5-10 mg		475	-14.9 (19.6[(b)])			
Fuschillo 2001 (7.5 months)	RIV 6-9 mg	PSMS	11	-0.5[(b)]	-0.4[(b)]	RIV < DON	n.r.
	DON 5 mg		16	-0.1[(b)]			
Wang 2001 (4 months)	RIV 3-6 mg	BRDS	59/60[(c)]	-1.8 (2.6)	-0.4[(b)] (n.r.)	RIV > DON	0.472
	DON 5-10 mg		61	-1.4 (3.2)			

a: Number of patients in the analysis.
b: Own calculation.
c: Inconsistent information provided in the publication (59 or 60 patients included in the analysis).

CI = confidence interval, DON = donepezil, N = number, n.r. =not reported, RIV = rivastigmine, SD = standard deviation, > = numerically greater treatment effect

5.3.4.2.2 Accompanying psychopathology

Accompanying psychopathological symptoms were only investigated in Bullock 2005. In the NPI-10, no treatment differences were shown between patients in the rivastigmine and donepezil group in the ITT-LOCF analysis. The change compared with baseline after 2 years was 2.4 points in the rivastigmine group and 2.9 points in the donepezil group (p = 0.554). No results were reported for subscales.

5.3.4.2.3 Cognitive function

In Bullock 2005, no difference between patients in the donepezil and rivastigmine group was shown for the primary outcome Severe Impairment Battery (SIB) after 2 years (ITT-LOCF analysis). The analyses for the secondary outcome MMSE confirmed these results.

For the ADAS-cog, Fuschillo 2001 again only reported results on intra-group comparisons. After 30 weeks, an improvement of 3.8 and 3.6 points compared with baseline was shown in the rivastigmine and donepezil group respectively (own calculation). A statistical significance of this minor difference between groups is not to be assumed.

In Wang 2001, there was no significant difference in the degree of improvement between groups in the MMSE after 16 weeks (p = 0.422).

Therefore, there is no evidence of a superiority of donepezil or rivastigmine regarding a positive effect on cognitive function.

Table 40. Rivastigmine vs. donepezil: Results on cognitive function

Study (duration)		**Out-come**	**N[a]**	**Mean difference from baseline (SD)**	**Treatment difference (RIV vs. DON)**		**P-value**
					Difference (95% CI)	**Direction of the effect**	
Bullock 2005 (24 months)	RIV 3-12 mg	SIB	471	-9.3 (23.9[b])	0.6[b] (n.r.)	RIV > DON	0.609
	DON 5-10 mg		483	-9.9 (24.2[b])			
Fuschillo 2001 (7.5 months)	RIV 6-9 mg	ADAS -cog	11	-3.8[b]	-0.2	RIV > DON	n.r.
	DON 5 mg		16	-3.6[b]			
Wang 2001 (4 months)	RIV 3-6 mg	MMSE	59/60[c]	2.5 (3.9)	0.6[b] (n.r.)	RIV > DON	0.422
	DON 5-10 mg		61	1.9 (3.4)			

a: Number of patients in the analysis.
b: Own calculation.
c: Inconsistent information provided in the publication (either 59 or 60 patients were included in the analysis).

CI = confidence interval, DON = donepezil, N = number, n.r. = not reported, SD = standard deviation, > = numerically greater treatment effect

5.3.4.2.4 Health-related quality of life

No data on the outcome "health-related quality of life" were reported in the studies.

5.3.4.2.5 Placement in a nursing home (institutionalisation)

No data on the outcome "placement in a nursing home (institutionalisation)" were reported in the studies.

5.3.4.2.6 Mortality

In Bullock 2005, mortality was comparable in both test groups (rivastigmine: 5.3%, donepezil: 6.8%). No deaths were reported in Fuschillo 2001 or Wang 2001.

5.3.4.2.7 Adverse events

In Bullock 2005, more discontinuations due to adverse events (26% vs. 16%) and more overall discontinuations (48% vs. 37%) occurred under rivastigmine than under donepezil. Results were presented separately for the dose-increase phase (16 weeks) and the maintenance

phase (Week 17 to 104). Regarding all adverse events, in the dose-increase phase a clear difference to the disadvantage of rivastigmine was shown. The proportion of patients with at least one adverse event in the dose-increase phase was 17 percentage points higher under rivastigmine than under donepezil (82% vs. 65%). The main differences between groups were shown for nausea (33% [rivastigmine] vs. 15% [donepezil]), vomiting (28% vs. 6%), loss of appetite (9% vs. 4%) and weight loss (6% vs. 2%).

Although in Bullock 2005 similar adverse event rates were shown between both groups in the maintenance phase (79% [rivastigmine] vs. 77% [donepezil]), with regard to nausea, vomiting, and loss of appetite, differences were still noticeable (nausea: 13% vs. 5%; vomiting: 15% vs. 4%, loss of appetite: 6% vs. 3%). When interpreting these maintenance phase data, it should be noted that patients who discontinued the study in the dose-increase phase due to adverse events were no longer included. The overall serious adverse event rate was the same for both drugs.

Fuschillo 2001 reported that the difference between groups regarding the incidence of adverse events was not statistically significant. Nausea and vomiting mainly occurred during the titration phase of rivastigmine. Dizziness and headache occurred more often with higher-dose rivastigmine and subsided without treatment. Neither serious adverse events nor study discontinuations due to adverse events occurred. However, the percentages presented in the publication on single adverse events are not plausible and therefore cannot be interpreted.

In Wang 2001, 2 patients in the rivastigmine group and 1 patient in the donepezil group discontinued because of adverse events. No evaluable data were provided on different adverse event rates.

Table 41. Rivastigmine vs. donepezil: Study discontinuations, deaths, and number of patients with adverse events

Study (duration)		**Dose increase within the first month**	**N[a]**	**Study discontinuations N (%)**	**Deaths N**	**Serious adverse events N (%)**	**Discontinuations due to adverse events N (%)**	**Overall adverse events N (%)**
Bullock 2005 (24 months)	RIV 3-12 mg	3 mg	498	237 (48)	26	157 (32)	128 (26)	406 (82)[b]
	DON 5-10 mg	5 mg	500	183 (37)	34	162 (32)	80 (16)	323 (65)[b]
Fuschillo 2001 (7.5 months)	RIV 6-9 mg	6 mg	11	n.r.	n.r.	0	0	n.r.[c]
	DON 5 mg	5 mg	16	n.r.	n.r.	0	0	n.r.[c]
Wang 2001 (4 months)	RIV 3-6 mg	3 mg	62	2 (3)	n.r.	n.r.	2 (3)	n.r.
	DON 5-10 mg	5 mg	62	1 (2)	n.r.	n.r.	1 (2)	n.r.

a: Number of randomised patients.
b: Data refer to the dose-adjustment phase (Week 1 to 16); maintenance phase (17-104): rivastigmine 79%, donepezil 77%.
c: In the text it is only reported that there was no difference between groups in the incidence of adverse events.

DON = donepezil, N = number, n.r. = not reported, RIV = rivastigmine

Table 42. Rivastigmine vs. donepezil: Adverse events

Study (duration)		**Dose increase within the first month**	**N[a]**	**Nausea**	**Vomiting**	**Diarrhoea**	**Dizziness**	**Lack of appetite**	**Weight loss**	**Agitation**	**Headache**	**Abdominal symptoms**	**Fatigue**	**Feeling of unwellness**
				Proportion (%) with AE										
Bullock 2005 (24 months) Dose-adjustment phase	RIV 3-12 mg DON 5-10 mg	3 mg	495[b]	33	28	8	n.r.	9	6	7	6	n.r.	n.r.	n.r.
		5 mg	499[b]	15	6	7	n.r.	4	2	10	5	n.r.	n.r.	n.r.
Fuschillo 2001[c] (7.5 months)	RIV 6-9 mg	6 mg	11											
	DON 5 mg	5 mg	16											

a: Number of randomised patients, unless otherwise stated.
b: Only patients who had taken the study medication were considered in the safety analysis.
c: In view of the number of participants (11 and 16), the reported percentages are not plausible and are therefore not reported here.

AE = adverse events, DON = donepezil, N = number, n.r. = not reported, RIV = rivastigmine

5.3.4.2.8 Quality of life of (caregiving) relatives

Bullock 2005 assessed the outcome relevant to relatives, "quality of life of (caregiving) relatives", by means of the NPI-D. Outcomes for subgroups according to age were reported in Bullock 2006 [84]. The NPI-D analysis for the overall study population has not been published. After a query from IQWiG, Novartis stated that the overall study population was only analysed descriptively for the OC. As this analysis is of limited evidential value, the data were not requested.

5.3.4.2.9 Degree of care provided by one or more caregiver(s) or institution(s)

No data in the studies were reported on the outcome relevant to relatives "degree of care provided by one or more caregiver(s) or institution(s)".

5.3.4.2.10 Additional information: clinical disease stage

Both in Bullock 2005 and in Wang 2001, the clinical disease stage was assessed my means of the GDS.

In Bullock 2005, an advantage was shown for rivastigmine in the ITT-LOCF analysis. After 2 years, the score on the scale was 0.69 points higher than at baseline in patients in the donepezil group; in the rivastigmine group, the score was only 0.58 points higher ($p = 0.049$; Wilcoxon test). However, the interpretation of these results is limited due to the high rate of study discontinuations, which differed between both groups.

In Wang 2001, no differences between the rivastigmine and donepezil group was shown in the change in the GDS after 16 weeks ($p = 0.126$).

5.3.4.3 Rivastigmine vs. donepezil vs. galantamine

Only Cumbo 2005 directly compared the 3 ChEIs rivastigmine, donepezil, and galantamine. In the study publication, only the results on the primary outcome were presented in an interpretable way. Therefore, in the following text, results are not organised according to the presentation of outcomes following Sections 4.1.3 and 4.4.2.

The primary outcome was the time to the appearance of behavioural symptoms associated with dementia. For this purpose, the NPI, NPI-D, and BEHAVE-AD were used. The probability to be free of corresponding symptoms after 18 months was 0.622 (SEM = 0.080) in the rivastigmine group, 0.484 (SEM = 0.090) in the donepezil group, and 0.546 (SEM = 0.087) in the galantamine group. No statistically significant differences were shown in this regard in the pairwise comparisons (rivastigmine vs. donepezil: $p = 0.055$ with a nominal advantage for rivastigmine; rivastigmine vs. galantamine: $p = 0.235$; galantamine vs.

donepezil: p = 0.365). However, the lack of information on sample size planning makes the interpretation of these statistically non-significant results difficult.

A total of 7 of the 101 patients suffered from nausea, which was the most common adverse event (rivastigmine: 8%, galantamine: 6%, donepezil: 6%). Other adverse events (vomiting, headache, loss of appetite, and weight loss) were in each case reported by 1 to 3 patients. Serious adverse events did not occur in the study.

5.3.4.4 Summary of the direct comparative studies

Due to the limited number of studies and the partially very different methods of operationalisation, a quantitative summary of the comparative results on single outcomes did not seem appropriate. Clear evidence of an additional benefit of one drug versus the other cannot be inferred from the data. However, only 2 of the 5 comparative studies had a sample size sufficient to detect moderate differences.

If one interprets the data cautiously, when the results alone are studied, a comparatively large study indicates a superiority of rivastigmine versus donepezil regarding the effect on activities of daily living. However, this observation is not supported by the results of 2 very small studies; furthermore, the high discontinuation rate, particularly under rivastigmine, makes the interpretation of results difficult. Noticeably higher rates were shown under rivastigmine for the occurrence of adverse events, especially nausea, vomiting, loss of appetite, and weight loss. With regard to accompanying psychopathology, one (small) study indicated an advantage of rivastigmine versus donepezil; however, this result was not confirmed by the large study. Even if the included 3 studies relatively consistently provided no evidence of the superiority of rivastigmine or donepezil regarding their effect on cognitive function, the comparability of both drugs may not be inferred from this finding, as no study was recognisably designed as an equivalence or non-inferiority study with an a priori definition of irrelevant differences. No comparative data were reported on health-related quality of life, institutionalisation, and on outcomes relevant to relatives.

Regarding the comparison between galantamine and donepezil, neither studies included indicated a superiority of either drug in respect of effects on activities of daily living, accompanying psychopathology, and cognition. No comparative or clearly interpretable data were reported on health-related quality of life, institutionalisation, or outcomes relevant to relatives.

5.3.5 Sensitivity analyses

After compilation of the available data, it was shown that the studies included in the meta-analyses mostly had minor deficiencies. With regard to the outcomes for which sufficient studies were included in the meta-analysis to perform a meaningful sensitivity analysis (after

the assessment of statistical quality), the studies showed homogeneous results; this particularly applied to cognitive function. Therefore, a corresponding sensitivity analysis was not performed. Besides ITT analyses, some studies also presented results of per-protocol analyses. The results of the meta-analyses based on per-protocol analyses mostly showed slightly more positive effects in favour of the interventions. As the deviations from the meta-analyses for ITT data were irrelevant in all cases, the results are not presented in this report.

5.3.6 Subgroup analyses

In view of the data reported in the individual publications within the framework of a meta-analysis, the performance of subgroup analyses (as planned in the report plan; see Section 4.4.5) was not possible (except for dose-effect relationships). In the following text, the results from published subgroup analyses are therefore presented as supplementary information. For donepezil, a meta-analysis of individual patient data from 10 studies was available, of which 5 lasted 24 weeks and were assessed within the framework of this evaluation [100]. In a further publication, data from 4 studies on donepezil were pooled [97]. Data on galantamine from Raskind 2000, Tariot 2000, Wilcock 2000, and Rockwood 2001[16] were summarised and analysed [94,95,101]. Furthermore, post-hoc analyses of single studies were performed [74]. For rivastigmine, several pooled analyses were also available in which data from Corey-Bloom 1998, Rösler 1999, and B351/B304 were analysed [91,93,96,99], as were reanalyses of single studies [77,81,84,85]. All subgroup analyses presented below were not recognisably planned a priori, so that a post-hoc character of the analysis must be assumed. The evidential value is further limited by the fact that no statistical interaction test was performed in any publication; only the group differences observed between the respective subgroups were compared. Therefore, the results can at best be seen as indications for generating hypotheses, but not, however, as conclusive evidence; for this, they would need to be reproduced in specifically planned studies.

5.3.6.1 Gender

Gender-specific analyses were only reported for donepezil [100]; no differences between men and women were shown. Therefore the data basis was insufficient to evaluate ChEIs regarding this issue.

5.3.6.2 Age

In the pooled analyses and post-hoc analyses available, age groups were defined differently. For donepezil [100] and galantamine [94], the patients investigated were dichotomised at an age limit of 80 years. For rivastigmine, the limit was 75 years [99]. The publications did not provide indications of clear differences in efficacy between subgroups. The detected effects

[16] Due to too short an observation period (3 months), Rockwood 2001 was not included in the evaluation.

on the NPI in younger patients found in a re-analysis of the study comparing rivastigmine and donepezil [84] could not be distinguished from differences between treatment groups already evident at baseline.

5.3.6.3 Severity of dementia (mild and moderate)

In a pooled analysis on donepezil [100] it was reported that an advantage in the ADAS-cog for donepezil (5 mg or 10 mg) versus placebo was shown, independent of disease severity. However, no data in this regard were presented. In several analyses on galantamine [74,95,101], subgroups according to disease severity were formed (in each case, with different methods of operationalisation). These analyses indicated that the treatment effect in more severely impaired patients was more noticeable than in less severely affected patients. Similar indications were also shown for rivastigmine [93,96].

5.3.6.4 Doses of cholinesterase inhibitors

In the present evaluation, stronger efficacy regarding cognition was shown for donepezil 10 mg daily than for a 5 mg or flexible dose (5 to 10 mg). This dose-effect relationship was confirmed by a meta-analysis of individual patient data [100]. An association with the dose level was also shown for the occurrence of adverse events [97] (see also Section 5.3.1.7). No statements on dose-dependent efficacy differences can be made for other therapy goals, as no summarisable data from studies using different doses were available. As described above, galantamine had comparable efficacy in doses of 16 and 24 mg; the 8 mg dose was not effective. In the present evaluation, rivastigmine showed greater effects in a higher dose (6–12 mg) than in a lower dose (1–4 mg). This dose-effect relationship was confirmed by a pooled analysis [91]. A difference between high-dose and low-dose rivastigmine was also shown regarding the adverse event rate.

5.3.6.5 Existence of different concomitant diseases

In all ChEI studies, according to the inclusion and exclusion criteria, patients were not allowed to have an active concomitant disease that could have endangered the completion of the study. In some studies, concomitant diseases or therapies leading to exclusion were listed separately (e.g., asthma/COPD, active stomach ulcers, insulin therapy, micturition disorders, and diseases that may lead to a cardiac syncope). Due to the similar mode of action and the lack of comparative studies regarding qualitative differences in interaction, a differential medical indication for the different ChEIs based on comorbidity cannot be inferred.

Some published subgroup analyses investigated treatment effects in patients with risk factors that may also point to the existence of mixed dementia. In a re-analysis of studies on rivastigmine, no clear differences in treatment effects were shown in patients with or without vascular risk factors (operationalised by means of the modified Hachinski Ischaemia Scale

[77]), as well as between patients with and without hypertension [81]; nor did the post-hoc analysis of the study comparing rivastigmine and donepezil show clear indications of differential efficacy regarding patients with possible Lewy body dementia [85].

5.4 Summary

In the present report, 27 studies with a total of 9883 randomised patients were included in order to compare the ChEIs donepezil, galantamine, and rivastigmine with placebo or with each other (Table 43). Studies comparing ChEIs with other drug and non-drug interventions approved and available in Germany were not identified.

Table 43. Number of studies included and patients randomised

Drug	**Number of studies**	**Patients randomised**	
Donepezil	12	5 mg	561
		(5-) 10 mg	347
		10 mg	821
		Placebo	1276
		∑	3005
Galantamine	6	8 mg	140
		16 mg	279
		16-24 mg	711
		24 mg	893
		Placebo	1201
		∑	3224
Rivastigmine	4	1-4 mg	476
		2-12 mg	456
		6-12 mg	564
		Placebo	720
		∑	2216
Direct comparative studies			
Galantamine vs. donepezil	1		188
Rivastigmine vs. donepezil	3		1149
Rivastigmine vs. donepezil vs. galantamine	1		101
∑	27		9883

The quality of the study publications was mainly mediocre, and in some cases poor. This assessment is in particular based on the lack of transparency in the presentation of patient flows and the lack of the consistent implementation of the ITT principle. In some studies, the proportion of patients not analysed, even though randomised in the analysis of primary outcomes, was at least 11% (rounded off), which was clearly a relevant deviation from the

ITT principle. For some secondary outcomes, this proportion was even higher. Four of the 5 studies comparing the different ChEIs with each other were not double blind, which per se in this area must be regarded as a major deficiency of design.

Except for 2 studies (both on donepezil; duration in each case about 1 year), all comparisons with placebo only had a maximum treatment or observation period of 26 weeks. Even if the longer studies did not in principle show different results, robust conclusions can in essence only be made for the 6-month period. In contrast, 3 of 5 studies comparing different ChEIs with each other lasted a year or longer. On the other hand, these studies (except for one on donepezil and rivastigmine), besides having limited validity due to an unblinded design, had sample sizes too small to detect differences or to demonstrate comparability.

Comparisons with placebo

The results from studies comparing donepezil, galantamine, and rivastigmine with placebo are summarised in Table 44. In all studies, a dose-dependent effect was observed: in the low-dose range, galantamine and rivastigmine (in contrast to donepezil) had no or uncertain efficacy. No noticeable difference was shown between galantamine 16 mg and 24 mg. A dose-effect relationship was confirmed regarding the adverse event rates reported in the studies.

There are indications of a favourable effect of all 3 drugs on the therapy goal "activities of daily living" in the medium and/or high dose range. The average effects detected by means of meta-analyses were about 3 points in the DAD and PDS scale for galantamine and rivastigmine. Corresponding estimates for donepezil cannot be inferred with sufficient certainty, as one must assume an overestimation of the effect in the relevant meta-analysis. Nevertheless, an indication of a favourable effect may also be assumed for donepezil.

In respect of accompanying psychopathology, no indications of a favourable or unfavourable effect through donepezil or rivastigmine can be inferred (regarding donepezil, due to unconvincing data; regarding rivastigmine, due to a lack of data). In contrast, there is an indication of a positive effect for galantamine; however, this effect (about 1 to 2 points on the NPI scale) can be classified as minor.

Table 44. Summary of results on therapy goals from placebo-controlled studies

Therapy goal	Donepezil	Galantamine	Rivastigmine
Patient-relevant therapy goals			
Activities of daily living	↑	↑	↑
Psychopathological symptoms	⇔	↑	No data available
Cognitive function	↑↑	↑↑	↑↑
Health-related quality of life	⇔	No data available	No data available
Nursing home care (institutionalisation)	No data available	No data available	No data available
Mortality	(⇔)	(⇔)	(⇔)
Adverse events	↓↓	↓↓	↓↓
Therapy goals relevant to relatives			
Quality of life of (caregiving) relatives	⇔	↑	No data (or only uncertain data) available
Degree of care provided	⇔	↑	No data available
Additional information			
Clinical disease stage	↑↑	↑↑	↑↑
Dose-effect relationship			
	Lower efficacy (cognition) and fewer adverse effects for low (5 mg) or flexible dose	No favourable effect, and not consistently more adverse effects with the 8 mg dose; otherwise no differences	Uncertain effect for 1–4 mg

↑↑, ↓↓ = Evidence of a favourable or unfavourable effect.
↑, ↓ = Indication of a favourable or unfavourable effect.
⇔ = No indication of a difference
( ) = Few data available

The 3 ChEIs investigated showed a benefit regarding a favourable effect on cognition compared with placebo. This effect was about 2 (donepezil 5 mg or flexible dose) to 3 points (donepezil 10 mg, galantamine, rivastigmine) on the ADAS-cog scale.

Data on the therapy goal "health-related quality of life" were only available in 2 studies on donepezil, which did not provide a clear indication of a favourable or unfavourable effect. No such data were reported for galantamine or rivastigmine in the studies.

No (interpretable) data were available for the therapy goal "placement in a nursing home (institutionalisation)".

Overall, only few deaths were reported in the studies; therefore no indications can be inferred of a favourable or unfavourable effect on mortality.

Higher study discontinuation rates due to adverse events were reported in the higher dose range for all 3 drugs. Furthermore, higher adverse event rates occurred that were consistent with the mode of action of ChEIs (e.g., nausea, vomiting, diarrhoea). There was no indication of a larger proportion of patients experiencing serious adverse events with ChEIs than with placebo; however, as a limitation it should be noted that reporting in this regard was in part insufficient. No statements can be made on rare or long-term adverse events, due to the study designs and reporting methods.

For donepezil, no indications of a favourable or unfavourable effect on quality of life of caregiving relatives can be inferred from the available data. For galantamine, there is an indication of a positive effect; however, with a dimension of 1/10 of a standard deviation, it can be classified as minor. No data on rivastigmine were found in this regard.

There are indications that data on rivastigmine concerning the therapy goal "degree of care" were collected in all 4 larger Phase III studies. However, these data have not yet been published, so that no conclusions in this regard can be made. For mainly methodological reasons, the data on donepezil are not very robust; therefore, neither do they provide indications of a favourable effect on caregiver time. A positive indication in this respect is available for galantamine in one study.

The global clinical impression was consistently improved by all substances.

For galantamine and rivastigmine, there are indications that the treatment effect was greater in more severely impaired patients than in those less severely impaired. No such differentiated statements can be made for age, gender, and comorbidity.

Comparisons of ChEIs with each other

The results of the studies comparing the different ChEIs with each other are presented in Table 45.

Table 45. Summary of results on therapy goals from comparative studies on ChEIs

Therapy goal	DON vs. GAL	DON vs. RIV	GAL vs. RIV
Patient-relevant therapy goals			
Activities of daily living	(⇔)	(🡻)[a]	No data available
Psychopathological symptoms	(⇔)	⇔	(⇔)
Cognitive function	(⇔)	⇔	No data available
Health-related quality of life	No data available	No data available	No data available
Placement in a nursing home (institutionalisation)	No data (or only uncertain data) available	No data available	No data available
Mortality	(⇔)	⇔	No data available
Adverse events	(⇔)	🡹🡹	(⇔)
Therapy goals relevant to relatives			
Quality of life of (caregiving) relatives	No data available	No data available	No data available
Degree of care provided	No data available	No data available	No data available
Additional information			
Clinical disease stage	No data available	No data available	No data available
Comments	In the larger study, possibly less favourable dose for DON	Possibly less favourable dose for DON	

a: Results affected by high discontinuation rates.

🡹🡹, 🡻🡻 = Evidence of a favourable or unfavourable effect.
🡹, 🡻 = Indication of a favourable or unfavourable effect.
⇔ = No indication of a difference
( ) = Few data available

DON = donepezil, GAL = galantamine, RIV = rivastigmine

A quantitive summary (meta-analysis) of comparative results on single outcomes was inappropriate, due to the limited number of studies available and due to the (in part) different methods of operationalisation. Only 2 of the 5 studies had a sample size that was sufficiently large to detect moderate differences between treatment groups.

For donepezil versus galantamine, neither study included provided a clear indication of a superiority of either drug concerning the effect on activities of daily living, accompanying psychopathology, cognition, and therapy-related adverse events. No comparative or clearly

interpretable data were reported for health-related quality of life of patients, institutionalisation, and outcomes relevant to relatives.

For donepezil versus rivastigmine, data from one study indicated a slight superiority of rivastigmine with regard to the effect on activities of daily living (effect estimate in the dimension of about 1/10 of the standard deviation); however, for methodological reasons, the validity of these data is doubtful. There was no clear indication of a difference between these 2 drugs in respect of accompanying psychopathology, cognition, and mortality. Substantially higher adverse event rates occurred under rivastigmine, in particular concerning nausea, vomiting, loss of appetite and weight. No comparative data were reported on health-related quality of life and outcomes relevant to relatives.

For galantamine versus rivastigmine, only results of a 3-arm comparison with very low sample sizes were available. In this comparison, no differences were noticeable with regard to the effect on psychopathological outcomes and the occurrence of adverse events. No data were available for other therapy goals.

Overall, in the comparative studies, no evidence of the superiority of one drug over the other can be inferred from the non-existing or at most minor differences (which were of some uncertainty) for efficacy parameters. However, nor can the results be interpreted as showing comparability between drugs, as the studies were not recognisably designed as equivalence or non-inferiority studies with an a priori definition of "irrelevant differences".

On the basis of the available data, statements can hardly be made on single subgroups of patients. It was noticeable that in nearly all studies, patients with clinically serious or uncontrolled internal diseases were excluded, so it is unclear whether the results are generally transferable to this patient population.

6 DISCUSSION

The 3 approved ChEIs donepezil, galantamine, and rivastigmine triggered cholinergic gastrointestinal adverse effects, which can be explained by their mode of action. These effects occurred particularly often (but not only) in the dose-increase phase. Depending on the drug and adverse event, 5 to 10% (donepezil), 5 to 20% (galantamine), and 10 to 40% (rivastigmine) of patients were affected.

On the other hand, for cognition, a consistent benefit versus placebo was shown, with an effect strength of about 0.5 standard deviations, which corresponds to about 3 points on the ADAS-cog scale. A possible benefit of ChEIs in further well-investigated areas was shown. Minor effects (activities of daily living) or minor and inconsistent effects were shown (galantamine: accompanying psychopathological systems and degree of care provided). Beyond this, no data or no interpretable data were found for other areas defined in the report plan referring to patient-relevant benefits. The fact that the clinical global impression was consistently improved by all 3 drugs is probably primarily due to their effects on cognition.

On the whole, the results of the present report are supported by current systematic reviews and HTA reports on this topic [49,108-113]. Differences at best exist in the quantitative classification of the indications found regarding a favourable effect on daily living skills and accompanying psychopathological symptoms.

Only one systematic review by Kaduszkiewicz et al (2005) came to a much more critical assessment [114,115]. This was justified by the major methodological deficits of the primary studies in view of only minor observed effects. Even though the present report in some cases identified major deficits regarding study and publication quality, and therefore queried the validity of single study results, a negative assessment solely based on these deficits does not seem appropriate, particularly as the relevance of single methodological points of criticism by Kaduszkiewicz et al may be questioned [116].[17]

The classification of the clinical relevance of the efficacy outcomes is problematical; particularly when considering adverse effects, which were in part considerable. If there are changes in a scale, what does a difference in the mean value of 3 points mean? A common argument in this regard refers to the range of the scale: as this, for example, comprises 70 points in the ADAS-cog scale, it is stated that a difference of 3 points is presumably not relevant. This line of argument is unconvincing, as in this case the range of the whole scale

[17] See also a response by the authors [117].

(the theoretical range) is not of interest, but the range that is actually made use of, i.e. ultimately the variability in the population to be investigated.[18]

The reference to a "minimal clinically important difference" (MCID) following requirements by regulatory authorities or from the literature is also not usually helpful. Such MCIDs are often defined as an individual response criterion and not as a range of irrelevance for group differences. For example, for the ADAS-cog, the FDA suggested a MCID of 4 points following a survey among experts (see [70,75,114]); if the situation arose where such an individual improvement on this scale existed, one therefore could speak of a benefit to the individual patient. Under the simplified assumption that the changes in ADAS-cog can be approximated by a normal distribution, and by applying the variability range of about 6 points for these changes (simple standard deviation, approximate median observed in the studies), as well as by making assumptions about the mean changes in the placebo group, the comparison of mean values can be recalculated to a comparison of (binary) response rates (see Table 46). A few publications reported results of responder analyses on the basis of empirical data (donepezil: Rogers 1998; galantamine: Erkinjuntti 2002, Raskind 2000, Tariot 2000, Wilcock 2000; rivastigmine: B304, Rösler 1999). The results of these empirical analyses (except for those from Rogers 1998) are highly consistent with results inferred theoretically.

This type of presentation of results leads to differences in response (success) rates between about 13 and 16 percentage points (improvement in the ADAS-cog by 4 points). The differences in the effect on daily living skills and, as far as recognisable, on psychopathological symptoms, are however substantially lower. With an optimistic estimate of a standardised mean difference of about a quarter standard deviation for activities of daily living, a difference in response rates of about 7 to 8 percentage points can be assumed if similar response criteria to the ADAS-cog (standard deviation of two thirds) apply.

[18] For example, one presumably would not ignore a difference in mean values of 10 kg body weight when comparing 2 weight-reducing interventions, just because the weight of adults in extreme cases can range between 35 and 350 kg.

Table 46. Estimated and observed proportion of responders for the ADAS-cog (response criterion: 4 points)

Group	**Change**	**Proportion of responders (%)**	**Change**	**Proportion of responders (%)**	**Study**
	Assumed	Estimated	Observed	Observed	
Test drug	-1.5	34	-1.1	54	Rogers 1998 (DON, 10 mg)
Placebo	+1.5	18	+1.8	27	
			-0.8	35	Erkinjuntti 2002 (GAL, 24 mg)
			+1.7	22	
			-1.9	34	Raskind 2000 (GAL, 24 mg)
			+2.0	17	
			-1.4	37	Tariot 2000 (GAL, 24 mg)
			+1.7	20	
Test drug	0.0	25	-0.5	29	Wilcock 2000 (GAL, 24 mg)
Placebo	+3.0	12	+2.4	15	
			-0.3	24	Rösler 1999 (RIV, 6-12 mg)
			+1.3	16	
			-0.2	23	B304 1998 (RIV, 2-12 mg)
			+2.8	13	
Estimated proportion of responders (assuming a normal distribution and a standard deviation of 6 points). DON = donepezil, GAL = galantamine, RIV = rivastigmine					

Even if such a form of presentation may seem easy to interpret, the question remains as to what a response (i.e. the change in an abstract score by a certain amount) directly and noticeably means for the individual patient. This question has still not been finally answered, and presumably will hardly be answered on the "score level" alone. Therefore, it may be helpful to approach the issue of the clinical relevance of effects of anti-dementia drugs by means of other outcomes.

The most recent study on galantamine included in this report (Rockwood et al [71]) used the degree of reaching individually determined goals, measured with the Goal Attainment Scale (GAS), as a primary outcome. For this purpose, aims in the areas cognition, function, behaviour, leisure time and social activities were defined by clinicians on the one hand and patients and relatives on the other with this scale, and later compared with the change versus baseline. The GAS is therefore an individualised outcome measure, which, depending on which outcomes were defined, covers various areas of life. In the ITT analysis, after 4 months an increased GAS score in the galantamine group was shown both in the assessment by patients/relatives and by clinicians (effect strength [standardised mean difference]: 0.20

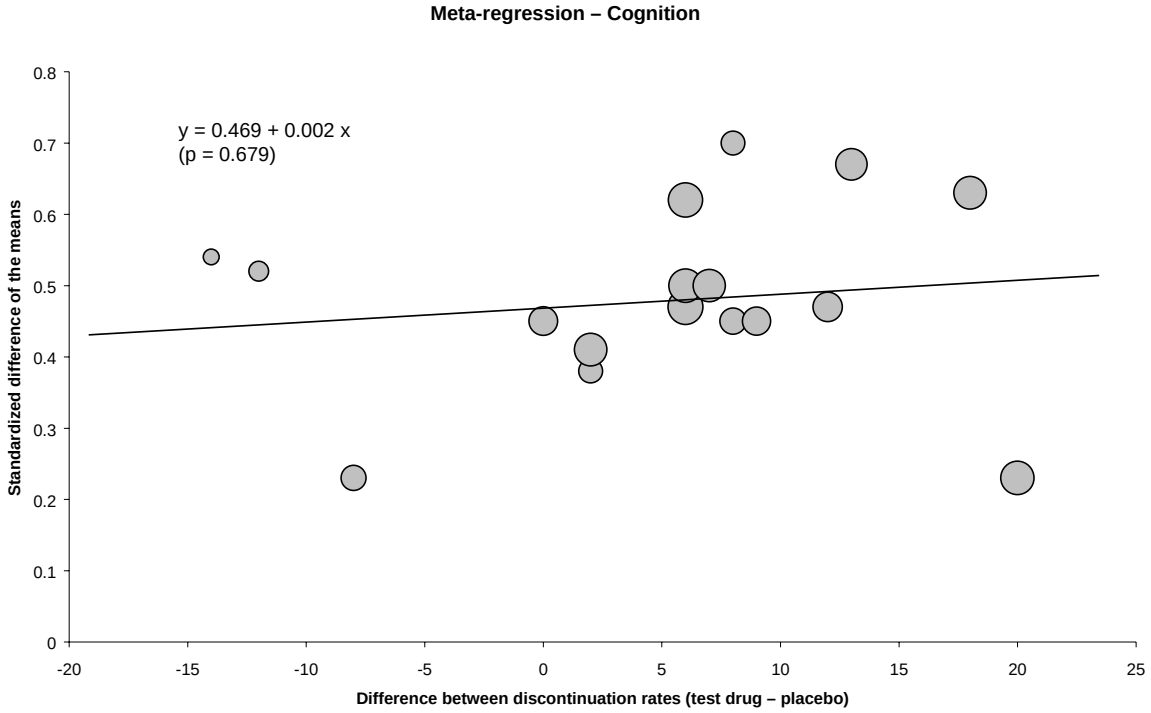
[patients/relatives] and 0.45 [clinicians] standard deviations). However, the difference compared with placebo was only statistically significant for goals defined by clinicians. The results regarding the change in DAD (activities of daily living) and ADAS-cog scale corresponded approximately to those of the other studies on galantamine. Even if a different way of presenting results would also have been desirable here, for example, stating the proportion of patients who (possibly differentiated according to various areas) had achieved the goals, such an outcome criterion approaches interpretability in respect of the immediate and noticeable interests of patients. Furthermore, it seems to be advantageous that negative consequences of an intervention (adverse effects) can also be considered, and that therefore a weighing of benefits and harms is made easier. Finally, a dichotomised presentation of results (proportion that achieved/did not achieve goals) would be a simple possibility to model missing values in an interpretable manner within the framework of sensitivity analyses.

The last aspect (handling of missing data in the analysis) is of special relevance in studies on ChEIs, as on the one hand a consistent implementation of the ITT principle was rarely observed, and on the other, the replacement strategy by means of the LOCF method (carrying forward the last observation) has repeatedly been the reason for methodological criticism [114]. This is based on the assumption that for a disease that deteriorates progressively, the early discontinuation of patients (e.g., due to adverse effects) may induce bias by carrying forward results that are still favourable at this point. Even though this assumption is plausible, it should be supported by empirical data (especially considering the comparatively abundant data) before it leads to a devaluation of the results obtained.

In the placebo-controlled studies included in the present report, median discontinuation rates of 22 percentage points were observed in the test group (range: 0 to 35%; without the study by Tune 2003: 14 to 35 %), and corresponding rates of 17 percentage points were observed in the placebo group (11 to 33%). About half of discontinuations in the test group were due to adverse events; under placebo, this proportion was 44% (median). Even though at the end of study, outcomes were not documented for all patients who discontinued medication, the replacement of missing values (by means of the LOCF method) is undoubtedly a problem. In particular, it remained unclear whether in cases of discontinuation where, even though a value was available at the end of study (retrieved drop outs, RDO), the value at the time of discontinuation was nevertheless carried forward.

The therapy effects observed in the available studies, for example for the outcome "cognition", showed no association with discontinuation rates (this also applied to differences in discontinuation rates between test group and placebo) (Figure 48). In a post-hoc analysis of 3 rivastigmine studies (Corey-Bloom 1998, Rösler 1999 as well as B351, which was not included in the present report), Farlow et al [118] assessed the subgroup of RDO patients. Patients who discontinued showed deterioration in cognition throughout the course of the study (difference in the ADAS-cog score: Week 26 minus baseline). This deterioration was

more marked under placebo than under rivastigmine, so that in these patients the application of the LOCF method may have led to a conservative bias of results. The limitation should be noted that only just under a third of all patients who discontinued were RDO patients, so that two thirds of patients could not be considered in this analysis, and that the ADAS-cog value was not assessed at the time of study discontinuation.



For multiple-arm studies, in each case the test group with the highest dose was chosen.

Figure 48: Association between the effect observed on cognition in placebo-controlled studies and the difference in discontinuation rates between test group and placebo group

The theoretical criticism of the methodology regarding the replacement of missing values in the studies included in the present report is therefore not supported by empirical data. Nevertheless, sensitivity analyses by means of other replacement strategies [119] would be desirable in order to give a better estimate of the robustness of the results.

Incidentally, the adverse effects of ChEIs observed in many patients may serve a different argumentation. Insofar as such adverse effects do not lead to study discontinuations, it may be speculated that they have a detrimental effect on the therapy goal "activities of daily living", so that the potential benefit of the drug might be greater if adverse effects were milder. This speculation, too, is hardly supported by empirical data from the present report; nor is it supported in the opposite direction, i.e. that higher discontinuation rates (overall or with the test drug vs. placebo) are associated with higher treatment effects.

The AD2000 study (sponsored by the British NHS), which assessed the effects of donepezil in a real-life setting, could not be included in the present evaluation. The primary outcome of

this study was the time to placement in a nursing home or to a defined loss in activities of daily living. The data and analyses presented in the publication on both of these, in principle highly relevant, primary outcomes were not interpretable for methodological reasons. This assessment has been shared by other systematic reviews [49,114] and has also recently been explained in detail elsewhere [120,121]. Several queries to the authors concerning these reservations remained unanswered.

In summary, for the future assessment of the potential beneficial and detrimental effects of ChEIS, it would be desirable to specifically identify those patients who experience a larger benefit, and those who do not benefit from ChEI therapy. The indication inferred from post-hoc subgroup analyses that more severely affected patients with dementia may benefit more than those less severely affected should be verified in future studies. Such results may possibly be explained by a difference in the sensitivity to change of the scales applied, depending on the disease severity of patients. A restriction of the medical indication for ChEIs to specific stages of disease severity cannot therefore be certainly inferred from the available data. Furthermore, longer-term studies would be welcomed, and outcomes should be used that immediately and noticeably reflect a benefit to patients.

Written comments and the scientific debate

A total of 17 substantial comments were submitted within the framework of the written hearing on the preliminary report of the present evaluation (see Appendix I). The persons submitting comments were invited to discuss unclear aspects of the comments in an oral scientific debate; representatives for all submitted comments attended (see Appendix H).

A total of 180 citations were quoted in the comments. Two RCTs and a meta-analysis were pointed out that had not been considered in the report (see comments; SN Gutzmann, SN Eisai, SN Pfizer, SN Wille). In Holmes 2004 [122], the controlled treatment phase only lasted for 12 weeks. Winblad 2006 [123] only investigated patients with severe Alzheimer's disease (MMSE 1-10). Therefore, for consideration in the present evaluation both publications did not fulfil the inclusion and exclusion criteria defined in the underlying report plan. The meta-analysis by Trinh 2003 [124] had already been screened for further relevant studies before the publication of the preliminary report (see Appendix C: list of screened systematic reviews).

The comments focussed on 6 main points of discussion, which were discussed in detail in the oral scientific debate. These points are presented and discussed in the following text.

- Study selection (duration and design)

The selected inclusion criterion for study duration was criticized in several comments. In some comments it was noted that shorter studies (≥ 12 weeks) should also have been included (see Appendix I; e.g., SN Eisai, SN Grass-Kapanke, SN Maier). In other comments it was stated that only longer-term studies (≥ 6 months) should have been considered (SN von Maxen, SN Wille) or that the choice of this inclusion criterion was arbitrary. The selected procedure, the inclusion of studies with a controlled observation phase of at least 16 weeks,

was based on a pragmatic decision. EMEA requires a study duration of at least 6 months [42]. However, on the other hand, regarding the individual course of therapy, it is assumed that a change compared with the spontaneous course of disease may already be evident earlier [43]. For donepezil and rivastigmine, this aspect in irrelevant for the present report: all studies included on donepezil lasted at least 6 months and, for rivastigmine, only one shorter study was available (Forette 1999; 18 weeks), which however did not provide interpretable data on the aspects "cognition" and "activities of daily living". Regarding galantamine, a procedure following EMEA would have led to the exclusion of 2 studies from the evaluation (Rockwood 2006 [4 months]; Tariot 2000 [5 months]). A sensitivity analysis in this regard showed that even after exclusion of these studies, almost identical estimates in the areas "cognition" and "activities of daily living" were achieved.

Within the framework of the submission of comments on the preliminary report, it was criticised that only RCTs were included in the evaluation (see comments: e.g., SN Gutzmann, SN Janssen-Cilag, SN Novartis, SN Pfizer, SN Wahler). In particular, it was noted that data from uncontrolled open-label follow-up phases, as well as comparisons with historical controls, should have been considered.

The present report was solely based on RCTs, as these are associated with the lowest uncertainty of results. A structural equality of groups, also regarding unknown confounders, can only be ensured by randomisation [125]. When assessing study phases from uncontrolled follow-up phases, the observed course under treatment cannot be distinguished from the natural course of disease; therefore the treatment effect cannot be assessed. The use of a historical control group, for example, leads to serious methodological problems due to the unclear comparability between the treated and untreated group.

The approach to consider only RCTs corresponds to international standards in research on ChEIs in Alzheimer's disease, and was also applied correspondingly in recent HTAs/systematic reviews [49,108,112]). For example, the recommendations on ChEIs in the guideline by the Scottish Intercollegiate Guidelines Network, differing from the presentation in the comments by Janssen-Cilag, were only based on data from RCTs (see comments: SN Janssen-Cilag; and [126]).

- Evaluation of single aspects of study design

In the comments on the preliminary report it was criticised that the aspects of the randomisation process, concealment of allocation to treatment groups, as well as blinding, were insufficiently reflected in the overall evaluation of study quality (see comments: SN von Maxen, SN Wille).

However, additional information provided by manufacturers in the comments largely clarified previously unclear aspects on main quality issues described in the preliminary report. In the written comments, the manufacturers Eisai and Janssen-Cilag explained that a computer-generated and central randomisation process was performed in all studies they conducted. The allocation of patients took place via randomisation numbers on the study medication, which in

each case was of identical appearance and packaging. On the basis of this information, allocation concealment was assessed as being adequate in most studies. The same applied to the information provided on the randomisation process.

The comments referred to methodological papers in which, for example, an overestimation of effects by 41% and 30% was demonstrated in cases of non-existing concealment and unclear concealment respectively (see comments: SN von Maxen, SN Wille). In view of the additional information provided by manufacturers, this problem of a possible overestimation of the effect by inadequate concealment is obviously hardly relevant in the underlying studies of the present report. Furthermore, when interpreting the data provided in the comments, it needs to be considered, for example, that the publication by Schulz refers to 33 meta-analyses in the area of obstetrics, which included 250 studies conducted between 1955 and 1992 (nearly 30% of these studies were conducted before 1980) [127]. Although the assessment of studies with adequate and unclear allocation concealment (under consideration of further quality aspects) showed a relative increase in therapy effect of 30% in studies with unclear allocation concealment, this relationship differed substantially in the individual meta-analyses and, according to the authors, should not be interpreted as a general value. In particular considering the age of the studies included and the limitation to the area of obstetrics, one may assume that – if at all – only few of these studies were relevant to approval procedures in the sense of the drug law and therefore conformed to GCP standards. Therefore, transferability to the studies included in this report is questionable.

Whereas (except for a few direct comparative studies) all studies were double-blinded, the blinding of outcome raters was hardly described in many publications. In the comments on the preliminary report, the manufacturers also provided information on this aspect and described the usual procedure. In this context, the companies stated that the CIBIC-plus was always evaluated by an independent rater who did not have access to any other information regarding patients (see comments: SN Pfizer, SN Janssen-Cilag on Tariot 2001, SN Novartis). Regarding the assessment of ADAS-cog, the requirements in the studies were evidently less strict. In this context, in the scientific debate, representatives of Novartis reported that this rating was usually performed by psychologists who did not normally have contact with the ward and often had no contact whatsoever with patient files (see minutes, Appendix H). It was outlined in the comments by Eisai that the ADAS-cog was not usually assessed by the main investigator, but by a different member of the study team, mostly before other assessments were made (see comments: SN Eisai). A formal blinding of the ADAS-cog raters was therefore not necessary, particularly as these persons generally did not have access to other study results (see comments: SN Eisai). For Tariot 2001, Janssen-Cilag outlined in its comments that the ADAS-cog rater was not involved in treatment and was not to have access to information on adverse events. If this was not possible, the rater performed the ADAS test before he or she documented adverse events (see comments: SN Janssen-Cilag). No additional information was provided by the manufacturers in their comments on the blinding of the outcome rating of activities of daily living or neuropsychiatric symptoms.

Therefore, in most studies, the blinding status regarding the rating of the outcomes defined as relevant to this report was not completely satisfactory and in these cases, on the basis of this information, was therefore classified with a limited "(yes)" within the framework of the quality assessment.

- Handling of missing values

Assessment of the implementation of the ITT principle

The ITT principle, i.e. the complete analysis of all randomised patients in the groups they were allocated to according to the randomisation code, is an important quality criterion in the assessment of clinical studies. This is the only way to prevent the structurally equality of groups achieved by randomisation from being destroyed by the non-consideration of patients with prognostically relevant characteristics. In the preliminary report, the implementation of the ITT principle was therefore assessed to be an essential quality criterion, and corresponding limits were set regarding the tolerated non-consideration rate. It was criticised in the comments that the percentages of 10.5% (for the overall proportion of missing patients in the [main] analysis) and 4.5% (for the absolute difference in the proportion of missing patients) seemed arbitrary and unfounded; with the same right, one could equally have set a limit of 4, 12, or 20% (see comments: SN Arznei-Telegramm, SN Kaduszkiewicz). In fact, no clear limits are determined in the literature. For example, in the Cochrane Handbook it is also noted that the evaluation of results from studies with more than minimum amounts of missing values is ultimately a question of judgement ([125], p. 113). As a "rule of thumb", Schulz and Grimes (2002) noted that missing data of less than 5% were usually less critical, but that a rate over 20% could seriously question the validity of the data [128]. They did not define a "still tolerable" limit for the differential loss of data, but noted that this type of missing data was even more problematical. Therefore, in a certain sense, the determination of a limit must be arbitrary. For the present report, it was assumed that a non-consideration rate of a least 11% (rounded off) was to be regarded as critical, just like a difference in the consideration rate between groups of at least 5 percentage points (rounded off). In order to consider the usual ways of rounding off (numbers over 10.5% and 4.5% rounded off to 11% and 5% respectively) in the preliminary report, numbers were reported including the digit after the decimal place. The sensitivity analyses for the ADAS-cog showed that due to the great homogeneity of study results, a moderate shift of the limits upwards or downwards did not lead to a change in the fundamental conclusion. For donepezil, a moderate shift of this limit for the non-consideration rate (see Section 4.3) would initially affect the studies by Gauthier 2002, Rogers 1998, and Krishnan 2003. A meta-analysis excluding studies that would thereby be assessed as having major deficiencies did not lead to a relevant change in the pooled estimate (-0.45). For galantamine, this would affect the studies by Brodaty 2005 and Tariot 2000; the non-consideration of these studies in the meta-analysis would result in a similar pooled estimate (-0.55). Even if stricter limits applied, no further studies on rivastigmine would be affected.

LOCF as a replacement strategy – Meta-regression

In the preliminary report, using the LOCF method as a replacement strategy regarding a disease that deteriorates progressively was a matter of discussion. In this context, it is assumed that, by using the LOCF approach, study results may be biased in favour of the test intervention if patients prematurely discontinue the study (in particular due to adverse events) (see p. 188). In his comments, Kaduszkiewicz criticised the meta-regression that was performed to assess the effect of the differential discontinuations in the present report and compared this regression with his own meta-regression (see comments: SN Kaduszkiewicz). In this process, studies that had been assessed as having "major deficits" in the preliminary report were not included. The justification provided was that that the assessment was mainly based on ambiguities or substantial deviations from the ITT principle, which may have grossly falsified results (see comments: SN Kaduszkiewicz). This modified meta-regression now resulted in a statistically significant association between the difference in discontinuation rates and the effect size. Our own re-analyses showed that this difference in the results was primarily due to the non-consideration of the study by Rösler 1999. In view of the fact that the inclusion or exclusion of single studies changes the result so noticeably, the instability and therefore limited evidential value of this analysis becomes clear. However, both meta-regressions (with equal discontinuation rates) showed a treatment effect of more than 0.4 standard deviations, which was only slightly lower than the globally estimated effect of 0.5 standard deviations. Consequently, this analysis also does not contradict the conclusion of the report.

Irrespective of this, a complete coverage of all patients should be required for future studies. Although different replacement strategies as an alternative to LOCF are discussed (e.g., multiple imputation methods [129]; see also comments by Eisai on the re-analysis of the study results by Rogers 1998: SN Eisai), ultimately it should be noted that the unavailability of information cannot be compensated by post-hoc evaluation methods. To tackle such problems and ensure that the potential loss of data is as low as possible, one possibility would be to decrease the effort for patients of participating in a follow-up by choosing pragmatic and less complex assessment instruments.

- Relevance of the CIBIC-plus

Some persons submitting written comments criticised that the CIBIC-plus was downgraded; this was not correct from a clinical point of view, as this instrument was specifically developed to assess clinically relevant changes (see comments: e.g., SN Burns, SN Eisai, SN Maier, SN Pfizer).

In the report plan of the present evaluation, the outcome "clinical disease stage according to the clinical impression" was not defined as a patient-relevant outcome. Nevertheless, the corresponding results were presented as supplementary information according to an amendment. By doing so, among other things, the fact is taken into account that "global response" is defined as one of the 3 relevant domains in the drug approval procedure [42].

Because of fundamental issues regarding the relevance to patients of instruments used to assess the global clinical impression (the CIBIC-plus was applied in most studies) the results were not primarily considered in the evaluation. These fundamental issues have also been discussed in detail by the Canadian Coordinating Office for Health Technology Assessment [130], which also reached the conclusion that such measures were not suitable as outcomes. Among other things, the criticism referred to the fact that, depending on who assessed global improvement (physicians, nurses, or relatives), different areas were focussed on (cognitive function, degree of care required, behaviour or activities of daily living). Therefore, these instruments do not so much reflect the individual degree of global improvement but rather improvement in the area considered relevant by the respective rater. Further problematical aspects exist, specifically for the CIBIC-plus. For example, the assessment varies depending on the sequence in which patient and caregiver are questioned, with a more unfavourable assessment if the caregiver is interviewed first [130].

- Relevance of therapy goals relevant to relatives

Some persons submitting comments (see comments: e.g., SN von Lützau-Hohlbein, SN Möller, SN Maier) criticised that in the amendment to the report plan, therapy goals relevant to relatives were downgraded. In fact, in the present report, a distinction was made between such goals that were directly relevant from the view of patients themselves, and those where the main focus was on the perspective of relatives. This referred to the goal "quality of life of (caregiving) relatives", as well as "degree of care provided by one or several caregiver(s) or institution(s)". Results on these therapy goals are listed and presented in the report, but are not of primary interest in the evaluation. Even if such a distinction is not necessarily fully selective, it was made with the aim of expressing that the evaluation of the benefits and harms of an intervention refers to the patient perspective, and the direct benefit to patients is therefore of primary interest. This seemed necessary as, for example, at least theoretically, constellations are imaginable in which the needs of patients and those of relatives are not necessarily consistent (e.g. if sedation of the patient eases the burden of caregivers). It is desirable that an improvement in the patient's condition eases the burden and increases the quality of life of the caregiver; consequently, such outcomes are presented within the framework of the present report. However, improvement in the patient's condition is the necessary prerequisite for this and is therefore the prime focus of the evaluation. Anyhow, the quality and quantity of the evidence available for outcomes relevant to relatives is clearly weaker than for the effects on cognitive function or daily living skills of patients. A stronger consideration of these aspects would therefore not have led to a different evaluation of the ChEIs.

- ADAS-cog scale

In some comments it was criticised that the scores investigated in the studies were merely surrogates (see comments: SN von Maxen, SN Wille). The ADAS-cog scale was also discussed in detail in the oral debate.

The relevance of the ADAS-cog scale is inferred from the symptoms of Alzheimer's disease. Alzheimer's disease is primarily characterised by the occurrence of observable cognitive deficits that are associated with restrictions in patients' social and occupational abilities [18]. The cardinal symptom of disease is the development of multiple cognitive deficits, which are characterised by memory impairment and at least one further cognitive deficit (aphasia, apraxia, agnosia, or deficit in executive functions) [18]. The ADAS-cog scale comprises 11 items and subscales for the areas memory and orientation, language, and praxis [130]. It therefore represents important areas of Alzheimer's disease, even if single areas (e.g., deficits in executive functions) are not covered [130]. The symptoms represented by the scale allow discrimination between persons without cognitive impairment and those with Alzheimer's disease [28,130]. As these symptoms represent the core of the disease, it does not seem plausible merely to regard the scale as a surrogate. In this context, it was also criticised in some comments that a clinically relevant point difference was not defined a priori (see comments: SN von Maxen, SN Wille).

Regarding clinical relevance, the relevant literature generally refers to the FDA, which sees a reversal of the natural course of disease by at least 6 months as clinically relevant (e.g., [131,132]), even if this statement cannot be clearly inferred from the citation used.[19] This interval is commonly (e.g., [130,132]) equated with a change of 4 points on the ADAS-cog scale, referring to a study from 1988 [134]. However, in the study in question, the changes in the persons investigated actually referred to the ADAS total scale, so that such a difference cannot necessarily be equated to a corresponding difference on the ADAS-cog subscale. In a further longitudinal study on the progression of the cognitive subscale, a converse U-shape association between severity of disease and the extent of deterioration of patients was shown, with a mean change over 12 months of 9.6 points (SD = 8.2) in patients with Alzheimer's disease and practically no change (improvement of 0.2 points; SD = 2.0) in healthy controls [135]. It was reported in patients in placebo groups of clinical studies that progression with a deterioration of about 5 to 6 points within a year [136] was evidently slightly more favourable than progression in other samples [132]. For this reason (assuming a linear progression), the natural deterioration over a period of 6 months would be about 2.5 to 3 points in the ADAS-cog.

[19] This refers to meeting minutes of the Peripheral and Central Nervous System Drugs Advisory Committee. The following contribution comes closest to such a statement: "In polling a lot of physicians who treat Alzheimer's patients – at least this came out at our symposium several weeks ago – most physicians polled felt that a three- or four-month improvement was worth taking a drug for, and that something much less than that was probably not worth taking a drug for" (p. 227) [133].

Furthermore, there is currently no consensus on how large the difference in the ADAS-cog has to be in order to be considered clinically relevant (see comments: SN Arznei-Telegramm) – neither on the individual nor on the group level. It therefore seems plausible, besides drawing on the statistical classification of the detected treatment effect (a mean difference of 0.5 SD is generally seen as the mean effect size [137]), to draw on the criterion of the 6-month delay in disease progression.

If such an effect is transferred to the individual (patient) level (in the sense of a response definition), this corresponds to an (absolute) difference in responders of about 15 percentage points – measured by means of cognitive function – between test drug and placebo (see Table 46[20]) or an increase in the chance of a response by the factor 2.3 to 2.5.

However, responder analyses were also discussed in the comments on the preliminary report. It was criticised that responder analyses may lead to an overestimation of treatment success if the results of the different treatment groups cluster round the cut-off point (see comments: SN Arznei-Telegramm). Such an argument can always be brought forward when quantitative data are categorised or dichotomised. It is an expression of the relation between the effect regarded as relevant on the individual level (individual change on the scale, response criterion) and the variability of this change. This again leads to the question as to whether the effect that is regarded as relevant is actually relevant, and is therefore recursive. Furthermore, in a comparison between groups, it applies equally to both groups (unless there is a different variability in the groups) and can have an effect in one direction ("overestimation") as well as in the other ("underestimation").

Furthermore, in one comment it was noted that the assumption of a normal distribution – as assumed in the present report for the theoretically inferred responder analyses – may lead to an increase in the effect if the distribution is actually skewed (see comments: SN Kaduszkiewicz). In fact, a violation of the assumption of normal distribution can lead to an over- or underestimation of the effect. However, the performed generation of a difference (difference between the value at the end of study and the baseline value) leads to a symmetrisation of the distribution. In addition, as described in Table 46, the data reported on responders in some studies were quite consistent with those theoretically expected.

As a limitation it should be noted that the responder analyses inferred from originally quantitative data represent here an attempt to approximate the relevance of the observed changes and differences in mean values. However, their evidential value is not usually comparable with corresponding analyses of actual dichotomous criteria. Yet overall, the effect consistently shown on a scale that represents a patient-relevant aspect of disease can be interpreted as a direct patient-relevant benefit [138]. This appraisal is supported by the effect (even though substantially lower) also shown across all drugs in scales that are supposed to represent restrictions in activities of daily living.

[20] A slightly higher response criterion was used there. A further responder definition was, for example, used in the analyses by Janssen-Cilag (see comments: SN Janssen-Cilag, as well as [46]).

As already discussed (see p. 190), independently of this, it would be desirable in future to develop instruments that would give greater information on the extent to which the achieved changes lead to a noticeable improvement for patients in their daily life.

According to some comments, the alternative outcome criteria to be applied, such as institutionalisation or degree of care, ultimately represent only surrogates for the direct patient-relevant benefit, as constellations are imaginable in which results on the one hand classified as unfavourable on this level (placement in a nursing home, greater degree of care) may on the other by all means be positive from the patient's point of view (e.g., conscious decision by the patient, greater possibility of participation). Furthermore, data on institutionalisation must be assessed in a differentiated way (depending on the definition of "institution"), and such data from studies conducted in a different health care setting are, if at all, only transferable with limitations to the German setting.

- Conclusion

Ultimately, the criticism voiced in the comments, which implies both too negative as well as too positive an evaluation of ChEIs in the present report, does not lead to a relevant change in the conclusions already drawn in the preliminary report.

Outlook

The necessary weighing of benefits and harms of an intervention also, of course, involves the consideration of therapy alternatives. Within the framework of the present report, no studies were identified (following the inclusion and exclusion criteria) that compared ChEIs with a drug or non-drug intervention. A recently published study comparing (among other things) patients treated with donepezil or ginkgo biloba, is of questionable methodological and reporting quality and also much too small – in view of the limited effect strength compared with placebo – to allow valid statements on the comparison between donepezil and ginkgo. The study was discussed in detail in the preliminary report A05-19B [139,140].

Another recently published paper is noteworthy; here, the effects of ergotherapy with a focus both on patients and on caregivers were evaluated in patients with mild to moderate dementia who were compared with controls without a corresponding setting (patients on a waiting list) [141]. Even if no differentiation according to dementia type and no comparison with ChEIs were made, and the study lasted only 3 months, the effect strengths observed (with a difference between groups > 2 standard deviations on the IDDD [activities of daily living] scale) far exceeded those observed in the studies included in the present report. Such an effect can almost be described as dramatic and certainly calls for reproduction and detailed discussion on the corresponding conditions and settings. In particular, the importance of using controls on a waiting list should be critically discussed. It also needs to be considered that all patients in this study were being treated either with ChEIs or memantine. Nevertheless, these study results challenge the commonly claimed lack of alternative therapies in patients with dementia.

In order to achieve a better classification of the relevance of effects induced by ChEIs compared with placebo, controlled studies of much longer duration are required. Meanwhile, there are ethical concerns about the conduct of placebo-controlled studies (see comments: e.g., SN Gutzmann, SN Janssen-Cilag, SN Novartis, SN Pfizer). In view of the results of a non-drug intervention briefly outlined above, a comparison of such an intervention versus treatment with a ChEI over a period of at least 1 to 2 years may possibly provide an escape from this (ethical) dilemma.

7 CONCLUSION

The ChEIs donepezil, galantamine, and rivastigmine have a benefit in patients with mild-to-moderate Alzheimer's disease regarding the therapy goal "improvement in or maintenance of cognitive function". This applies to all administered doses of donepezil, and only to medium and high doses of galantamine and rivastigmine.

Moreover, for all 3 drugs, there are indications of a benefit in respect of the therapy goal "improvement in or prevention of restriction in activities of daily living".

Furthermore, for galantamine there are indications of a benefit in respect of accompanying psychopathological symptoms. For donepezil, no corresponding benefit can be inferred from the available data, and for rivastigmine, no data were available.

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).

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

All 3 drugs triggered therapy-related adverse events in a dose-dependent manner. An effect on mortality cannot be inferred from the available data; however, the studies were not designed to draw conclusions in this regard.

Whereas the direct comparison between rivastigmine and donepezil showed indications of an additional benefit of rivastigmine regarding activities of daily living, rivastigmine also had higher potential to cause harm. No conclusions can be made on the other 2 possible comparisons (galantamine vs. donepezil or galantamine vs. rivastigmine). Overall, no clear advantage of any of the 3 drugs investigated can be inferred from the available data.

The statements made above mainly refer to a study period of up to 6 months. For a further weighing of benefits and harms, direct comparative studies including other therapy options (other drug or non-drug treatment strategies) would be desirable.

Due to the lack of data, the relevance of ChEIs versus other drug or non-drug interventions is unclear.

8 LIST OF INCLUDED STUDIES

Donepezil vs. placebo

Burns 1999 [51]

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Gauthier 2002 [52-54]

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Homma 2000 [55]

Homma A, Takeda M, Imai Y, Udaka F, Hasegawa K, Kameyama M, Nishimura T. Clinical efficacy and safety of donepezil on cognitive and global function in patients with Alzheimer's disease. A 24-week, multicenter, double-blind, placebo-controlled study in Japan. E2020 Study Group. Dement Geriatr Cogn Disord 2000; 11: 299-313.

Krishnan 2003 [57]

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Tariot 2001 [63]

Tariot PN, Cummings JL, Katz IR, Mintzer J, Perdomo CA, Schwam EM, Whalen E. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc 2001; 49: 1590-1599.

Tune 2003 [64]

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Winblad 2001 [65-67]

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Galantamine vs. placebo

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Brodaty H, Corey-Bloom J, Potocnik FC, Truyen L, Gold M, Damaraju CR. Galantamine Prolonged-Release Formulation in the Treatment of Mild to Moderate Alzheimer's Disease. Dement Geriatr Cogn Disord 2005; 20: 120-132.

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Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ 2000; 321: 1445-1449.

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Rivastigmine vs. placebo

B304 1998 [48]

Novartis Pharma AG. Final Study Report. Prospective, randomised, multicentre, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of individual highest well tolerated doses (range 2-12 mg/day) of SDZ ENA 713 given b.i.d. or t.i.d. in patients with mild to moderate probable Alzheimer's disease (Study ENA B304-E-00). 28.01.1998. Unpublished.

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Corey-Bloom J, Anand R, Veach J. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor in patients with mild to modeate severe Alzheimer's disease. Int J Geriatr Psychopharmacol 1998; 1: 55-65.

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Rivastigmine vs. donepezil vs. galantamine

Cumbo 2005 [90]

Cumbo E. Differential effects of rivastigmine, galantamine and donepezil on behavioral and psychological symptoms in patients with Alzheimer's disease: 18-month, randomized, open-label trial. Prim Care Comm Psych 2005; 10: 95-102.

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APPENDIX A: SEARCH STRATEGY

Primary search

Databases MEDLINE 66 and Pre-MEDLINE (search date: 13.04.2005; search mask: Ovid)

#	Query	Hits
1	exp Alzheimer Disease	34415
2	dement$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	49046
3	alzheimer$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	44711
4	((cognit$ or memory$ or mental$) and (decline$ or impair$ or los$ or deteriorate$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	52641
5	1 or 2 or 3 or 4	119445
6	randomi?ed-controlled-trial.pt.	197725
7	controlled-clinical-trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	3893
8	randomi?ed-controlled-trials.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	39655
9	random-allocation.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	52978
10	double-blind-method.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	80556
11	single-blind-method.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	8724
12	clinical-trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	32003
13	clin$ near trial$.pt.	0
14	clin$ trial$.pt.	0
15	clin$-trial$.pt.	0
16	(clin$ adj trial$).pt.	0
17	(clin$ adj trial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	186734
18	(clin$ adj trial$).pt.	0
19	(clin$ adj trial$).ti,ab.	83731
20	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	106636
21	placebo$.ti,ab.	87216
22	random$.ti,ab.	302049
23	research-design.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	46392
24	6 or 7 or 8 or 9 or 10 or 11or 12.mp. or 17 or 19 or 20 or 21 or 22 or 23 [mp=title, original title, abstract, name of substance word, subject heading word]	602212
25	5 and 24	9744
26	(HIV$ or AIDS or stroke or diabet# or heart or epilep# or schizophre#).mp. or child#.ti. [mp=title, original title, abstract, name of substance word, subject heading word]	869555
27	(normal control# or healthy control# or healthy volunteer#).mp. or normal volunteer#.ti. [mp=title, original title, abstract, name of substance word, subject heading word]	78924

28	26 or 27	940842
29	25 not 28	8426
30	(TG=animal not (TG=human and TG=animal)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	0
31	donepezil.rn.	715
32	aricept.ti,ab.	53
33	exp galantamine/	522
34	Galantamin#.ti,ab.	242
35	galanthamin#.ti,ab.	227
36	nivalin#.ti,ab.	23
37	Lycoremin#.ti,ab.	0
38	reminyl.ti,ab.	21
39	rivastigmin#ti,ab.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	0
40	rivastigmin#.ti,ab.	313
41	exelon#.ti,ab.	0
42	31 or 32 or 33 or 34 or 35 or 36 or 38 0r 40.mp. or 41 [mp=title, original title, abstract, name of substance word, subject heading word]	1296
43	42 and 29	**324**

Database EMBASE 88 (search date: 13.04.2005; search mask: Ovid)[22]

#	Query	Hits
1	exp Alzheimer Disease	
2	dement$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
3	alzheimer$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
4	((cognit$ or memory$ or mental$) and (decline$ or impair$ or los$ or deteriorate$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
5	1 or 2 or 3 or 4	
6	randomi?ed-controlled-trial.pt.	
7	controlled-clinical-trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
8	randomi?ed-controlled-trials.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
9	random-allocation.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
10	double-blind-method.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
11	single-blind-method.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
12	clinical-trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
13	clin$ near trial$.pt.	
14	clin$ trial$.pt.	
15	clin$-trial$.pt.	

[22] For this search, the hits for the single search steps were not documented.

16	(clin$ adj trial$).pt.	
17	(clin$ adj trial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
18	(clin$ adj trial$).pt.	
19	(clin$ adj trial$).ti,ab.	
20	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
21	placebo$.ti,ab.	
22	random$.ti,ab.	
23	research-design.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
24	6 or 7 or 8 or 9 or 10 or 11or 12.mp. or 17 or 19 or 20 or 21 or 22 or 23 [mp=title, original title, abstract, name of substance word, subject heading word]	
25	5 and 24	
26	(HIV$ or AIDS or stroke or diabet# or heart or epilep# or schizophre#).mp. or child#.ti. [mp=title, original title, abstract, name of substance word, subject heading word]	
27	(normal control# or healthy control# or healthy volunteer#).mp. or normal volunteer#.ti. [mp=title, original title, abstract, name of substance word, subject heading word]	
28	26 or 27	
29	25 not 28	
30	(TG=animal not (TG=human and TG=animal)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
31	donepezil.rn.	
32	aricept.ti,ab.	
33	exp galantamine/	
34	Galantamin#.ti,ab.	
35	galanthamin#.ti,ab.	
36	nivalin#.ti,ab.	
37	Lycoremin#.ti,ab.	
38	reminyl.ti,ab.	
39	rivastigmin#ti,ab.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	
40	rivastigmin#.ti,ab.	
41	exelon#.ti,ab.	
42	31 or 32 or 33 or 34 or 35 or 36 or 38 0r 40.mp. or 41 [mp=title, original title, abstract, name of substance word, subject heading word]	
43	42 and 29	**255**

Database Cochrane Library (CLIB) (search date: 14.04.2005)

#	Query	Hits
1	MeSH descriptor Alzheimer Disease explode all trees in MeSH products	1140
2	alzheimer* in All Fields, from 1800 to 2005 in CENTRAL	2392
3	alzheimer* in All Fields, from 1800 to 2005 in CENTRAL	2392
4	dement* in All Fields, from 1800 to 2005 in CENTRAL	2471
5	(cognit* or memory* or mental*) and (decline* or impair* or los*or deteriorate*) in All Fields, from 1800 to 2005 in CENTRAL	3353
6	(#1 OR #2 OR #4 OR #5)	7919
7	HIV*:ti or aids:ti or stroke:ti or diabet*:ti or heart:ti or epilep*:ti or schizophre*:ti or child*:ti OR Parkinson* :TI in All Fields, from 1800 to 2005 in CENTRAL	2
8	HIV* or aids or stroke or diabet* or heart or epilep* or schizophre* or child* OR Parkinson* in Record Title, from 1800 to 2005 in CENTRAL	44002
9	normal next control* OR healthy next control* OR healthy next volunteer* OR normal next volunteer* in Record Title, from 1800 to 2005 in CENTRAL	3734
10	(8 OR 9)	51139
11	(6 AND NOT 10)	7058
12	donepezil in All Fields, from 1800 to 2005 in CENTRAL	270
13	aricept in All Fields, from 1800 to 2005 in CENTRAL	12
14	galantamin* in All Fields, from 1800 to 2005 in CENTRAL	110
15	galanthamin* in All Fields, from 1800 to 2005 in CENTRAL	21
16	nivalin* in All Fields, from 1800 to 2005 in CENTRAL	2
17	lycoremin* in All Fields, from 1800 to 2005 in CENTRAL	0
18	reminyl in All Fields, from 1800 to 2005 in CENTRAL	11
19	Rivastigmin* in All Fields, from 1800 to 2005 in CENTRAL	33
20	exelon* in All Fields, from 1800 to 2005 in CENTRAL	27
21	(12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20)	503
22	(11 AND 21)	**347**

Database CHID (Search date: 25.04.2005)

Search by means of the drug names according to the user interface. Hits: **54.**

Search update 1

Databases: MEDLINE 66 and Pre-MEDLINE (search mask: Ovid; search date: 03.11.2005)

#	Query	Hits
1	exp Alzheimer Disease	36708
2	dement$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	52206
3	alzheimer$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	49608
4	((cognit$ or memory$ or mental$) and (decline$ or impair$ or los$ or deteriorate$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	58390
5	1 or 2 or 3 or 4	130648
6	randomi?ed-controlled-trial.pt.	207743
7	controlled-clinical-trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	4265
8	randomi?ed-controlled-trials.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	44316
9	random-allocation.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	54519
10	double-blind-method.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	83751
11	single-blind-method.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	9397
12	clinical-trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	35248
13	clin$ near trial$.pt.	200265
14	clin$ trial$.pt.	93852
15	clin$-trial$.pt.	112804
16	(clin$ adj trial$).pt.	0
17	(clin$ adj trial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	200265
18	(clin$ adj trial$).pt.	0
19	(clin$ adj trial$).ti,ab.	93852
20	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	112804
21	placebo$.ti,ab.	93570
22	random$.ti,ab.	335625
23	research-design.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	49373
24	6 or 7 or 8 or 9 or 10 or 11or 12.mp. or 17 or 19 or 20 or 21 or 22 or 23 [mp=title, original title, abstract, name of substance word, subject heading word]	654081
25	5 and 24	10792
26	(HIV$ or AIDS or stroke or diabet# or heart or epilep# or schizophre#).mp. or child#.ti. [mp=title, original title, abstract, name of substance word, subject heading word]	913602
27	(normal control# or healthy control# or healthy volunteer#).mp. or normal volunteer#.ti. [mp=title, original title, abstract, name of substance word, subject heading word]	85025
28	26 or 27	990487

29	25 not 28	9303
30	(TG=animal not (TG=human and TG=animal)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	0
31	donepezil.rn.	794
32	aricept.ti,ab.	62
33	exp galantamine/	567
34	Galantamin#.ti,ab.	303
35	galanthamin#.ti,ab.	249
36	nivalin#.ti,ab.	23
37	Lycoremin#.ti,ab.	0
38	reminyl.ti,ab.	26
39	rivastigmin#ti,ab.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	0
40	rivastigmin#.ti,ab.	390
41	exelon#.ti,ab.	0
42	31 or 32 or 33 or 34 or 35 or 36 or 38 0r 40.mp. or 41 [mp=title, original title, abstract, name of substance word, subject heading word]	1458
43	42 and 29	369
44	limit 43 to yr="2005 - 2006"	34
45	"2005".ed,yr.	513026
46	43 and 45	**34**

Database EMBASE 88 (search date: 03.11.2005; search mask: Ovid)

#	Query	Hits
1	exp Alzheimer Disease/	45187
2	dement$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	41257
3	alzheimer$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	50468
4	((cognit$ or memory$ or mental$) and (decline$ or impair$ or los$ or deteriorate$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	56430
5	1 or 2 or 3 or 4	119027
6	randomi?ed-controlled-trial.pt.	0
7	controlled-clinical-trial.mp.	3797
8	randomi?ed-controlled-trials.mp.	7098
9	random-allocation.mp.	509
10	double-blind-method.mp.	181
11	single-blind-method.mp.	26
12	clinical-trial.mp.	374849
13	(clin$ adj trial$).mp.	405792
14	(clin$ adj trial$).ti,ab.	84184
15	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp.	96186
16	(clin$ adj trial$).pt.	0
17	(clin$ adj trial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	405792
18	(clin$ adj trial$).pt.	0
19	(clin$ adj trial$).ti,ab.	84184

20	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	96186
21	placebo$.ti,ab.	88076
22	random$.ti,ab.	286857
23	research-design.mp.	5708
24	6 or 7 or 8 or 9 or 10 or 11or 12.mp. or 17 or 19 or 20 or 21 or 22 or 23	626965
25	5 and 24	13615
26	(HIV$ or AIDS or stroke or diabet# or heart or epilep# or schizophre#).mp.	823909
27	(normal control# or healthy control# or healthy volunteer#).mp. or normal volunteer#.ti.	77408
28	26 or 27	893027
29	25 not 28	11009
30	(TG=animal not (TG=human and TG=animal)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	0
31	donepezil.rn.	0
32	aricept.ti,ab.	69
33	exp GALANTAMINE/	1560
34	galantamin#.ti,ab.	343
35	galanthamin#.ti,ab.	207
36	nivalin#.ti,ab.	1
37	lycoremin#.ti,ab.	0
38	reminyl.ti,ab.	36
39	rivastigmin#ti,ab.mp.	0
40	rivastigmin#.ti,ab.	436
41	exelon#.ti,ab.	0
42	31 or 32 or 33 or 34 or 35 or 36 or 38 0r 40.mp. or 41	1649
43	42 and 29	587
44	limit 43 to yr="2005 - 2006"	78
45	"2005".em,yr.	382835
46	43 and 45	**78**

Database Cochrane CENTRAL (CCTR) (search date: 03.11.2005)

#	Query	Hits
#1	MeSH descriptor **Alzheimer Disease** explode all trees in **MeSH products**	1231
#2	**alzheimer*** in **All Fields**, from 2004 to 2005 in **CENTRAL**	264
#3	**dement*** in **All Fields**, from 2004 to 2005 in **CENTRAL**	235
#4	**(cognit* or memory* or mental*) and (decline* or impair* or los* or deteriorate*)** in **All Fields**, from 2004 to 2005 in **CENTRAL**	498
#5	(**#1** OR **#2** OR **#3** OR **#4**)	2600
#6	**HIV* or aids or stroke or diabet* or heart or epilep* or schizophre* or child* or parkinson*** in **Record Title**, from 2004 to 2005 in **CENTRAL**	3628
#7	**normal next control* or healthy next control* or healthy next volunteer* or normal next volunteer*** in **Record Title**, from 2004 to 2005 in **CENTRAL**	210
#8	(**#6** OR **#7**)	4805
#9	(**#5** AND NOT **#8**)	2373
#10	**donepezil** in **All Fields**, from 2004 to 2005 in **CENTRAL**	65
#11	**aricept** in **All Fields**, from 2004 to 2005 in **CENTRAL**	2

#12	**galantamin*** in **All Fields**, from 2004 to 2005 in **CENTRAL**	38
#13	**galanthamin*** in **All Fields**, from 2004 to 2005 in **CENTRAL**	1
#14	**nivalin*** in **All Fields**, from 2004 to 2005 in **CENTRAL**	0
#15	**lycoremin*** in **All Fields**, from 2004 to 2005 in **CENTRAL**	0
#16	**reminyl** in **All Fields**, from 2004 to 2005 in **CENTRAL**	2
#17	**Rivastigmin*** in **All Fields**, from 2004 to 2005 in **CENTRAL**	9
#18	**exelon*** in **All Fields**, from 2004 to 2005 in **CENTRAL**	1
#19	(**#10** OR **#11** OR **#12** OR **#13** OR **#14** OR **#15** OR **#16** OR **#17** OR **#18**)	140
#20	(**#9** AND **#19**)	**103**

Cochrane Reviews [9] | DARE [5] | **CENTRAL [76]** | Methodology Reviews [0] | CMR [0] | HTA [3] | NHS EED [9] | About [1]

Database CHID (search date: 03.11.2005)

Search by means of the drug names according to the user interface. Hits: **1.**

Search update 2

Databases: Ovid MEDLINE(R) In-Process, Other Non-Indexed Citations, Ovid MEDLINE(R), Ovid MEDLINE(R) Daily Update (search mask: Ovid; search date: 12.06. 2006)

#	Query	Hits
1	exp ALZHEIMER DISEASE/	39086
2	alzheimer$.ti,ab,ot.	46136
3	*DEMENTIA/	16991
4	(dementia or dement or demenz or demenc$).ti,ot.	17072
5	or/1-4	66764
6	donepezil.ti,ab,ot,nm.	1175
7	aricept.ti,ab,ot,nm.	72
8	exp GALANTAMINE/	634
9	galantamin$.ti,ab,ot,nm,rn.	739
10	galanthamin$.ti,ab,ot,nm,rn.	273
11	nivalin$.ti,ab,ot,nm,rn.	51
12	lycoramin$.ti,ab,ot,nm,rn.	5
13	reminyl$.ti,ab,ot,nm,rn.	32
14	rivastigmin$.ti,ab,ot,nm,rn.	547
15	exelon$.ti,ab,ot,nm,rn.	29
16	or/6-15	2080
17	exp RANDOM ALLOCATION/	57438
18	random$.ti,ot.	54898
19	prospectiv$.ti,ot.	42256
20	exp RANDOMIZED CONTROLLED TRIALS/	45681
21	randomized controlled trial.pt.	226483
22	exp CONTROLLED CLINICAL TRIALS/	48478
23	controlled clinical trial.pt.	73383
24	exp DOUBLE-BLIND METHOD/	88351
25	((single or double or triple) adj5 (mask$ or blind$) adj5 (study or trial or method)).ti,ab,ot,sh.	61082
26	or/17-25	426956
27	5 and 16 and 26	**316**

Database: EMBASE 88 (search date: 12.06.2006; search mask: Ovid)

#	Query	Hits
1	exp ALZHEIMER DISEASE/	48042
2	alzheimer$.ti,ab,ot.	42924
3	*DEMENTIA/ or exp SENILE DEMENTIA/	18743
4	(dementia or dement or demenz or demenc$).ti,ot.	15480
5	or/1-4	66663
6	exp DONEPEZIL/	3068
7	donepezil.ti,ab,ot,tn.	1030
8	aricept.ti,ab,ot,tn.	745
9	exp GALANTAMINE/	1811
10	galantamin$.ti,ab,ot,tn.	410
11	galanthamin$.ti,ab,ot,tn.	230
12	nivalin$.ti,ab,ot,tn.	61
13	lycoramin$.ti,ab,ot,tn.	14
14	reminyl$.ti,ab,ot,tn.	390
15	exp RIVASTIGMINE/	1731
16	rivastigmin$.ti,ab,ot,tn.	496
17	exelon$.ti,ab,ot,tn.	481
18	or/6-17	4238
19	exp RANDOMIZATION/	19225
20	exp RANDOMIZED CONTROLLED TRIAL/	106163
21	random$.ti,ot.	46724
22	prospectiv$.ti,ot.	35371
23	exp DOUBLE-BLIND PROCEDURE/	59969
24	((single or double or triple) adj5 (mask$ or blind$) adj5 (study or trial or method)).ti,ab,ot,sh.	58088
25	or/19-24	208444
26	5 and 18 and 25	**340**

Database Cochrane CENTRAL (CCTR) (search date: 12.06.2006)

#	Query	Hits
#1	MeSH descriptor Alzheimer Disease explode all trees in MeSH products	1309
#2	**alzheimer*** in **Title, Abstract or Keywords** in **all products**	2866
#3	MeSH descriptor **Dementia**, this term only in **MeSH products**	677
#4	**demen*** in **Record Title** in **all products**	1794
#5	(**#1** OR **#2** OR **#3** OR **#4**)	4254
#6	**donepezil** in **All Fields** in **all products**	426
#7	**aricept** in **All Fields** in **all products**	23
#8	**galantamin*** in **All Fields** in **all products**	206
#9	**galanthamin*** in **All Fields** in **all products**	32
#10	**nivalin*** in **All Fields** in **all products**	2
#11	**lycoramin*** in **All Fields** in **all products**	0
#12	**reminyl** in **All Fields** in **all products**	21
#13	**rivastigmin*** in **All Fields** in **all products**	181
#14	**exelon*** in **All Fields** in **all products**	40
#15	(**#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12** OR **#13** OR **#14**)	722
#16	(**#5** AND **#15**)	**564**

Cochrane Reviews [24] | Other Reviews [13] | **Clinical Trials** [**477**] | Methods Reviews [0] | Methods Studies [1] | Technology Assessments [15] | Economic Evaluations [33] | Cochrane Groups [1]

Database CHID: This database was no longer available at the time of the second search update.

APPENDIX B: LIST OF STUDIES PERUSED IN FULL TEXT BUT EXCLUDED (AND REASONS FOR EXCLUSION)

Not I1: Specified indication not fulfilled (5)

Ballard C, Margallo-Lana M, Juszczak E, Douglas S, Swann A, Thomas A, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ 2005; 330: 857-858.

Lopez-Pousa S. Pilot, multicenter, randomized, double-blind, controlled, parallel efficacy and safety study of rivastigmine vs placebo in the treatment of cognitive and non-cognitive symptoms in patients with moderate-to-severe Alzheimer's disease. IFPMA Register 2005.

Passmore AP, Bayer AJ, Steinhagen-Thiessen E. Cognitive, global, and functional benefits of donepezil in Alzheimer's disease and vascular dementia: results from large-scale clinical trials. J Neurol Sci 2005; 229-230: 141-146.

Salloway S, Ferris S, Kluger A, Goldman R, Griesing T, Kumar D, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. Neurology 2004; 63: 651-657.

Salloway SP, Pratt RD, Perdomo CA. Donepezil is well tolerated in patients with vascular dementia: a comparison of tolerability in vascular dementia patients and Alzheimer's disease patients. Eur J Neurol 2002; 9: 165-224.

Not I2: Specified test or comparator intervention not fulfilled (8)

Finkel SI, Mintzer JE, Dysken M, Krishnan KR, Burt T, McRae T. A randomized, placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated with donepezil. Int J Geriatr Psychiatry 2004; 19: 9-18.

Kristensen M, Richardson A, Van Osselaer N, Vangeneugden T. European multicentre placebo-controlled trial to determine the safety and efficacy of galantamine hydrobromide 40 mg/d in patients diagnosed with Alzheimer type dementia (GAL-95-05). 1997.

Onofrj M, Thomas A, Luciano AL, Iacono D, Di RA, D'Andreamatteo G, et al. Donepezil versus vitamin E in Alzheimer's disease: Part 2: mild versus moderate-severe Alzheimer's disease. Clin Neuropharmacol 2002; 25: 207-215.

Patterson CE, Passmore AP, Crawford VL. A 6-month open-label study of the effectiveness and tolerability of galantamine in patients with Alzheimer's disease. Int J Clin Pract 2004; 58: 144-148.

Santens P, Ventura M. Donepezil in the treatment of mild to moderate Alzheimer's disease: report of a Belgian multicenter study. Acta Neurol Belg 2003; 103: 159-163.

Suh GH, Yeon JH, Uk LC, Hoon OB, Nam BJ, Jung HY, et al. A prospective, double-blind, community-controlled comparison of three doses of galantamine in the treatment of mild to moderate Alzheimer's disease in a Korean population. Clin Ther 2004; 26: 1608-1618.

Suh GH, Jung HY, Lee CU, Oh BH, Lee SK, Lee N, Kim J et al. Effect of the apolipoprotein E epsilon4 allele on the efficacy and tolerability of galantamine in the treatment of Alzheimer's disease. Dement Geriatr Cogn Disord 2006; 21: 33-39.

Weiser M, Rotmensch HH, Korczyn AD, Hartman R, Cicin SA, Anand R, et al. A pilot, randomized, open-label trial assessing safety and pharmakokinetic parameters of co-administration of rivastigmine with risperidone in dementia patients with behavioral disturbances. Int J Geriatr Psychiatry 2002; 17: 343-346.

Not I3: No relevant outcomes (1)

Parnetti L, Amici S, Lanari A, Romani C, Antognelli C, Andreasen N, Minthon L et al. Cerebrospinal fluid levels of biomarkers and activity of acetylcholinesterase (AChE) and butyrylcholinesterase in AD patients before and after treatment with different AChE inhibitors. Neurol Sci 2002; 23 Suppl 2: S95-S96.

Not I4: No RCT (33)

Aguglia E, Onor ML, Saina M, Maso E. An open-label, comparative study of rivastigmine, donepezil and galantamine in a real-world setting. Curr Med Res Opin 2004; 20: 1747-1752.

Albuquerque EX, Santos MD, Alkondon M, Pereira EF, Maelicke A. Modulation of nicotinic receptor activity in the central nervous system: a novel approach to the treatment of Alzheimer disease. Alzheimer Dis Assoc Disord 2001; 15 Suppl 1: S19-S25.

Almkvist O, Darreh ST, Stefanova E, Spiegel R, Nordberg A. Preserved cognitive function after 12 months of treatment with rivastigmine in mild Alzheimer's disease in comparison with untreated AD and MCI patients. Eur J Neurol 2004; 11: 253-261.

Baladi J-F, Bailey PAB, Black S, Bouchard RW, Farcnik KD, Gauthier S, Kertesz A et al. Rivastigmine for Alzheimer's disease: Canadian interpretation of intermediate outcome measures and cost implications. Clin Ther 2000; 22: 1549-1561.

Blesa R. Galantamine: therapeutic effects beyond cognition. Dement Geriatr Cogn Disord 2000; 11 Suppl 1: 28-34.

Böttcher BE. Therapie der Alzheimer-Demenz mit Donepezil: gut verträglich, wirksam und kostengünstig. Neurol Rehabil 2000; 6: 332-333.

Bullock R, Truyen L. Not all head-to-head trials are created equal: results from an open-label, short-term study seem inconsistent with previous donepezil literature. Int J Geriatr Psychiatry 2005; 20: 85-87.

Caro J, Ward A, Ishak K, Migliaccio-Walle K, Getsios D, Papadopoulos G, et al. To what degree does cognitive impairment in Alzheimer's disease predict dependence of patients on caregivers? BMC Neurol 2002; 2: 6.

Caro JJ, Getsios D. Long-Term Effects of Second-Generation Cholinesterase Inhibitors on Clinical Outcomes and Costs of Alzheimer's Disease. Dis Manage Health Outcomes 2003; 11.

Doody RS, Dunn JK, Clark CM, Farlow M, Foster NL, Liao T, et al. Chronic donepezil treatment is associated with slowed cognitive decline in Alzheimer's disease. Dement Geriatr Cogn Disord 2001; 12: 295-300.

Doody RS, Geldmacher DS, Gordon B, Perdomo CA, Pratt RD, Donepezil Study Group. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. Arch Neurol 2001; 58: 427-433.

Desai AK, Grossberg GT. Rivastigmine for Alzheimer's disease. Expert rev neurotherapeutics 2005; 5: 563-580.

Ebell M. Does donepezil help patients with moderate Alzheimer's dementia preserve their ability to function independently? Evidence Based Practice 2002.

Farlow MR, Hake A, Messina J, Hartman R, Veach J, Anand R. Response of patients with Alzheimer disease to rivastigmine treatment is predicted by the rate of disease progression. Arch Neurol 2001; 58: 417-422.

Farlow MR. Update on rivastigmine. Neurology 2003; 9: 230-234.

Froelich L, Gertz HJ, Heun R, Heuser I, Jendroska K, Kornhuber J, et al. Donepezil for Alzheimer's disease in clinical practice--The DONALD Study. A multicenter 24-week clinical trial in Germany. Dement Geriatr Cogn Disord 2004; 18: 37-43.

Gasser US, Gasser T. Vergleich der Wirksamkeit von Cholinesterasehemmern und Ginkgo. MMW Fortschr Med 2001; 143: 40-41.

Gu P, Jing QW, Ding XS, et a. Observation of effect on Alzheimer disease treated by Galanthamine hydrobromide capules. Practical Geriatrics 2000; 14: 307-308.

Ieni J, Warner JP. Donepezil improved cognitive and global function in mild-to-moderate Alzheimer disease. Evid-based Med 1998; 3: 155.

Joffres C, Bucks RS, Haworth J, Wilcock GK, Rockwood K. Patterns of clinically detectable treatment effects with galantamine: a qualitative analysis. Dement Geriatr Cogn Disord 2003; 15: 26-33.

Kurz A, Van BB. Ginkgo biloba compared with cholinesterase inhibitors in the treatment of dementia: a review based on meta-analyses by the cochrane collaboration. Dement Geriatr Cogn Disord 2004; 18: 217-226.

Lilienfeld S, Parys W. Galantamine: Additional benefits to patients with Alzheimer's disease. Dement Geriatr Cogn Disord 2000; 11: 19-27.

Lilienfeld S. Galantamine - A novel cholinergic drug with a unique dual mode of action for the treatment of patients with Alzheimer's disease. CNS Drug Rev 2002; 8: 159-176.

Luckmann R. Donepezil improved the clinical state and quality of life in moderate-to-severe Alzheimer disease. ACP J Club 2002; 136: 59.

Mani RB. The evaluation of disease modifying therapies in Alzheimer's disease: A regulatory viewpoint. Stat Med 2004; 23: 305-314.

Mossello E, Tonon E, Caleri V, Tilli S, Cantini C, Cavallini MC, et al. Effectiveness and safety of cholinesterase inhibitors in elderly subjects with Alzheimer's disease: a "real world" study. Arch Gerontol Geriatr Suppl 2004; 297-307.

Nobili F, Vitali P, Canfora M, Girtler N, De LC, Mariani G, et al. Effects of long-term Donepezil therapy on rCBF of Alzheimer's patients. Clin Neurophysiol 2002; 113: 1241-1248.

Peters O, Frolich L, Heuser I. Antidementive Kombinationstherapie. Nervenheilkunde 2005; 24: 476-482.

Relkin NR, Reichman WE, Orazem J, McRae T. A large, community-based, open-label trial of donepezil in the treatment of Alzheimer's disease. Dement Geriatr Cogn Disord 2003; 16: 15-24.

Schreiter GU, Gasser T. Ein Vergleich von Cholinesterasehemmern und Ginkgo-Extrakt in der Behandlung der Alzheimer-Demenz. Fortschr Med 2001; 135-138.

Vennerica A, Shanks MF, Staff RT, Pestell SJ, Forbes KE, Gemmell HG, Murray AD. Cerebral blood flow and cognitive responses to rivastigmine treatment in Alzheimer's disease. Neuroreport 2002; 13: 83-87.

Vetter C. Stabilization of cognition and everyday performance with galantamine therapy in dementia patients. Tw Neurol Psychiatr 2001; 24-25.

Ward A, Caro JJ, Getsios D, Ishak K, O'Brien J, Bullock R, AHEAD Study Group. Assessment of health economics in Alzheimer's disease (AHEAD): treatment with galantamine in the UK. Int J Geriatr Psychiatry 2003; 18: 740-747.

E1: Study duration less than 16 weeks (15)

Agid YDBA. Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. Curr Ther Res Clin Exp 1998; 59: 837-845.

Boada-Rovira M, Brodaty H, Cras P, Baloyannis S, Emre M, Zhang R, et al. Efficacy and safety of donepezil in patients with Alzheimer's disease: results of a global, multinational, clinical experience study. Drugs Aging 2004; 21: 43-53.

Greenberg SM, Tennis MK, Brown LB, Gomez-Isla T, Hayden DL, Schoenfeld DA, et al. Donepezil therapy in clinical practice: a randomized crossover study. Arch Neurol 2000; 57: 94-99.

Hegerl U, Mergl R, Henkel V, Gallinat J, Kotter G, Muller-Siecheneder F, Pogarell O et al. Kinematic analysis of the effects of donepezil hydrochloride on hand motor function in patients with Alzheimer dementia. J Clin Psychopharmacol 2003; 23: 214-216.

Holmes C, Wilkinson D, Dean C, Vethanayagam S, Olivieri S, Langley A, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. Neurology 2004; 63: 214-219.

Homma A, Imai N, Hagiguchi S, Hasegawa H, Kameyama M. Late phase II clinical study of acetyl choline esterase E 2020 in patients with Alzheimer type dementia. Clin Eval 1998; 26: 251-284.

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APPENDIX C: LIST OF SCREENED SYSTEMATIC REVIEWS

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APPENDIX D: OVERVIEW OF THE OUTCOME PARAMETERS ASSESSED IN THE STUDIES

The following table provides an overview of the outcome parameters assessed in the studies included and can be allocated to the target criteria according to section 4.1.3.

In the present evaluation, if several scales on one therapy goal (e.g., cognitive function) were reported in the studies, in general, only one scale is reported in each case (preferably the one most used) (see Section 4.4.2). The outcomes not analysed are placed in brackets. If, in individual cases, outcomes were excluded for reasons other than redundancy, or if for specific reasons more than one outcome on a therapy goal was analysed, this is marked accordingly.

Table 47. Comparison of therapy goals defined in the report plan and outcome parameters used in the studies

	Activities of daily living[a]	Psycho-pathological symptoms[a]	Cognitive function[a]	Health-related quality of life[a]	Placement in a nursing home[a]	Quality of life of relatives[b]	Degree of care[b]	Clinical disease stage[c]
Donepezil vs. placebo								
Burns 1999	IDDD		ADAS-cog	QoL				CIBIC-plus (CDR-SB)
Gauthier 2002	DAD PSMS-plus[d] IADL-plus[d]	NPI	sMMSE (SIB)			CSS (SF-36)[e]	Time invested in IADL and PSMS	CIBIC-plus (FRS)
Homma 2000	CMCS		ADAS-J cog					J-CIGIG (MENFIS) (CDR-SB)
Krishnan 2003			ADAS-cog					
Mohs 2001	ADFACS		MMSE					CDR-SB
Moraes 2006			ADAS-cog					
Prasher 2002		NPI (ABS)	SIB					(DMR)[f] General impression of caregivers [g]
Rogers 1998			ADAS-cog (MMSE)	QoL				CIBIC-plus (CDR-SB)
Seltzer 2004			ADAS-cog13 (MMSE) (CMBT)					CDR-SB (PGAS)
Tariot 2001	PSMS	NPI-NH	MMSE					(CDR-SB)
Tune 2003		NPI	ADAS-cog					

(continued)

Table 47 (continued). Comparison of therapy goals defined in the report plan and outcome parameters used in the studies

	Activities of daily living[a]	Psycho-pathological symptoms[a]	Cognitive function[a]	Health-related quality of life[a]	Placement in a nursing home[a]	Quality of life of relatives[b]	Degree of care[b]	Clinical disease stage[c]
Winblad 2001	PDS	NPI	MMSE					GBS (GDS)
Galantamine vs. placebo								
Brodaty 2005	ADCS-ADL	NPI	ADAS-cog11 (ADAS-cog13) (memory/non-memory ADAS-cog)			NPI-D		CIBIC-plus
Erkinjuntti 2002	DAD	NPI	ADAS-cog11 (ADAS-cog13)			NPI-D		CIBIC-plus
Raskind 2000	DAD		ADAS-cog11 (ADAS-cog13)					CIBIC-plus
Rockwood 2006	GAS DAD[h]		ADAS-cog11 (Examination of Memory and Temporality)[e] (Red Pen Task)[e]			CBS	(ACTS)[e]	CIBIC-plus
Tariot 2000	ACDS-ADL	NPI	ADAS-cog11 (ADAS-cog13)			NPI-D		CIBIC-plus
Wilcock 2000	DAD		ADAS-cog11					CIBIC-plus
Rivastigmine vs. placebo								
B304 1998	PDS		ADAS-cog (ADAS-cogA) (MMSE)				CAS[e]	CIBIC-plus (GDS)
Corey-Bloom 1998	PDS		ADAS-cog (MMSE)					CIBIC-plus (GDS)

(continued)

Table 47 (continued). Comparison of therapy goals defined in the report plan and outcome parameters used in the studies

	Activities of daily living[a]	Psycho-pathological symptoms[a]	Cognitive function[a]	Health-related quality of life[a]	Placement in a nursing home[a]	Quality of life of relatives[b]	Degree of care[b]	Clinical disease stage[c]
Forette 1999		NOSGER	ADAS-cog (Wechsler Tests)[i]					CIBIC-plus
Rösler 1999	PDS		ADAS-cog (MMSE)					CIBIC-plus (GDS)
Galantamine vs. donepezil								
Wilcock 2003	BADLS	NPI	ADAS-cog (MMSE)			SCGB		
Rivastigmine vs. donepezil								
Bullock 2005	ADCS-ADL	NPI	SIB (MMSE)					GDS
Fuschillo	PSMS		ADAS-cog (MMSE)					
Wang 2001	BRDS		MMSE					GDS
Rivastigmine vs. donepezil vs. galantamine								
Cumbo 2005		NPI BEHAVE-AD				NPI-D		

a: Patient-relevant therapy goals.
b: Therapy goals relevant to relatives.
c: Additional information.
d: Supplementary scales that represent different aspects and were therefore also analysed.
e: No publication in this regard could be identified.
f: Not analysed, as no good documentation of disease progression (screening instrument).
g: Not analysed, as validity unclear.
h: As the Goal Attainment Scale clearly differs from other psychometric procedures to assess activities of daily living, for the study by Rockwood 2006 both the results from the DAD and from the GAS are presented here.
i: Wechsler logical memory, digit span, word fluency test.

( ) = Not analysed within the framework of the present report.

APPENDIX E: SHORT DESCRIPTION OF THE OUTCOME PARAMETERS USED

Short description of the outcome parameters and instruments used in Alzheimer's disease, which were analysed within the framework of the present evaluation

Instrument	Comment
Global outcome parameter	
Clinical Global Impression of Change Scale (CGIC) Also as CIBIC with caregiver input: CIBIC-M or CIBIC-plus	CIBIC is a commonly used scale. The change is assessed relative to baseline using all available information. Average to good test-retest and interrater reliability and agreement validity. Scores on the CGIC/CIBIC do not reflect the extent of individual global improvement. However, physicians often use the clinical psychopathology as a basis to determine global improvement; nursing staff to determine the degree of care needed. In the version with caregiver input, the results may depend on whether the caregiver or the affected patient is interviewed first.
Clinical Dementia Rating Scale (CDR) Also: Clinical Dementia Rating Scale Sum of Boxes (CDR-SB)	Commonly used measure to determine severity of dementia with good interrater reliability and average to good agreement validity. Mainly measures cognitive aspects of dementia, not the global health status.
Global Deterioration Scale (GDS)	Commonly used instrument to classify disease stages. Can however incorrectly express disease severity and should not therefore be used to classify disease stages in drug trials.
Gottfries-Bråne-Steen scale (GBS)	Instrument that is not commonly used. Satisfactory to very good psychometric characteristics. This instrument is suited to quantify dementia in drug trials. Covers cognitive, functional, and behavioural aspects and can therefore be regarded as a global instrument.
Cognitive outcome parameters	
Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog)	Scale with high reliability that is commonly used as a primary parameter. Most ADAS-cog subscales have limitations in their ability to recognise a change at both ends of the spectrum of disease severity.
Mini Mental State Examination (MMSE)	Scale with high retest reliability commonly used as a screening instrument for disease severity. The benefit of the MMSE as a measure to assess change in individual patients is limited; the scale cannot detect minor changes in cognitive function. The sensitivity to change is better in mild to moderate dementia, and insufficient in severe dementia.
Severe Impairment Battery (SIB)	The SIB was developed to assess cognitive function in persons too severely impaired for assessment in other neuropsychological tests. The subscales cover, among other things, attention, orientation, language, memory, and spatio-visual abilities.

Instrument	Comment
Functional outcome parameters and quality of life of patients	
Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)	Common, structured questionnaire to assess instrumental and basic activities of daily living over a broad spectrum of disease severity. The sensitivity and reliability of this scale have been established.
Alzheimer's Disease Functional Assessment and Change Scale (ADFACS)	Covers instrumental activities of daily living (10 items). A detailed assessment of psychometric characteristics has, however, not been made. The items seem sensitive to change and have good test-retest reliability.
Blessed-Roth Dementia Scale (BRDS)	Few data on validity and reliability exist. The sensitivity to change is unclear. The use of different modifications makes the comparison across studies more difficult.
Bristol Activities of Daily Living Scale (BADLS)	Assessment of 20 activities of daily living by a caregiver. The scale is specific for dementia patients, has good validity of content, and good test-rest validity. Correlates well with cognitive function tests.
Caregiver-rated modified Crichton Scale (CMCS)	Modification of the Crichton Geriatric Rating Scale. 7-item scale with questions on understanding of time and place, holding a conversation, cooperation, restlessness, getting dressed, social and leisure activities. Reliability demonstrated; validity unclear.
Disability Assessment for Dementia (DAD)	46-item structured interview or questionnaire for caregivers. The impairments covered correspond to the WHO definition. Common instrument with a high degree of internal consistency, interrater and test-retest reliability. Covers instrumental and basic activities of daily living.
Goal Attainment Scale (GAS)	Individual problem areas are defined, and goals modified accordingly are defined. Later the change compared with baseline is assessed. The GAS therefore represents an individualised outcome parameter, which, depending on which goals are defined, covers various areas of life. Higher sensitivity to change than, for example, the PSMS or IADL (Rockwood et al, 2003).
Instrumental Activities of Daily Living (IADL, iADL)	A commonly used and quoted instrument. The scale is theoretically well founded and the activities that are covered are very probably impaired in early stages of dementia. However, good reliability tests are lacking.
Interview for Deterioration in Daily Living in Dementia (IDDD)	Seems appropriate to assess daily living skills in mild and moderate dementia; measures functional impairment in self-care and complex activities. Psychometric data are lacking.
Physical Self-Maintenance Scale (PSMS)	Coverage of 6 basic activities. Theoretically well founded and suitable for institutionalised patients. In patients who do not live in nursing homes, a strong ceiling effect is possible. The testing of psychometric characteristics is incomplete.
Progressive Deterioration Scale (PDS)	The scale is sensitive to stages and has a good reliability and validity. Not suited in moderate to severe patients, as several basic activities are not covered.
Quality of Life Scale (QoL)	The scale reflects the concept of quality of life according to the WHO definition. However, data are lacking on reliability, validity, and sensitivity to change. In view of other instruments available on quality of life, the application of this scale seems rather questionable.
Quality of life and burden on relatives	
Caregiver Activity Survey (CAS)	Measures the time that relatives invest in supporting patients in their activities of daily living. 6-item version covers the following aspects: communication, transport, eating, getting dressed, taking care of the patient's

	appearance, supervision. Adequate retest-reliability and convergent validity (Davis et al 1997).
Caregiver Stress Scale (CSS)	Rarely used instrument. Building on a comprehensive stress model, it covers various aspects of the burden of caring for relatives (e.g., problematical behaviour, conflicts within the family, compatibility with work, economic burden, degree of experienced support) (Pearlin 1990). Applied in Gauthier 2002 (details in [53]) and adapted for use within the framework of studies on Alzheimer's disease.
Screen for Caregiver Burden (SCGB)	Scale for swiftly assessing the burden for caregiving relatives. Internal consistency, test-retest reliability and validity are sufficient.
Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D)	Assesses the burden for caregiving relatives associated with the psychiatric symptoms of Alzheimer's disease. For the symptom domains of the NPI, the associated emotional/mental burden experienced is reported on a 6-stage scale. Appropriate retest and interrater reliability (Kaufer 1998).
Psychopathological symptoms	
Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-D)	Third-party assessment scale for the evaluation of global severity, as well as for the differentiated description of behavioural disorders and psychopathological symptoms in patients with Alzheimer's disease. Sensitivity to stages, good validity. Little testing of reliability.
Nurses' Observation Scale for Geriatric Patients (NOSGER)	The NOSGER instrument covers observable behaviour in different domains (memory, instrumental activities of daily living, personal care, mood, social behaviour, disruptive behaviour). Rarely used; validated; with high interrater and test-retest reliability.
Neuropsychiatric Inventory (NPI)	Common instrument to assess behaviour and accessory neuropsychiatric symptoms. Satisfactory reliability and validity. The modified version NPI-Nursing Home (NPI-NH) is available for nursing home inhabitants.

Unless otherwise stated, the information is based on the following sources:

1. Collegium Internationale Psychiatriae Scalarum (Hrsg.). Internationale Skalen für Psychiatrie. Göttingen: Belz Test GmbH; 2000.
2. Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E and Clegg A. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. Health Technol Assess 2006; Vol. 10: No. 1.
3. Wolfson C, Moride Y, Perrault A, Momoli F, Demers L, Oremus M. Drug treatments for Alzheimer's disease. II. A review of outcome measures in clinical trials. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2000.

Additional publications were consulted regarding individual scales:

1. Davis KL, Marin DB, Kane R, Patrick D, Peskind ER, Raskind MA et al. The Caregiver Activity Survey (CAS): development and validation of a new measure for caregivers of persons with Alzheimer's disease. Int J Geriatr Psychiatry, 1997; 12: 978-988.
2. Kaufer DI, Cummings JL, Christine D, Bray T, Castellon S, Masterman D et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's Disease: the Neuropsychiatric Inventory Caregiver Distress Scale. J Am Geriatr Soc, 1998; 46: 210-215.
3. Pearlin LI, Mullan JT, Semple SJ, Skaff MM. Caregiving and the stress process: an overview of concepts and their measures. Gerontologist, 1990; 30: 583-594.
4. Rockwood K, Howlett S, Stadnyk K, Carver D, Powell C, Stolee P. Responsiveness of goal attainment scaling in a randomized controlled trial of comprehensive geriatric assessment. J Clin Epidemiol, 2003; 56: 736-743.

APPENDIX F: PREVIOUSLY UNPUBLISHED INFORMATION FROM PHARMACEUTICAL COMPANIES

Summary of the B304 study (1998)

The B304 study in patients with mild to moderate dementia was a 26-week, multicentre, randomised, double-blind, parallel, 3-arm phase II/III study in which the highest individually tolerated dose of rivastigmine (2–12 mg/day), administered 2 or 3 times daily, was compared with placebo.

The primary objective was to compare efficacy and tolerability of the highest individually well-tolerated dose of rivastigmine (given 2 or 3 times daily) versus placebo in patients with probable Alzheimer's disease. The secondary objective was to compare the various dose schemes (2 or 3 times daily administration of rivastigmine) with each other in respect of efficacy and safety, and to assess changes in activities of daily living.

The primary outcomes of the study were the changes after 26 weeks compared with baseline regarding ADAS-cog and CIBIC-plus. Secondary outcomes included the PDS and the ADAS-cogA. The CAS was a tertiary outcome.

Patients were allocated to treatment groups according to a computer-generated randomisation list. Sealed envelopes contained the information on the allocation to groups and were distributed in the centres. The appearance of the capsules containing rivastigmine or placebo was identical. The number of capsules taken was equal in all groups.

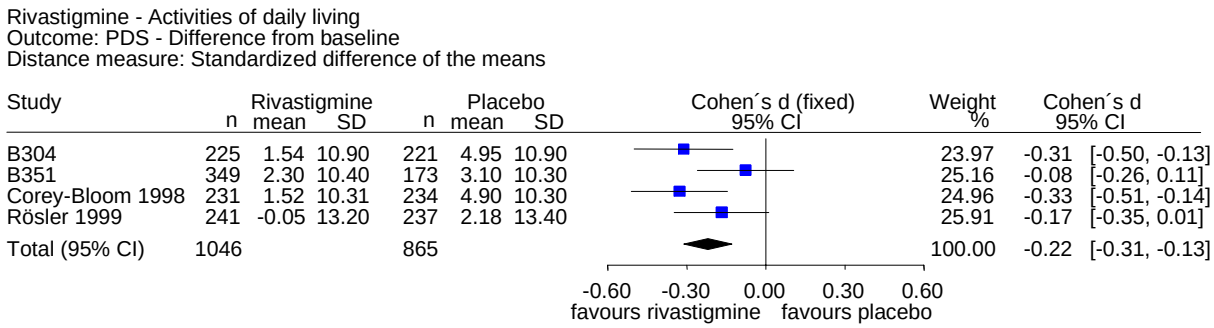
The study comprised a screening phase of approximately 42 days in which patients were examined, the inclusion criteria were assessed, and medication that was not permitted (e.g., psychostimulants, anticholinergic drugs, etc.) were stopped. Subsequently, the baseline evaluation of the various outcome measures was performed, and then the randomisation process took place.

The outcome measures CIBIC-plus, ADAS-cog, and PDS were assessed at Week 12, 18 and 26, the MMSE and GDS were only assessed at Week 26. If a patient prematurely discontinued the study, these outcome measures were each to be assessed at the time of discontinuation. The CAS scale was assessed at Week 6, 12, 18, and 26. Adverse events were documented during the course of the study.

Data and study information that were considered in the present evaluation are presented in the tables and report text of this evaluation.

APPENDIX G: ADDITIONAL META-ANALYSES

Meta-analyses on rivastigmine that considered outcomes of the B351 studies (from [49] in each case) are presented below.



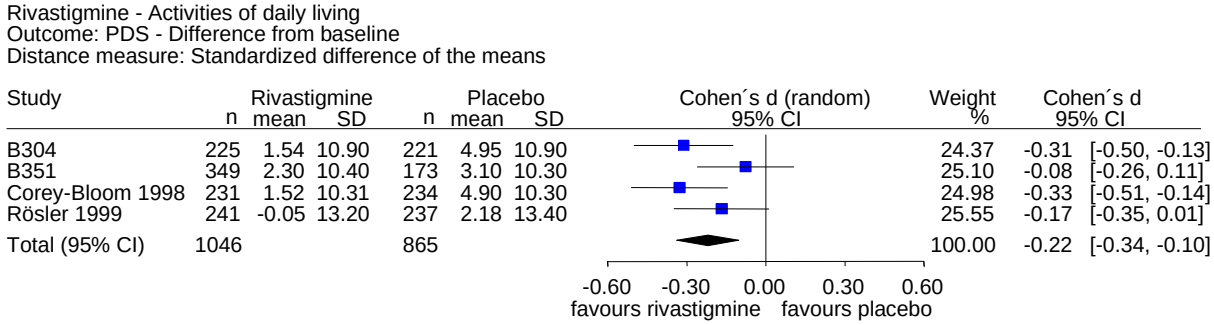
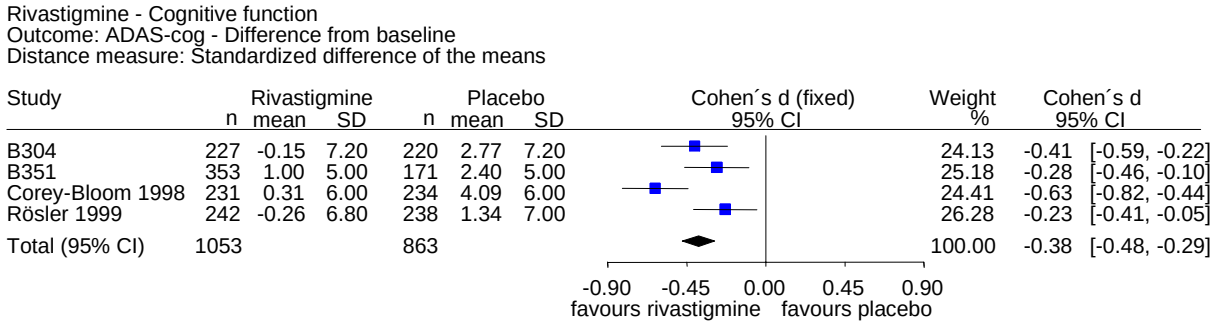


Figure 49. Rivastigmine: Meta-analysis of daily living skills (including B351; fixed and random effects)



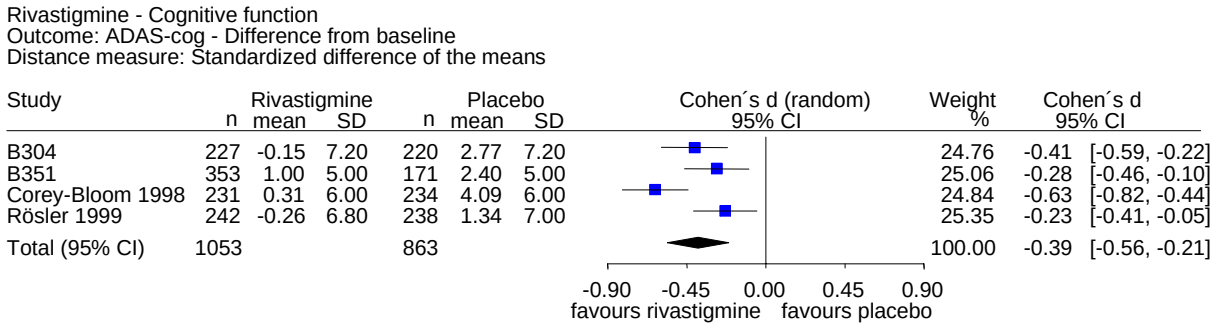


Figure 50. Rivastigmine: Meta-analysis of cognitive function (including B351; fixed and random effects)

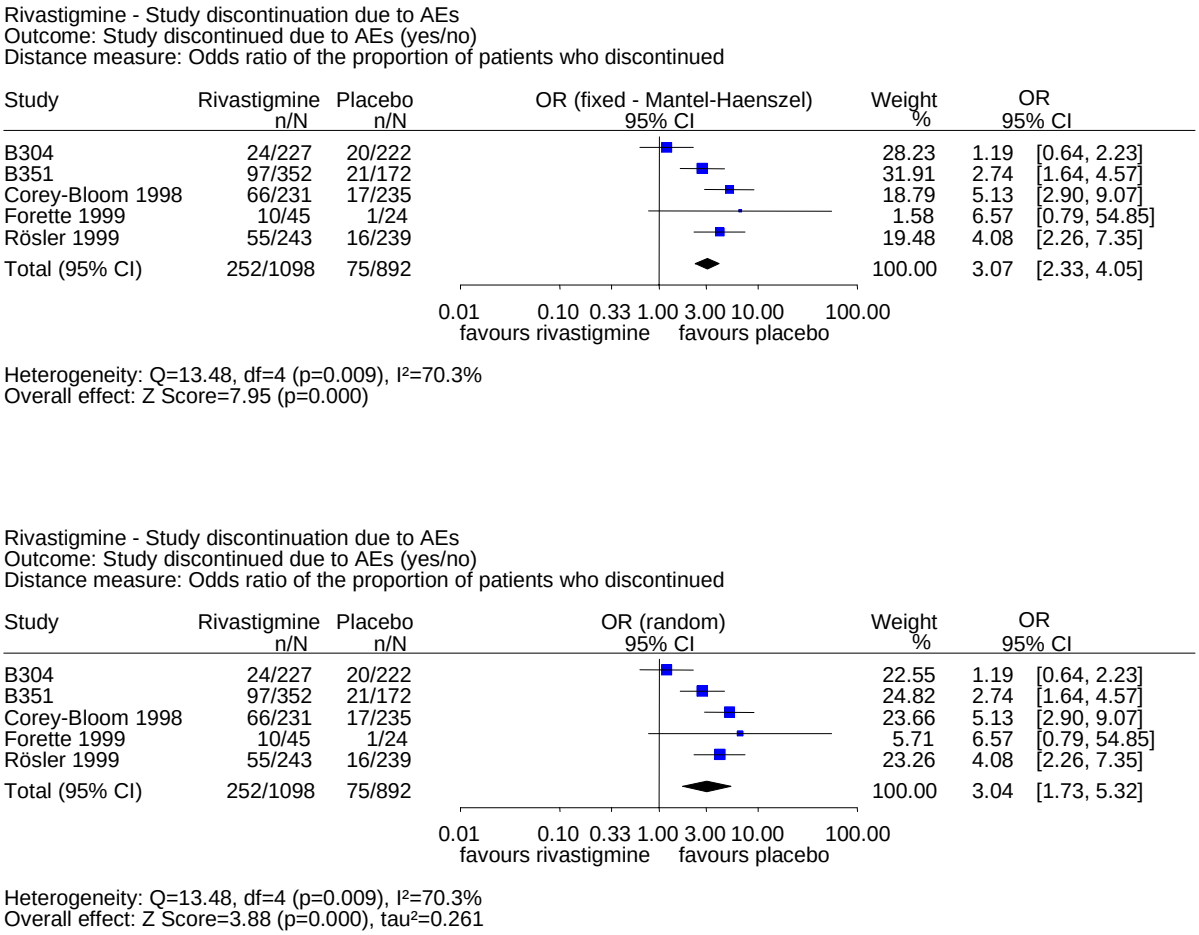


Figure 51. Rivastigmine: Meta-analysis of study discontinuations due to adverse events (including B351; fixed and random effects)

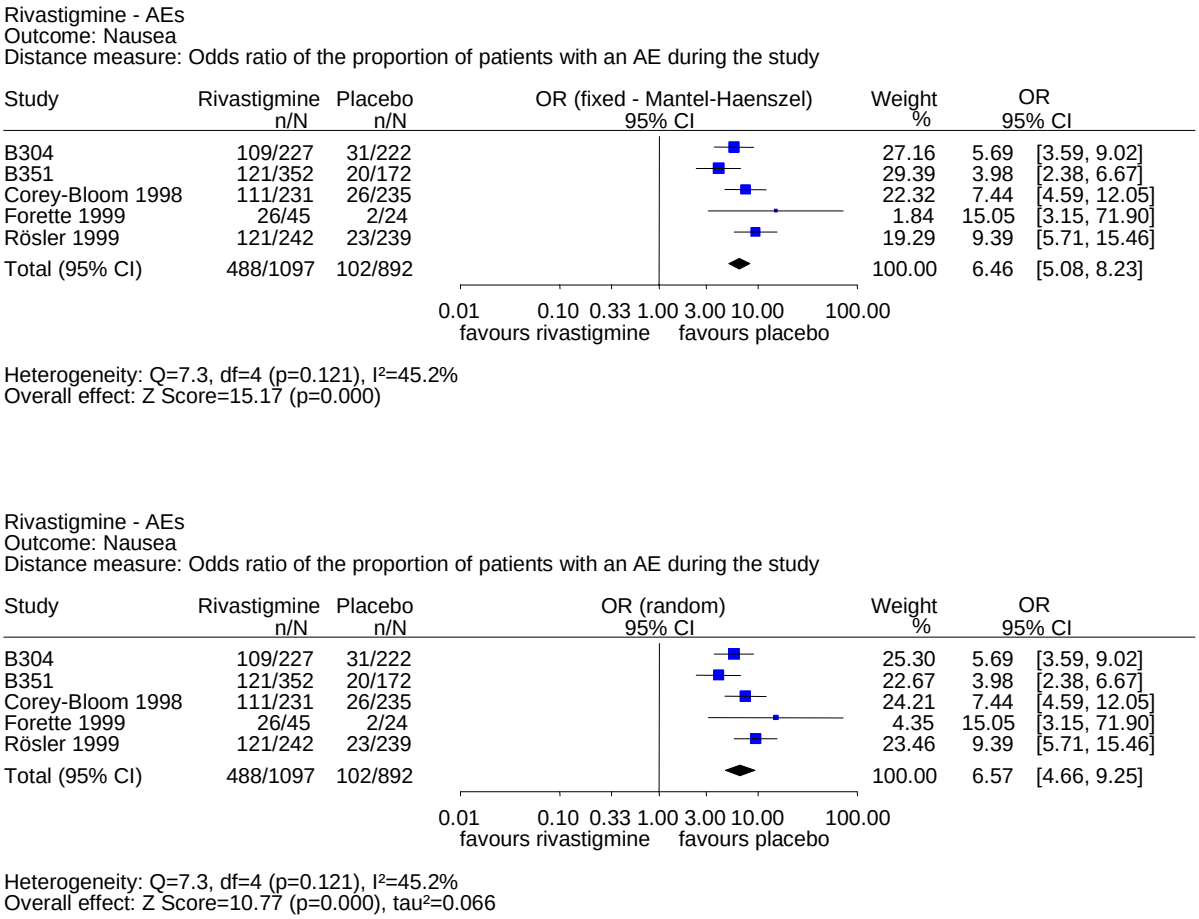


Figure 52. Rivastigmine: Meta-analysis of the outcome "nausea" (including B351; fixed and random effects)

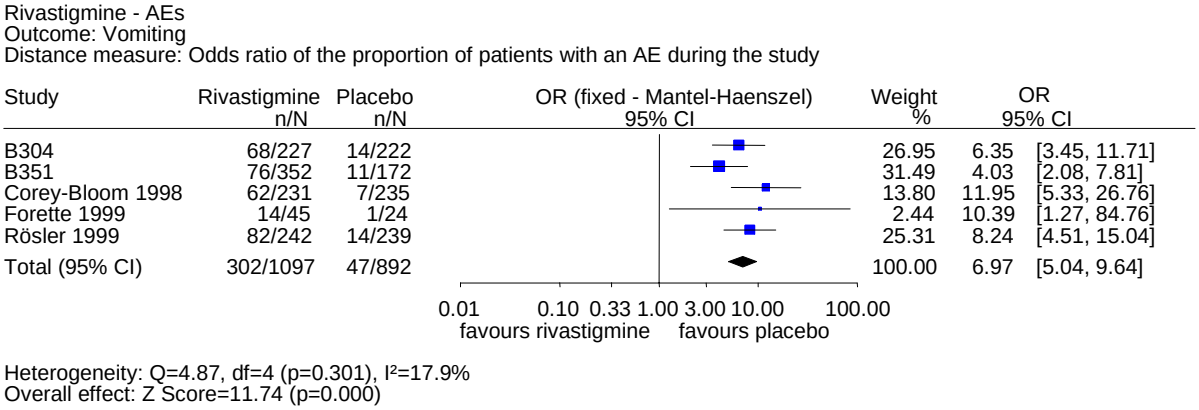


Figure 53. Rivastigmine: Meta-analysis of the outcome "vomiting" (including B351)

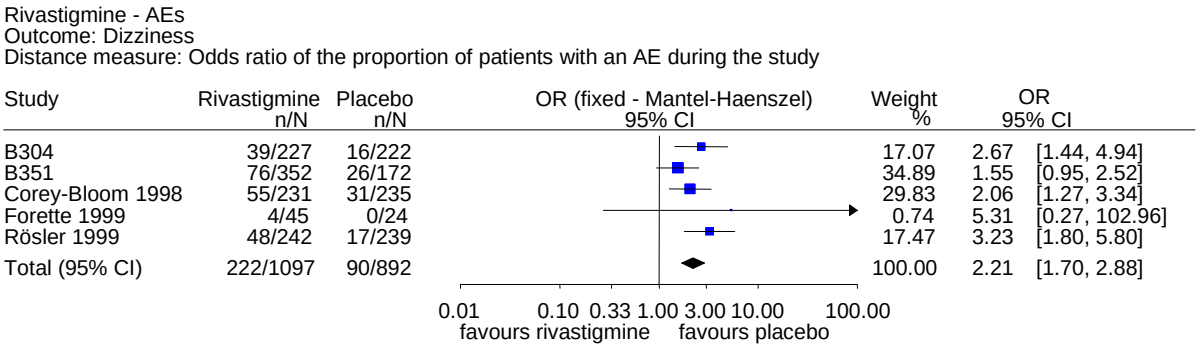


Figure 54. Rivastigmine: Meta-analysis of the outcome "dizziness" (including B351)

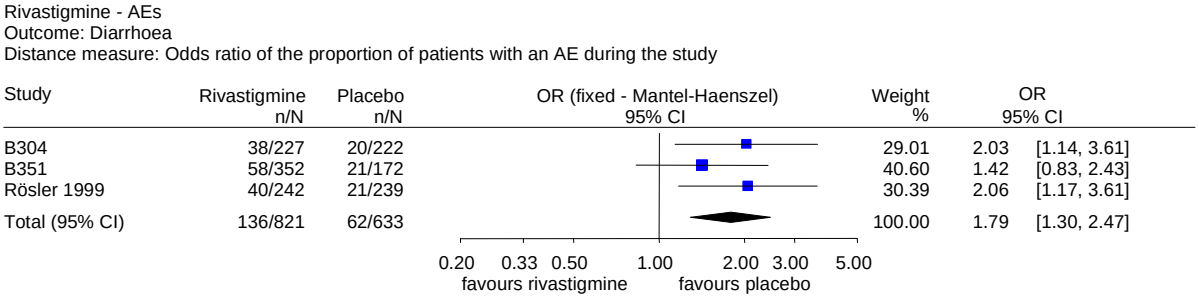


Figure 55. Rivastigmine: Meta-analysis of the outcome "diarrhoea" (including B351)

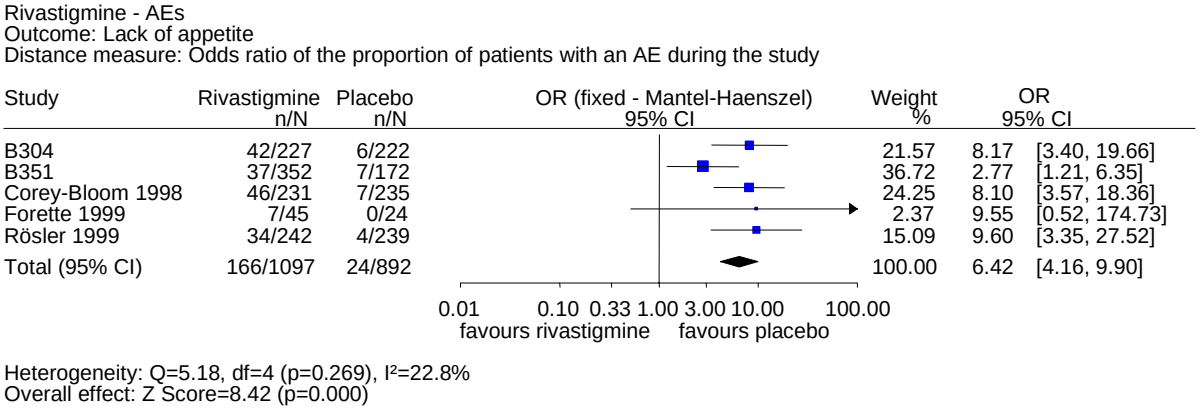


Figure 56. Rivastigmine: Meta-analysis of the outcome "lack of appetite" (including B351)

APPENDIX H: MEETING MINUTES OF THE SCIENTIFIC DEBATE

(available in German under http://www.iqwig.de/download/A05-19A_Abschlussbericht_Cholinesterasehemmer_bei_Alzheimer_Demenz.pdf)