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Federal Department of Home Affairs

Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Health Technology Assessment (HTA)

HTA Report

Title	Medicines for Dementia due to Alzheimer's and Parkinson's Disease
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Technology	donepezil, galantamine, rivastigmine, memantine
Type of Technology	Pharmaceuticals
Date	30 September 2022

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Abbreviations and acronyms

Aβ	Beta amyloid protein
ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer’s disease
ADL	Activities of daily living
AHEAD	Assessment of Health Economics in Alzheimer’s Disease
BADL	Bristol Activities of Daily Living Scale
BPSD	Behavioral and psychological symptoms
CDR-SB	Clinical Dementia Rating scale Sum of Boxes
CEA	Cost-effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHF	Swiss francs
CIBIC-plus	The Clinician's Interview-Based Impression of Change Plus caregiver input
CUA	Cost-utility analyses
DALYs	Disability adjusted life years
DES	Discrete event simulation
DSM	Diagnostic and Statistical Manual
ELSO	Ethical, legal, social and organizational
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
FOPH	Federal Office of Public Health
FTC	Full-time care
GDS	Global Deterioration Scale
GP	General practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	National Authority for Health (Haute Autorité de Santé)
HTA	Health Technology Assessment
INAHTA	International HTA database
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LB	Lewy bodies

MCID	Minimal Clinically Important Difference
MD	Mean difference
MMSE	Mini mental state examination
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMDA	N-methyl-D-aspartate
NPT	Non-pharmacological treatment
NR	Not reported
PD	Parkinson’s disease
PICO	Population, intervention, comparator, outcome
POP	Planned and Ongoing Projects
pre-FTC	Pre full-time care
QALY	Quality adjusted life years
RCT	Randomized Controlled Trial
RoB	Risk of Bias
RQ	Research question
RWE	Real world evidence
SC	Standard of Care
SD	Standard deviation
SE	Standard error
SL	List of pharmaceutical specialties (Spezialitätenliste)
WHO	World Health Organization

Executive Summary

Background: Currently, no disease-modifying treatment is available for Alzheimer disease (AD) or Parkinson's disease dementia (PD). Professional societies in Switzerland generally recommend symptomatic treatment using non-pharmacological therapies, and to add antidementia drugs when needed. However, scientific literature is inconclusive about the clinical benefit of antidementia drugs. A health technology assessment (HTA) was requested to compare the available evidence on Acetylcholinesterase (AChE) inhibitors and memantine for the symptomatic treatment of AD and PD.

Objective: This HTA examines the efficacy, effectiveness, safety and cost-effectiveness of antidementia drugs compared to treatment without antidementia drugs or placebo in AD and PD and presents the health economic impact of a potential removal of these drugs from the list of pharmaceutical specialties in Switzerland. Furthermore, ethical, legal, social and organizational aspects are considered.

Research questions: Is it efficacious, effective, safe and cost-effective 1) to treat **mild to moderately severe AD** patients with **donepezil, galantamine or rivastigmine** compared to not treating them with antidementia drugs? 2) to treat **moderate to severe AD** patients with **memantine** compared to not treating them with memantine? 3) to treat **mild to moderately severe PD** patients with **rivastigmine** compared to not treating them with rivastigmine? What is the **budget impact** of donepezil, rivastigmine, galantamine and memantine? Are there **ethical, legal, social, or organizational issues** related to antidementia drugs?

Methods: We conducted systematic literature reviews of evidence on the efficacy, effectiveness and safety and of health economic evaluations regarding the treatment with antidementia drugs compared to treatment without antidementia drugs or placebo in AD and PD. For the clinical evidence meta-analysis was performed for outcomes with sufficient available evidence. The certainty of evidence for relevant outcomes was assessed by applying the GRADE approach. The cost-effectiveness and cost-utility were assessed by transferring the results from international studies to Switzerland, while a budget impact model was built for the Swiss setting. Furthermore, a targeted search for evidence on the ethical, legal, social and organizational aspects of antidementia drugs was conducted and findings were qualitatively summarized and discussed.

Results: Regarding treatment with donepezil, galantamine or rivastigmine in mild to moderately severe AD patients, 24 RCTs were included in the analysis. 15 trials investigated donepezil, 6 trials rivastigmine and 3 trials galantamine. The certainty of evidence for the critical outcomes was judged as low to high, with evidence pointing at better results on cognition, function and global outcomes for AChE inhibitors compared to placebo in patients with mild to moderate dementia due to AD. Serious adverse events were higher for AChE inhibitors at one year of follow-up. Regarding treatment with memantine in moderate to severe AD patients, only two RCTs were identified. We found better results for memantine compared to placebo in patients with moderate to severe dementia due to AD on the domains of function and global outcomes with moderate certainty. With low certainty, there were no statistically significant differences with respect to mortality and serious adverse events. Regarding treatment with rivastigmine in mild to moderately severe PD patients, only one RCT was identified. This trial was rated with a high

risk of bias and showed statistically significant better results on cognition, function, neuropsychiatric symptoms and global outcomes for rivastigmine compared to placebo in patients with mild to moderate dementia due to PD. Regarding safety, no statistically significant differences were identified.

Based on a systematic review of health economic evaluations we retrieved 30 studies, 17 of which were considered transferable and were adapted for Switzerland. Seven studies investigated donepezil, galantamine or rivastigmine in mild to moderately severe AD patients and ten studies memantine in moderate to severe AD patients. Only one study was identified regarding rivastigmine in mild to moderately severe PD patients but was not considered transferable. Of the seven studies investigating donepezil, galantamine or rivastigmine in mild to moderately severe AD patients, four were regarding donepezil, three galantamine and no study was considered transferable regarding rivastigmine. Although these studies were considered transferable there is uncertainty related to their input parameters and assumptions. Regarding donepezil, galantamine or rivastigmine in mild to moderately severe AD patients, the results suggest that donepezil is not cost-effective over a time-horizon of up to 1.5 years. Over a time-horizon of 10 years, donepezil becomes dominant. Similarly, treatment with galantamine seems to be cost-effective over a time-horizon of 5 years. Regarding memantine in moderate to severe AD patients, four out of the seven adapted studies indicate memantine to be dominant. The other three studies indicate that memantine is cost-effective below a hypothetical threshold of CHF 100,000 per QALY.

Regarding budget impact, a total removal of the AChE inhibitors or memantine would lead to additional costs ranging from CHF 1.01 million for galantamine to CHF 12.42 million for rivastigmine for the healthcare payers, attributable mostly to higher rates of institutionalization. In the extreme assumption that there is no treatment effect on institutionalization, stopping AD treatment with one of the AChE inhibitors or memantine would lead to savings that vary from CHF 0.80 million for galantamine to CHF 7.87 million for rivastigmine.

Several ethical, legal, social, and organizational issues were identified concerning the use of antidementia drugs. A decision that would affect the use of these medications should respect patient autonomy and consider the consequences for the proxies. Another crucial ethical issue is the focus on cognitive and global outcomes in the trials that might leave out many much more relevant signs and symptoms, such as alterations of mood, anxiety, psychotic symptoms, and insomnia. From a legal perspective, a decision by the competent authorities must guarantee the protection of people with disabilities and elderly persons and consider the capacity of judgment. On the social domain, a high level of burden was noted in caregivers of dementia patients, and problems with access to antidementia drugs for some patients. A variety of organizational issues were discussed in the literature, from national dementia strategies to variations in antidementia treatment between different regions.

Conclusion: Our results are consistent with previous findings from Cochrane reviews and other systematic reviews including meta-analysis. Despite statistically significant differences for many outcomes investigated, we come to the conclusion that the clinical relevance of the differences between the treatment with and without antidementia drugs is questionable based on published cut-off values for Minimal Clinically Important Difference (MCID). There is also no strong evidence in support of a difference on the safety outcomes between the two groups. All antidementia drugs can be cost-effective except for rivastigmine when used for the treatment of PD due to lack of published transferrable health economic

studies. The budget impact caused by total removal of the AChE inhibitors or memantine could range between additional costs of up to CHF 12.42 million to savings of up to CHF 7.87 million in 2021. This remarkable range is related to the uncertainty of evidence regarding the delay of need of being transferred to institutionalized care.

Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in a HTA report include clinical effectiveness and safety, costs, cost-effectiveness and budget impact, ethical, legal, social and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1 Policy question and context

The World Health Organization (WHO) considers dementia as a public health priority.[1] Currently around 144'000 people suffer from dementia in Switzerland.[2] Furthermore, the total annual cost of dementia (direct and indirect costs) in Switzerland was estimated at CHF 11.8 billion for the year 2017.[3]

The two main causes for dementia are either disturbed central blood flow (central ischemia or bleeding) or a progressive neurodegeneration. Both lead to a disturbance of cognitive function which is often accompanied by further dementia symptoms such as changes in emotional control, motivation, social behaviour, or sleep-wake rhythm. In dementia due to Alzheimer's Disease (AD) and Parkinson's Disease (PD), loss of cholinergic neurons lead to reduced production of the neurotransmitter acetylcholine (ACh).[4] Acetylcholinesterase (AChE) inhibitors and memantine (a N-methyl-D-aspartate (NMDA) receptor antagonist) are two antidementia drugs that target to alleviate or avoid worsening of cognitive and neuropsychiatric symptoms.[5]

In Switzerland, AChE inhibitors donepezil, rivastigmine and galantamine are reimbursed for the treatment of mild to moderate dementia due to AD (mini mental state examination (MMSE) ≥ 10; MMSE is a common tool for measuring cognitive function and the score ranges from 0 (most severe) to 30 (normal)). Rivastigmine is also reimbursed for the treatment of mild to moderate dementia due to PD. For the symptomatic treatment of moderate to severe dementia (MMSE 3-19) due to AD, memantine is reimbursed.[6] Based on the list of pharmaceutical specialties ("Spezialitätenliste" or SL) these medications are only reimbursed as monotherapies and under the condition that the cognitive functions are assessed with the MMSE at the beginning of treatment, after three months and subsequently every six months.[7]

The "Therapy Guidelines for the Behavioural and Psychological Symptoms of Dementia" issued by several professional societies from Switzerland recommends starting with non-pharmacological therapies and only add antidementia drugs where needed.[8] The NICE guidance as well as the "S3-Leitlinie" recommend the use of AChE inhibitors in mild to moderate AD and memantine in moderate to severe AD.[5,9] Furthermore, AChE inhibitors and memantine are reimbursed in most European countries.[10] However, AChE inhibitors and memantine were removed from the list of reimbursable products in France in 2018. This decision was based on the 2016 report by the French National Authority for Health (HAS).[11] This report concluded that, based on the available clinical data, the drugs have a positive effect on short-term cognitive symptoms compared to placebo. However, the clinical benefit in the real-world setting remains unclear. In addition, side effects were observed in both AChE inhibitors and memantine.

In 2009, the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany assessed the evidence on the benefits and harms of various drug and non-drug therapies for AD.[12] According to their study, AChE inhibitors have positive effects on cognition in patients with mild to moderate AD that use

the drug for at least four months. For other outcomes, such as associated symptoms (e.g. agitation and depression), quality of life or need for care, there was not enough evidence, or the evidence could not be interpreted with sufficient certainty. This study also found that there was no evidence to support the benefit of treating moderate to severe dementia due to AD with memantine in cognitive performance and in activities of daily living (ADL). However, in 2010 IQWiG conducted a further analysis with additional data they received from Merz Pharma, the manufacturer of memantine. The updated results indicated a positive effect of memantine on cognition and ADL.[13] Nevertheless, IQWiG noted that especially the results related to ADL should not be regarded as evidence, due to the uncertainty of the responses and the small effect size. It also noted that the observation period in all studies was up to six months and long-term studies would be required.

Considering this uncertainty regarding the clinical benefit of AChE inhibitors and memantine, and the fact that this HTA topic was submitted twice to the Federal Office of Public Health (FOPH), the treatment of dementia due to AD and PD using these medications was selected in 2019 in Switzerland to be re-evaluated based on an HTA. Consequently, this HTA summarizes the evidence base on AChE inhibitors and memantine for use in patients with dementia due to AD or PD, to inform policy makers in their decision if AChE inhibitors or memantine should continue to be reimbursed by the Swiss social health insurance.

2 Research question

1. What are the benefits and harms of the treatment with donepezil, galantamine, rivastigmine or memantine compared to treatment without these drugs in patients with dementia due to AD or PD?
2. How cost-effective is the treatment with donepezil, galantamine, rivastigmine or memantine compared to treatment without these drugs in Switzerland?
3. What is the annual budget impact of the treatment with donepezil, galantamine, rivastigmine and memantine compared to treatment without these drugs in Switzerland?

3 Medical background

3.1 Description of dementia

Dementia is “A syndrome consisting of progressive impairment in memory and at least one other cognitive deficit (aphasia, apraxia, agnosia, or disturbance in executive function) in the absence of another explanatory central nervous system disorder, depression, or delirium”.[14]

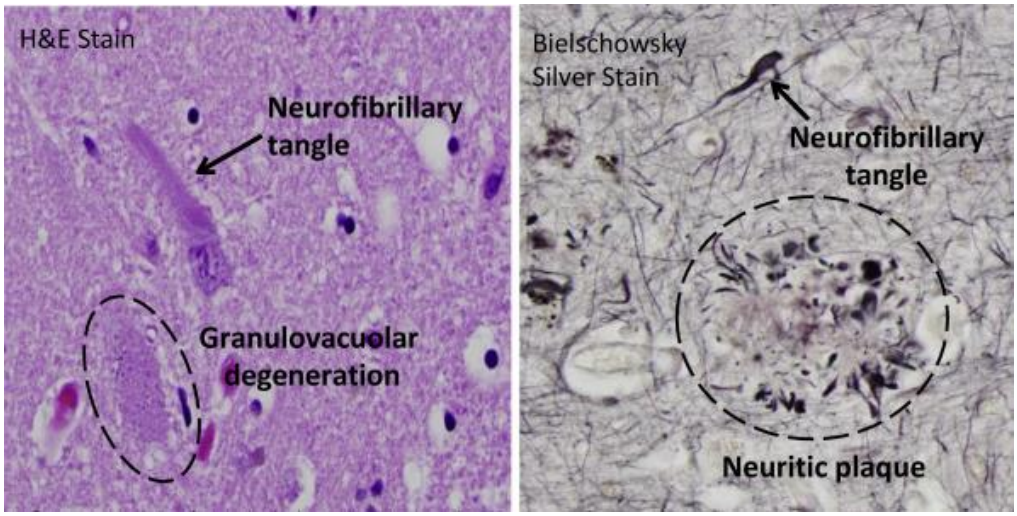
Dementia mainly occurs due to a disturbed central blood flow (central ischemia or bleeding) or a progressive neurodegeneration. Furthermore, dementia can occur as a consequence of many different diseases and injures that primarily or secondarily affect the brain.[1,15]

Dementia due to Alzheimer’s disease (AD) is with 60-70% of the cases the most common type of dementia followed by vascular dementia (5-10%).[1,15] Other types of dementia include dementia due to Parkinson’s disease (PD), lewy body dementia, a group of diseases that contribute to frontotemporal dementia, and Huntington’s disease dementia. There are no clear margins between the different forms of dementia and multiple forms of dementia can occur simultaneously.[1,15] This HTA is focusing on dementia due to AD and PD.[16] While each patient with AD has dementia not every PD patient has dementia. Up to 80% of PD patients develop dementia. [17]

3.1.1 AD pathology

General loss of nerve cells, neuritic plaques, neurofibrillary tangles and granulovacuolar degeneration of neurons are pathological indicators of AD (Figure 1).[18–21] The hippocampus, entorhinal cortex, subiculum, and the amygdala are the main brain areas affected by these changes, characteristic of AD.[20] Neurofibrillary tangles are filaments within the cytoplasm of nerve cells that look like fibres that result from the hyperphosphorylation and aggregation of Tau protein[21]; Neuritic plaques are circular accumulations of material, comprised mainly of protein amyloid and degenerated nerve terminals that surround it, present across the cerebral cortex; Granulovacuolar degeneration of neurons reflects a problem in phagocytosis of broken proteins. These changes are believed to be those leading to neuronal degeneration and AD pathology.[20]

Figure 1 Pathological indicators for AD



Source: Jentoft, 2016[22]

When amyloid precursor protein (APP) is split first by beta (β) secretase, and then gamma (γ) secretase, beta amyloid protein (Aβ) 40 or 42 can be produced.[19–21] Aβ42 is neurotoxic and causes nerve damage in AD. Mutations in APP, γ secretase and Apo E4 increase toxicity of Aβ42.[20] This is currently the most often cited hypothesis for the pathogenesis of the disease, as increased levels of Aβ42 are followed by neurofibrillary tangles and neuritic plaques.[20]

There is however uncertainty in the relationship between amyloid deposition, NFTs formation, neuronal death and atrophy.[19–21] Some of the uncertainty can be explained through genetic risk factors.[20,21]

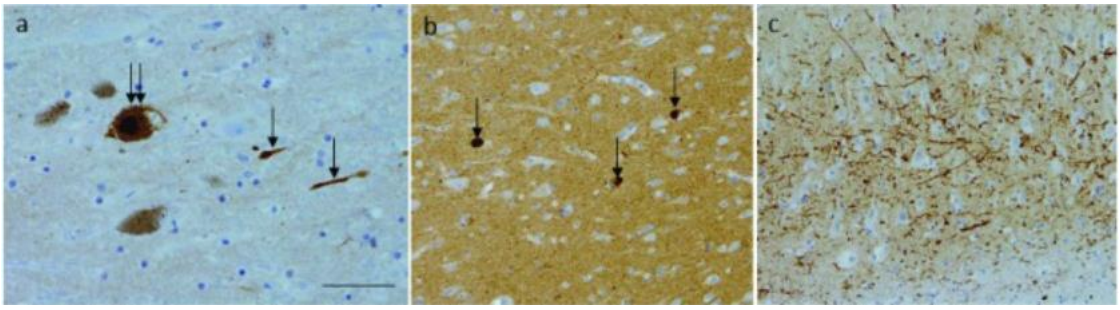
In dementia due to AD (and PD), loss of cholinergic neurons leads to reduced production of the neurotransmitter acetylcholine (ACh), a neurotransmitter, which is responsible for attentional and memory processes.[4] ACh gets metabolized by the enzyme acetylcholinesterase (AChE). The inhibition of AChE by AChE-inhibitors leads to more available ACh in the synaptic cleft, which is associated with an improvement of cognition. The levels of several other neurotransmitters are also reduced in patients with AD.[19,20]

Excessive flow of calcium into neurons due to dysfunction of the N-methyl-D-aspartate (NMDA) glutamate receptors caused by neuroinflammation contribute also to the AD pathology.[23] Blocking NMDA receptors reduces this continuous stimulation, which prevents apoptosis and enables the neurons to better communicate.

3.1.2 PD pathology

Dementia due to PD is characterized by deposits of Lewy bodies (LB) composed primarily of protein α-synuclein aggregations (Figure 2).[24] LB concentrate primarily in entorhinal and anterior cingulate cortex brain regions in this disease.[24] Patients typically present with widespread areas of cortical atrophy and grey matter reductions in the temporal and frontal lobes and the left parietal lobe.[24]

Figure 2 Pathological indicators for PD



Source: Weil, 2017[25]

(a) Lewy body found in the dopaminergic cells of the substantia nigra (double arrow) along with Lewy neurites (arrows). (b) Lewy bodies observed in the cingulate gyrus (arrows). (c) A dense network of Lewy neurites in the CA2 subregion of the hippocampus. Bar = 50 µm (a) and 100 µm (b, c).

As compared to AD, PD patients have a loss in thalamic cholinergic neurons and a larger dysfunction in cholinergic mechanisms, which are associated with cholinergic basal forebrain neurons loss, problems with working memory, attention, executive function, depression and visual hallucinations which constitute common neuropsychological and behavioral symptoms shared with lewy body dementia but not AD and are attributes of dysexecutive syndrome, also called LB pathology.[24,26,27] This cholinergic loss doesn't correlate with the severity of motor symptoms, which is a prominent feature in PD, nor with AD-type pathology.[24]

A much smaller proportion of PD patients experience an AD-like pathology, also known as amnestic syndrome, where NFTs and neuritic plaques are encountered but are much smaller correlated to dementia, and Aβ and tau pathologies play a similar role as in AD, resulting in the expression of similar symptom.[24] When the pathologies of LB and AD are combined in one PD patient, there is a mutation in the LRRK2, SNCA or especially in the APOE or GBA genes, there is a higher likelihood of the development of dementia.[24,28,29]

A variety of neurotransmitters are believed to be involved in the pathology of PD. However, substantial evidence exists only for AChE and dopamine.[24,25] As opposed to PD without dementia, in PD with dementia here are lower brain levels of dopamine, homovanillic acid, dopamine transporter (DAT), AChE,

cortical choline acetyltransferase (ChAT), and higher neuronal loss associated with these neurotransmitter changes.[24]

In PD, there is believed to be a compensation in homovanillic acid/dopamine ratios and dopamine D2 receptor density as a response to lower dopamine levels and high activity of striato-pallidal neurons, respectively, mechanisms that start failing into PD progression as this ratio and receptor density decrease.[24] PD patients also experience disturbed consciousness which is associated with higher D2 receptor binding in the thalamus.[24] The neurotransmitter system that is most closely associated with PD symptoms, is the cholinergic system.[24]

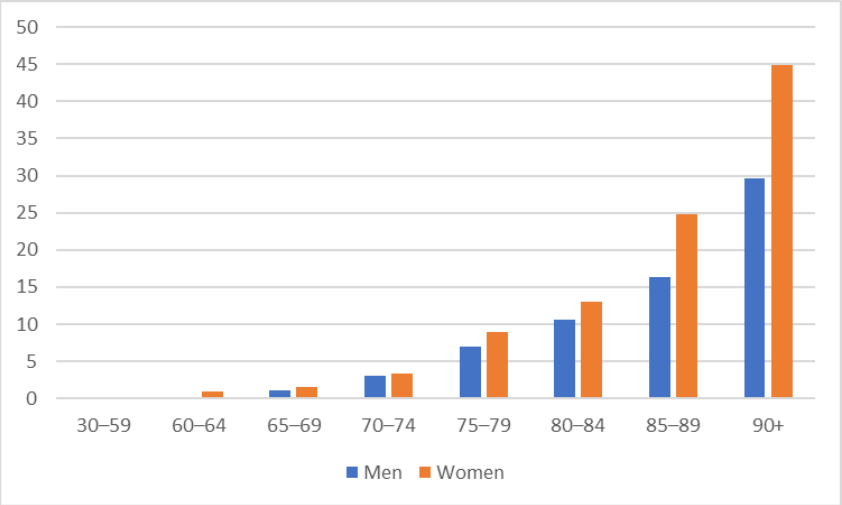
As compared to PD cases, patients with dementia due to PD have lower DAT levels and D2 receptor density in the caudate ventromedial section and the temporal cortex, respectively, which is correlated with extrapyramidal symptoms or cognitive decline as measured by MMSE.[24]

3.1.3 Risk factors

The main risk factor for dementia is age (Figure 3).[10] Female gender is also associated with dementia, which is amongst others attributed to longer life expectancy.[30] Other risk factors include those modifiable: physical and cognitive inactivity, smoking, alcohol, weight, diet, blood pressure, cholesterol and blood sugar levels, which account for up to 50% of the risk of dementia[6,30–32] and disease-specific non-modifiable factors such as traumatic brain injury and Down's syndrome for AD[14,33], whereas PD dementia is more frequent in males, those who had previous exposure to herbicides and pesticides, and is more prevalent in patients that have lived longer with PD.[14] As many as 75% of PD patients eventually develop dementia).[14,17]

There are also genetic risk factors for dementia. Presenilin genes on chromosome 14 might account for up to 50% of familial AD cases, and those on chromosome 1 might account for a large share of the remaining cases.[20] The existence of APP mutations and UBQLN1 increase the risk of AD, whereas E4, an isoform of Apo E, can increase the risk of sporadic AD threefold.[20] TREM2 polymorphism also increases the risk, by causing problems in the removal of amyloid.[20]

Figure 3 Age and gender distribution of dementia in Switzerland



Own figure based on data from Alzheimer Europe 2019[10]

3.1.4 Diagnosis

Multiple criteria exist for the diagnosis of dementia. The most well-known criteria are that described in the Diagnostic and Statistical Manual of Mental Disorders[14], which provides a set of criteria for the diagnosis of dementia, referred to as neurocognitive disorder in the DSM-5, and its etiological subtypes (e.g. dementia due to AD or PD) (Figure 4, Figure 5, Figure 6).[10,22,25] In 2018, with the objective of fostering the "Development and expansion of regional and networked centres of competence for diagnostics" in the framework of the National Dementia Strategy 2014–2019, the working group consisting of the Swiss Memory Clinics (SMC) association, the Swiss Society for Geriatric Psychiatry and Psychotherapy (SGAP), the Swiss Society of Geriatrics (SFGG), the Swiss Neurological Society (SNG), the Swiss Association of Neuropsychologists (SVNP) and other experts published guidelines for the diagnosis of dementia and its subtypes.[34] These closely follow the procedure presented in DSM-5. In the UK, NICE has published similar guidelines, which however recommend the procedure published by the National Institute on Aging-Alzheimer's Association (NIA-AA) for AD dementia diagnosis[35], and Movement disorders Society criteria for PD dementia[36], which are most often used in the research setting. The European Federation of Neurological Societies and the European Neurological Society (EFNS-ENS) recommend the use of the same guidelines for AD and PD dementia diagnosis, and DSM-5 for general dementia diagnosis.[37]

Figure 4 DSM-5 diagnostic criteria for dementia

A. Evidence of [modest/significant*] cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild/significant* decline in cognitive function; and
2. A modest/substantial* impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits [don't/interfere*] with independence in everyday activities [i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required/at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications*].

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Specify:

Without behavioral disturbance: If the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.

With behavioral disturbance (specify disturbance): If the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioral symptoms).

Specify current severity:

Mild: Difficulties with instrumental activities of daily living (e.g., housework, managing money).

Moderate: Difficulties with basic activities of daily living (e.g., feeding, dressing).

Severe: Fully dependent.

Source: Adapted for illustration purposes from DSM-5[14]

**Note: here, mild and major dementia are different from MMSE-diagnosed mild/moderate dementia.*

**Squared brackets designate that information pertains first to mild dementia, then to major dementia.*

Figure 5 DSM-5 diagnostic criteria for AD

A. The criteria are met for major or mild neurocognitive disorder.

B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired).

C. Criteria are met for either probable or possible Alzheimer's disease as follows:

For major neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if either of the following is present; otherwise, **possible Alzheimer's disease** should be diagnosed.

1. Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing.

2. All three of the following are present:

a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).

b. Steadily progressive, gradual decline in cognition, without extended plateaus.

c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).

For mild neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history.

Possible Alzheimer's disease is diagnosed if there is no evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history, and all three of the following are present:

1. Clear evidence of decline in memory and learning.

2. Steadily progressive, gradual decline in cognition, without extended plateaus.

3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline).

D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

Source: Adapted for illustration purposes from DSM-5[14]

Figure 6 DSM-5 diagnostic criteria for PD

A. The criteria are met for major or mild neurocognitive disorder.

B. The disturbance occurs in the setting of established Parkinson's disease.

C. There is insidious onset and gradual progression of impairment.

D. The neurocognitive disorder is not attributable to another medical condition and is not better explained by another mental disorder.

Major or mild neurocognitive disorder probably due to Parkinson's disease should be diagnosed if 1 and 2 are both met. Major or mild neurocognitive disorder possibly due to Parkinson's disease should be diagnosed if 1 or 2 is met:

1. There is no evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).

2. The Parkinson's disease clearly precedes the onset of the neurocognitive disorder.

Source: Adapted for illustration purposes from DSM-5[14]

Underdiagnosis and misdiagnosis

As the prevalence of dementia increases with age, also more cases of dementia remain undiagnosed. One of the reasons is that with older age symptoms that could be interpreted as manifestations of dementia are attributed to normal aging.[14] Also, in advanced ages, individuals experience more comorbidities and sensory deficits that make the diagnosis of dementia vs. other diseases more challenging. The

subtypes of dementia are more difficult to be diagnosed as well due to the high number of possible sources of neurocognitive problems. As a direct consequence, most individuals with dementia are not officially diagnosed with this condition. Instead, 1/3 are diagnosed with dementia, 1/3 are suspected to have dementia, and the remaining third are not recorded.[6,38]

This picture of dementia underdiagnosis presents a problem in a context where some dementia subtypes are treatable, and others such as those etiologically due to AD and PD could be better managed through earlier pharmaceutical and non-pharmaceutical (psychosocial) treatment.[6] In Switzerland, the MMSE is the most widely used test for cognitive examinations [1,2], however, it is not sensitive enough to detect early stages of dementia. Improving early detection of dementia was one of the aims in the Swiss National Dementia Strategy 2014–2017.[39]

Early diagnosis enables the organization of appropriate drug and psychosocial therapy as well as preventive measures to reduce complications[6], which stabilizes symptoms, maximizes treatment benefit, leads to longer term autonomy, lower burden on relatives and societal costs[8,40]; it can also give patients autonomy by allowing them to decide on their treatment[40] and help to solve organizational issues: select type of living, manage the finances, writing the will.[6] Disease-modifying therapies, in particular, might be more effective when administered early on the disease stage, as this is the population that was investigated during the clinical trials.[6] A study exploring the early diagnosis and management of dementia in Switzerland found that only 64% of GPs felt confident in the early diagnosis of patients with dementia, whereas around 75% GPs carried the assessment of dementia themselves.[38]

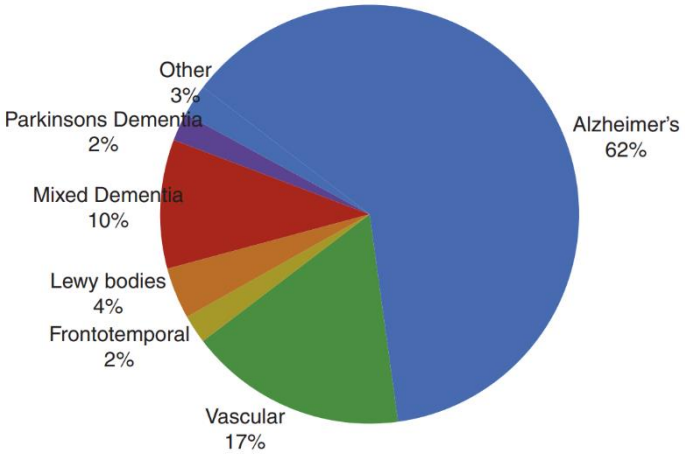
Beside underdiagnosis, misdiagnosis can be an additional issue. Three types of misdiagnosis have been reported.[41] First, dementia can be confused with normal cognition (as boundaries are arbitrary), with delirium, a major depressive disorder, or a learning disorder. Second, a dementia subtype can be confused with another subtype with similar symptoms: e.g. AD with vascular dementia. Additionally, one patient may suffer from more than one dementia subtype. Third, dementia subtypes can be mistaken by other diseases that often co-occur such as delirium or cerebrovascular disease in AD. As a result of the difficulty in the diagnosis of dementia and its associated subtypes, it has been noted that in 25% of AD diagnosis cases an adjustment was required following a PET scan, and a 30% misdiagnosis rate after a post-mortem follow-up has been reported.[41] Misdiagnosis is an important issue as the type of diagnosis determines the treatment decisions and the treatment outcomes.

3.2 Epidemiology and burden of dementia

3.2.1 Epidemiology

It is estimated that around 144'000 people currently suffer from dementia in Switzerland.[2] In addition, there are more than 25'000 new dementia cases every year.[6] The largest share of these numbers are attributed to the six most common types of dementia (Figure 7). AD is very uncommon under the age of 65, over this threshold, the average prevalence has been estimated at about 5.05% through a meta-analysis of European studies.[42,43] If we apply this number to the population size reported by the Swiss Federal Statistical Office, we get approximately 90'000 AD patients over 65 years of age living with the disease in Switzerland in 2020.[44] The analogous figure for PD is approximately 3'000 patients. This number was calculated from a prevalence of PD in Switzerland of 0.12% in the general population, and an estimated prevalence of dementia in PD of 31.3% as reported in a systematic review.[17] Because of the risk of underdiagnosis, the figures might be up to three times higher. It is projected that dementia prevalence will reach 315'400 people by the year 2050.[2]

Figure 7 Most common types of dementia globally



Own figure based on data from Dierckx, 2020[45]

3.2.2 Disease burden

Globally, of all diseases, dementia is the 7th leading cause of death and a major cause of disability and dependency in the elderly.[1] In Switzerland, AD is the 2nd cause of death after ischemic heart disease, and the 7th leading cause of death and disability combined[46], triggering a loss of 100'000 disability adjusted life years (DALYs) in 2019. In dementia, patients suffer from an impairment in executive functions, but also experience behavioral and psychological symptoms (BPSD) such as delusions, hallucinations,

aggression, agitation, sleep problems, fear, disinhibition, euphoria and irritability which lead to a deterioration in quality of life.[8] Dementia also constitutes a significant burden for the Swiss healthcare system. A health workforce of around 300'000 professionals is involved in the care of dementia patients.[6]

One of the particularities of dementia is that the disease not only affects the patient, but also their caregiver. It is estimated that there are around three directly affected relatives for each patient. A caregiver is defined as "a person in the immediate circle of an individual who is dependent on assistance with certain activities of daily living, who, on a non-professional and informal basis, provides him/her with regular support services of care or presence, of a varied nature and intensity designed to compensate disabilities, difficulties, ensure security, maintenance identity and social bond. Caregivers can be family members, neighbours or friends. This does not concern organized forms of volunteering".[47]

Cognitive decline and BPSD introduce difficulties in carrying basic activities of daily living such as bathing and dressing, and instrumental such as paying bills, shopping and making use of transportation, increasing dependence on their caregivers.[6,48] Caregivers help to manage aggression, depression, anxiety, sleep problems and health problems, help to adhere to medication regimens and treatment recommendations, and provide emotional support.[48] With increasing severity of the disease, caregivers must provide more of their time to the patient, often providing care 24/7, resulting in a substantial physical, emotional and financial burden.[47,49,50] Consequently, there is a spillover effect of health problems such as stress, depression, sleep, and chronic illnesses (hypertension, arthritis, heart disease) to caregivers.[8,49,51] There is some evidence that compared to a control group, caregivers have a higher consumption of healthcare services.[52,53,51,54,55] One study estimated an average increase of 25% in all healthcare services.[51] Caregivers consume more pharmacological treatment (anxiolytics, antidepressants, and antiplatelet) and nonpharmacological treatment, have more emergency room and hospital visits.[51]

As a result of the time-consuming duty of caregiving, many caregivers are unable to dedicate time to personal activities or to exercise their duties, and up to 2/3 of caregivers have an increased absence from work and 31% give up work to attend to the needs of a patient with dementia.[51]

The cost of dementia in Switzerland was estimated at CHF 11.8 billion when caregiver (47% of total) costs were included using a method that calculates "the actual cost that would arise if relatives could no longer take care of the person with dementia"[56], and CHF 6.25 billion when only direct costs were considered, with 2017 as the reference year.[57]

Radically different conclusions can be made if caregiver costs are considered as opposed to the scenario when these costs are not considered: If caregiver costs are not considered, we can conclude that living at home always incurs lower costs than living at a nursing home no matter the stage of dementia, whereas when caregiver costs are considered, patients incur significantly lower costs at home than at

the institution at the moderate and severe stages of the disease. This is due to the multiplicity of tasks and services involved in caregiving, which leads many caregivers to give up work and, some caregivers to undergo training to be able to keep up with these tasks.[48]

3.3 Treatment of dementia

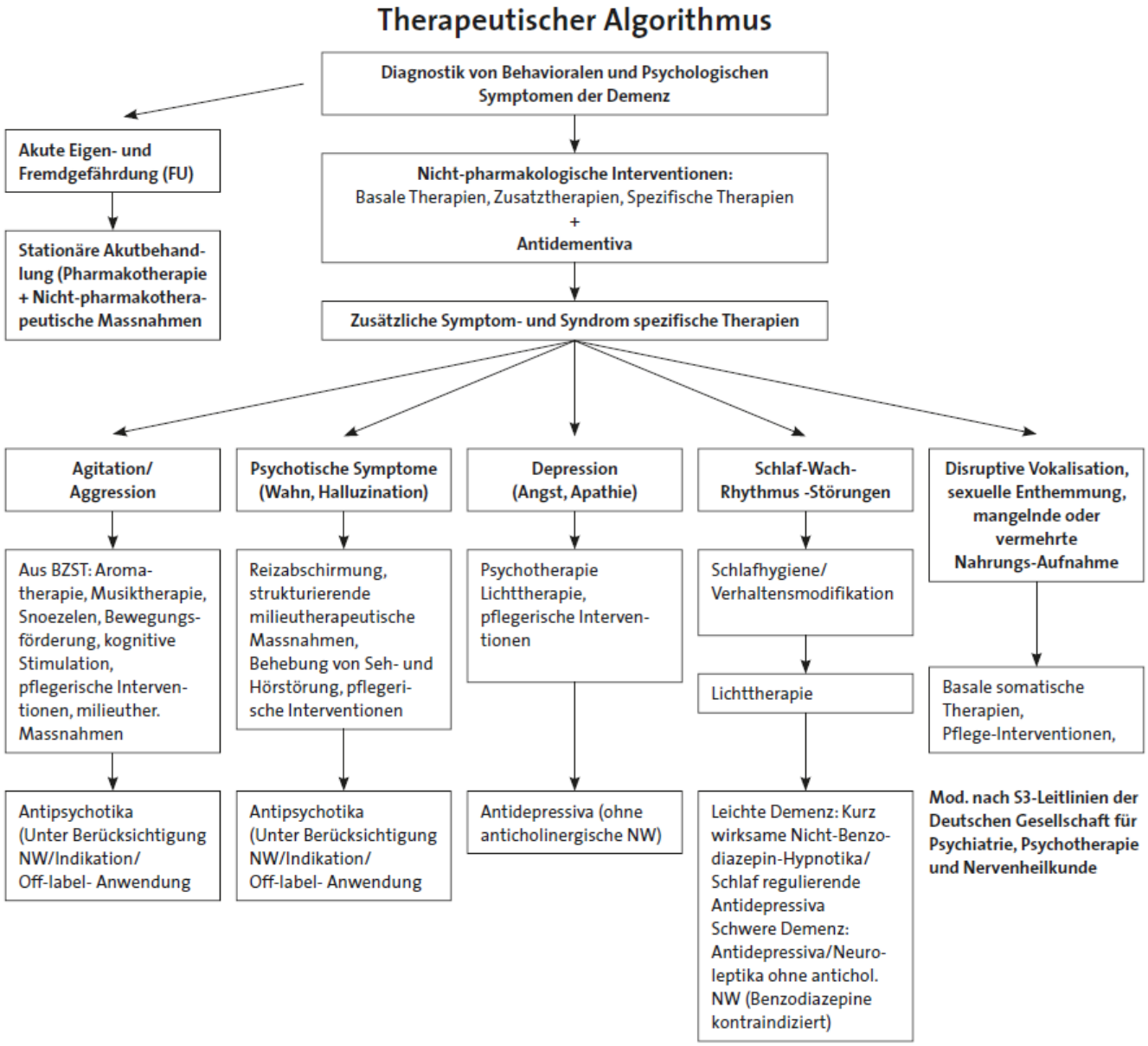
At the moment, there is no disease-modifying treatment available for AD or PD in Switzerland. Treatment of these diseases aims to improve or avoid worsening of cognitive, functional, behavioral, and neuropsychiatric symptoms, as well as quality of life of patients and their caregivers.[5]

However, several disease modifying drugs are currently investigated in clinical trials. The United States Food and Drug Administration (FDA) recently approved under an accelerated approval pathway Biogen's amyloid beta-directed antibody aducanumab for the treatment of AD. It is the first novel approval for AD since 2003 and it is the first treatment that targets the pathophysiology of the condition.[58] However, the clinical benefit of aducanumab seems to be controversial.[59]

The "Therapy Guidelines for the Behavioural and Psychological Symptoms of Dementia" issued by several professional societies from Switzerland also recommends starting with non-pharmacological therapies and only add antidementia drugs where needed (Figure 8).[8] Non-pharmacological treatment options are numerous and include psychoeducation, social support, aroma therapy, physical activity, cognitive therapies, chronobiological therapies (light therapy), etc (Figure 8).

Antidementia drugs reimbursed in Switzerland are AChE inhibitors and memantine. AChE inhibitors include donepezil, rivastigmine and galantamine (for more details see Section 4).

Figure 8 "Therapy Guidelines for the Behavioural and Psychological Symptoms of Dementia in Alzheimer disease and Parkinson disease after failure of antiparkinson-medication"



Source: Savaskan et al.[8]

4 Technology

4.1 Technology description

4.1.1 AChE ihibitors

As described in section 3, dementia is related to a loss of cholinergic neurons which leads to reduced production of the neurotransmitter ACh. ACh gets metabolized by the enzyme AChE. The inhibition of AChE by AChE inhibitors leads to more available ACh in the synaptic cleft, which is associated with an improvement of cognition. Route of administration, administration interval and dosages for AchE inhibitors are shown in Table 1.

4.1.2 Memantine

The dysfunction of the NMDA glutamate receptors caused by neuroinflammation leads to excessive flow of calcium into neurons which contributes also to dementia. Blocking NMDA receptors reduces this continuous stimulation, which prevents apoptosis and enables the neurons to better communicate. Memantine is a NMDA receptor antagonist. See Table 1 for information regarding route of administration, administration interval and dosages for memantine.

Table 1 Overview on route of administration, interval and dosages

Preparation	Route of administration	Interval	Initial dosage	Maximum dosage
Donepezil	Tablets, orally disintegrating tablets, lactabs: 5 mg, 10 mg	1 time per day	5 mg	10 mg
Rivastigmine	Capsules: 1.5 mg, 3 mg, 4.5 mg, 6 mg Solution: 2 mg/l Patch: 4.6 mg/24h, 9.5 mg/24h, 13.3 mg/24h	Capsules and solution: 2-3 times per day Patch: 1 patch per day	Capsules and solution: 3 mg Patch: 4.6 mg	Capsules and solution: 12 mg Patch: 13.3 mg
Galantamine	Capsules (retarding): 8 mg, 16 mg, 24 mg	1 time per day	8 mg	24 mg
Memantine	Film-coated tablets, lactabs: 10 mg, 20 mg; plus starterpacks are available: 7x5, 7x10, 7x15, 7x20mg Solution: 10 mg/g	1 time per day	5 mg	20 mg

Source: Compendium.ch

4.2 Alternative technologies

There are currently no alternative pharmacological technologies available in Switzerland for treating dementia due to AD or PD.

4.3 Regulatory status and reimbursement

4.3.1 Regulatory status

The first donepezil and rivastigmine medication received regulatory approval in Switzerland in 1997, the first memantine medication was approved in 2003 and the first galantamine medication in 2005.[60]

4.3.2 Reimbursement in Switzerland

In the same year the first medications received regulatory approval, they were also included in the SL. AChE inhibitors and memantine are reimbursed under the condition that the cognitive functions are assessed with the MMSE at the beginning of treatment, after three months and subsequently every six

months.[7] MMSE is a common tool for measuring cognitive function and the score ranges from 0 (most severe) to 30 (normal) (see section 7.1.3 for more details). The MMSE needs to be for AChE inhibitors ≥10 and for memantine between 3 and 19.[7] Furthermore, these medications are only reimbursed as monotherapies.[7]

4.3.3 Reimbursement in other countries

AChE inhibitors and memantine are reimbursed in most European countries.[10] As already mentioned in chapter 1, however, AChE inhibitors and memantine were removed from the list of reimbursable products in France in 2018.

5 Population, Intervention, Comparator, Outcome (PICO)

Population, intervention, comparator and outcomes (PICO) are defined as:

PICO 1 (mild to moderate dementia due to AD treated with cholinesterase inhibitors)

P:	Patients with mild to moderate dementia due to AD, diagnosed according to established criteria (e.g. DSM-III, DSM-IIIR, DSM-IV, DSM-5, ICD-10, NIA-AA, NINCDS-ARDA)
I:	Cholinesterase inhibitors donepezil, rivastigmine and galantamine according to the approved dosage
C:	Treatment without donepezil, rivastigmine or galantamine / placebo
O:	• Effectiveness: Delayed nursing home placement, cognitive function (ADAS-Cog, MMSE, MoCA, executive functioning, episodic memory etc.), functional capacity (ADCS-ADL-sev, etc.), neuropsychiatric symptoms (NPI, BEHAVE-AD etc.), BPSD, QoL, etc. • Safety: serious adverse events, mortality • Costs, cost-effectiveness, cost-utility and budget impact

Abbreviations: AD, Alzheimer's Disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL-sev, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease; BEHAVE-AD, Behavioural Pathology in Alzheimer's Disease; BPSD, behavioural and psychological symptoms of dementia; DSM-III, Diagnostic and statistical manual of mental disorder, 3rd edition; DSM-IIIR, Diagnostic and statistical manual of mental disorder, 3rd edition revision; DSM-IV, Diagnostic and statistical manual of mental disorder, 4th edition; DSM-5, Diagnostic and statistical manual of mental disorder, 5th edition; ICD-10, International Classification of Diseases 10th revision; MoCA, Montreal Cognitive Assessment; NIA-AA, National Institute on Aging and Alzheimer's Association; NINCDS-ARDA, National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; NPI, Neuropsychiatric inventory; QoL, Quality of Life

PICO 2 (moderate to severe dementia due to AD treated with memantine)

P:	Patients with moderate to severe dementia due to AD, diagnosed according to established criteria (e.g. DSM-III, DSM-IIIR, DSM-IV, DSM-5, ICD-10, NIA-AA, NINCDS-ARDA)
I:	NMDA antagonist memantine according to the approved dosage
C:	Treatment without memantine / placebo
O:	• Effectiveness: Delayed nursing home placement, cognitive function (ADAS-Cog, MMSE, MoCA, executive functioning, episodic memory etc.), functional capacity (ADCS-ADL-sev, etc.), neuropsychiatric symptoms (NPI, BEHAVE-AD etc.), BPSD, QoL, etc. • Safety: serious adverse events, mortality • Costs, cost-effectiveness, cost-utility and budget impact

Abbreviations: AD, Alzheimer's Disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL-sev, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease; BEHAVE-AD, Behavioural Pathology in Alzheimer's Disease; BPSD, behavioural and psychological symptoms of dementia; DSM-III, Diagnostic and statistical manual of mental disorder, 3rd edition; DSM-IIIR, Diagnostic and statistical manual of mental disorder, 3rd edition revision; DSM-IV, Diagnostic and statistical manual of mental disorder, 4th edition; DSM-5, Diagnostic and statistical manual of mental disorder, 5th edition; ICD-10, International Classification of Diseases 10th revision; MoCA, Montreal Cognitive Assessment; NIA-AA, National Institute on Aging and Alzheimer's Association; NINCDS-ARDA, National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; NPI, Neuropsychiatric inventory; QoL, Quality of Life

PICO 3 (mild to moderate dementia due to PD treated with rivastigmine)

P:	Patients with mild to moderate dementia due to PD, diagnosed according to established criteria (e.g. DSM-III, DSM-IIIR, DSM-IV, DSM-5, ICD-10, NIA-AA, NINCDS-ARDA)
I:	Rivastigmine according to the approved dosage
C:	Treatment without rivastigmine / placebo
O:	• Effectiveness: Delayed nursing home placement, cognitive function (ADAS-Cog, MMSE, MoCA, executive functioning, episodic memory etc.), functional capacity (ADCS-ADL-sev, etc.), neuropsychiatric symptoms (NPI, BEHAVE-AD etc.), BPSD, QoL, etc. • Safety: serious adverse events, mortality • Costs, cost-effectiveness, cost-utility and budget impact

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL-sev, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease; BEHAVE-AD, Behavioural Pathology in Alzheimer's Disease; BPSD, behavioural and psychological symptoms of dementia; DSM-III, Diagnostic and statistical manual of mental disorder, 3rd edition; DSM-IIIR, Diagnostic and statistical manual of mental disorder, 3rd edition revision; DSM-IV, Diagnostic and statistical manual of mental disorder, 4th edition; DSM-5, Diagnostic and statistical manual of mental disorder, 5th edition; ICD-10, International Classification of Diseases 10th revision; MoCA, Montreal Cognitive Assessment; NIA-AA, National Institute on Aging and Alzheimer's Association; NINCDS-ARDA, National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; NPI, Neuropsychiatric inventory; PD, Parkinson's disease; QoL, Quality of Life

6 HTA key questions

For the evaluation of the technology the following key questions covering the central HTA domains are addressed:

1. Is donepezil, rivastigmine, galantamine or memantine efficacious/effective compared to treatment without these drugs in the specified populations?
2. Is donepezil, rivastigmine, galantamine or memantine safe compared to treatment without these drugs in the specified populations?
3. What are the annual costs of donepezil, rivastigmine, galantamine and memantine in the specified populations?
4. Is donepezil, rivastigmine, galantamine or memantine cost-effective compared to treatment without these drugs in the specified populations?
5. What is the budget impact of donepezil, rivastigmine, galantamine and memantine compared to treatment without these drugs in the specified populations?
6. Are there ethical, legal, social, or organisational issues related to antidementia drugs?

7 Effectiveness, efficacy and safety

Summary statement efficacy, effectiveness and safety

For PICO 1, 24 RCTs were included in the analysis. 15 trials investigated donepezil, 6 trials rivastigmine and 3 trials galantamine. We found statistically significant better results for AChE inhibitors compared to placebo in patients with mild to moderate dementia due to AD in regard to cognition, when patient results for the 24 and 26 weeks follow-up were combined. When cognition was measured with the ADAS-cog the MD was -2.15 (95%CI: -2.56 to -1.73) with the certainty of evidence rated as high according to GRADE. When cognition was measured with the MMSE the MD was 0.85 (95%CI: 0.49 to 1.22) with low certainty of evidence. Results for the one year follow-up were still in favour of the AChE inhibitors but not statistically significant. Furthermore, statistically significant better results were found for function when measured with the ADCS-ADL (MD 1.65 (95%CI: 0.48 to 2.83), low certainty of evidence) and global outcomes when measured with the CIBIC-plus (MD -0.37 (95%CI: -0.48 to -0.29), moderate certainty of evidence) and the CDR-SB (MD -0.45 (95%CI: -0.66 to -0.23), low certainty of evidence) when combining 24 and 26 weeks follow-up data. No longer follow-up data was available for these instruments. In addition, favourable but statistically not significant results were found for neuropsychiatric symptoms in up to 24 weeks of follow-up (measured with the NPI-12, MD -2.84 (95%CI: -8.28 to 2.60), very low certainty of evidence). Regarding mortality (RR 1.14 (95%CI: 0.60-2.18), moderate certainty of evidence) and serious adverse events (RR 1.03 (95%CI: 0.87 to 1.21), low certainty of evidence) no statistically significant differences were observed in up to 26 weeks of follow-up. These findings continued up to one year of follow-up for mortality, however, serious adverse events were statistically significantly higher for AChE inhibitors at the one year follow-up (RR 1.59 (95%CI: 1.10 to 2.31)). The difference in adverse events was also statistically significant at 24 weeks (RR 1.15 (95%CI: 1.09-1.21).

For PICO 2, only two RCTs were identified. We found statistically significant better results for memantine compared to placebo in patients with moderate to severe dementia due to AD in regard to function (measured with the ADCS-ADL, MD 1.41 (95%CI: 0.04 to 2.78), moderate certainty of evidence) and global outcomes (measured with CIBIC-plus, MD -0.3 (95%CI: -0.47 to -0.13), moderate certainty of evidence) up to 28 weeks of follow-up. In addition, favourable but statistically not significant results were found for cognition measured with the SIB (MD 3.26 (95%CI: -2.23 to 8.75), very low certainty of evidence) up to 28 weeks follow-up. Regarding mortality (RR 0.85 (95%CI: 0.22-3.32), very low certainty of evidence) and serious adverse events (RR 0.79 (95%CI: 0.54-1.15), low certainty of evidence), no

statistically significant differences were observed up to 28 weeks of follow-up. No longer follow-up data than 28 weeks was available for PICO 2.

For PICO 3, only one RCT was identified. This trial showed statistically significant better results for rivastigmine compared to placebo in patients with mild to moderate dementia due to PD in regard to cognition measured with ADAS-cog (MD 0.50 (95%CI: 0.24 to 0.76)) and MMSE (MD -1.00 (95%CI: -1.67 to -0.34)), function measured with ADCS-ADL (MD -2.50 (95%CI: -4.63 to -0.37)), neuropsychiatric symptoms measured with NPI-10 (MD of 2.00 (95%CI: 0.18 to 3.82)) and global outcomes measured with ADCS-CGIC (MD 2.80 (95%CI: 1.37 to 4.23)) up to 24 weeks of follow-up. However, risk of bias was rated high for these outcomes due to missing outcome data according to the Risk of Bias (RoB) 2 tool. Regarding mortality and serious adverse events, no statistically significant differences were observed.

Our results are consistent with previous findings from Cochrane reviews and other systematic reviews including meta-analysis. Although we observed statistically significant differences for many outcomes investigated, we have to come to the conclusion that the clinical relevance of our statistically significant differences is questionable based on published cut-off values for Minimal Clinically Important Difference (MCID).

7.1 Methodology effectiveness, efficacy and safety

7.1.1 Databases and search strategy

Search strategy

We developed search strategies based on the PICO criteria in collaboration with a medical librarian and according to current best practice guideline.[61] The systematic literature search was conducted in the following databases: Cochrane Library, Embase and Medline (see Section 13 for the detailed search strategy per database). The final search was conducted on 21 October 2021. We also screened the references of included studies after full-text screening to identify additional relevant evidence.

Several Cochrane reviews have already addressed the effectiveness, efficacy and safety aspects of the treatments under investigation.[23,62–68] Several additional systematic reviews including meta-analyses are also available.[69–78] These studies were considered when building our search strategy and we used these studies to check if we identified all relevant randomised controlled trials (RCTs). This allowed us to obtain a synthesis using inclusion/exclusion criteria approved by the FOPH and include the most

recent evidence, e.g. recent studies that were not available to existing systematic reviews. In addition, we searched for ongoing Randomized Controlled Trials (RCTs) on clinicaltrials.gov, the EU Clinical Trials Register (www.clinicaltrialsregister.eu) and the WHO International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform).

Study inclusion and exclusion criteria

Inclusion and exclusion criteria were defined according to the PICO criteria (Section 5) and were kept broad, without restricting the publication period or study quality. However, we restricted inclusion to RCTs. As previous systematic reviews identified RCTs with a rather small sample size (i.e., Tricco et al., 2018[75]) and such studies do not contribute much to meta-analyses, we included only studies with at least 50 patients. Based on the design of RCTs used to achieve regulatory approval of the drugs under investigation and the current reimbursement scheme in Switzerland, we included only trials with a follow-up duration of at least 24 weeks. Regarding outcomes, any related to cognitive functioning, functional capacity, neuropsychiatric symptoms, global measures, and safety were considered. Furthermore, we included studies with adult populations, in line with the age of dementia onset. Studies with a published full text in English, French, German, or Italian were eligible.

Inclusion/exclusion criteria for studies on efficacy, effectiveness and safety are listed in Table 2.

Table 2 Inclusion criteria for studies on efficacy, effectiveness and safety

Criterion	Inclusion	Exclusion
Publication period	No restrictions	—
Publication status	Published full text available	Published full text not available (including conference abstracts)
Language	English, French, German or Italian	Not English, French, German or Italian
Setting	No restrictions	—
Study design/type	RCT	Not RCT
Study sample size	Sample size ≥50 patients	Sample size <50 patients
Study follow-up	Follow-up ≥24 weeks	Follow-up <24 weeks
Study quality	No restrictions	—
Study population	• PICO 1: Adults (≥ 18 years) with mild to moderate dementia due to AD, diagnosed according to established criteria • PICO 2: Adults (≥ 18 years) with moderate to severe dementia due to AD, diagnosed according to established criteria • PICO 3: Adults (≥ 18 years) with mild to moderate dementia due to PD, diagnosed according to established criteria	• Animal studies • PICO 1: Adults (≥ 18 years) without mild to moderate dementia due to AD • PICO 2: Adults (≥ 18 years) without moderate to severe dementia due to AD • PICO 3: Adults (≥ 18 years) without mild to moderate dementia due to PD
Study intervention	• PICO 1: Donepezil, rivastigmine, galantamine as monotherapies according to the approved dosage • PICO 2: Memantine as monotherapy according to the approved dosage • PICO 3: Rivastigmine as monotherapy according to the approved dosage	• PICO 1: Other drugs than donepezil, rivastigmine, galantamine or combinations of these drugs with memantine • PICO 2: Other drugs than memantine or combinations of memantine with AChE inhibitors • PICO 3: Other drugs than rivastigmine or rivastigmine in combination with memantine
Study comparator	Treatment without drugs under investigation / placebo	Any other comparator
Study outcomes	Any related to cognitive functioning, functional capacity, neuropsychiatric symptoms, global measures, and safety	—

Abbreviations: AChE, Acetylcholinesterase; AD, Alzheimer's disease; PD, Parkinson's disease; PICO, Population, intervention, comparator and outcomes; RCT, Randomized Controlled Trial

Study selection

In a first step, the studies were title-and-abstract-screened in duplicate according to the inclusion/exclusion criteria. In a second step, full texts of studies retained from the first step were reviewed in duplicate. Any disagreement was solved by consensus. Where consensus could not be found, a third reviewer was consulted. To increase consistency between reviewers, prior training sessions were held.

7.1.2 Assessment of quality of evidence

Risk of bias

We assessed the risk of bias according to the Cochrane handbook.[79] If a study adequately addressed the specific risk of bias domain (e.g. adequate generation of random sequence for randomisation), it was judged as "low risk of bias" in this domain. Description of an inadequate method was judged as "high risk of bias" and, if incomplete information was given, as "unclear risk of bias". The assessment was performed in duplicate and inconsistencies were solved by consensus. Where consensus could not be found, a third reviewer was consulted.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment

To obtain an overall rating of confidence in the estimates of effects, the GRADE approach was applied and the certainty of evidence of effect for relevant outcomes was rated in duplicate.[80] Inconsistencies were again solved by consensus. Where consensus could not be found, a third reviewer was consulted. For the specific question under study, we specified the decision rule for judging the GRADE item "inconsistency" as serious, if heterogeneity in statistical meta-analysis was at least substantial (i.e. I^2 at least 50 to 90%). The GRADE evidence table was derived using the online tool.[81]

7.1.3 Methodology data extraction, analysis and synthesis of the domains efficacy, effectiveness and safety

Data extraction

One reviewer extracted data into a predefined work sheet, which was pilot-tested with selected studies retained after full-text screening. Extracted data was checked by a second reviewer. Any disagreement was solved by consensus. Where consensus could not be found, a third reviewer was consulted.

We extracted the following data:

- Population data, i.e. sample size, age and gender structure, MMSE at baseline
- Intervention data, i.e. dose, frequency and treatment duration
- Comparator data, i.e. dose, frequency and treatment duration
- Follow-up time points
- Actual results on safety and clinical efficacy outcomes
- Information to assess the quality of studies, i.e. risk of bias

Data synthesis

For each PICO a separate meta-analysis was performed for those instruments which were most frequently reported by RCTs and are related to critical outcomes. As dementia very often leads to diverse symptoms (not just cognitive), we treated cognitive functioning, functional capacity, neuropsychiatric symptoms, and global measures as critical outcomes in the sense of the GRADE approach.[82] In addition, mortality and serious adverse events were considered as critical safety outcomes. Instruments for cognitive function included the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog), the Mini-Mental State Exam (MMSE), and the Severe Impairment Battery (SIB); for functional capacity the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL), and the Disability Assessment for Dementia (DAD); for neuropsychiatric symptoms the Neuropsychiatric Inventory (NPI); and for global measures the Alzheimer's Disease Cooperative Study-Clinicians Global Impression of Change (ADCS-CGIC), the Clinical Dementia Rating (CDR), the Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus), and the Global Deterioration Scale (GDS). These instruments are further described in Table 3. Regarding safety we analysed mortality, serious adverse events, adverse events, discontinuation due to adverse events and discontinuation due to any reason.

The values from the intention to treat analysis (ITT) population with last observation carried forward (LOCF) were used as this was the method that was most often reported in the identified RCTs. The safety population was used for the analysis of safety outcomes, as recommended in the Cochrane handbook.[61] When a study reported more than one intervention arm that was relevant for our PICO (e.g. intervention arm 1 was donepezil 5mg/day and intervention arm 2 was donepezil 10 mg/day), we combined the results.[61] According to the PICOs, no differentiation was made between the different drugs. As we assumed effect sizes to vary from study to study, the meta-analysis was conducted using the random-effects model.[83] Binary data was pooled using effect measures such as relative risk.[61] Continuous data was pooled using mean differences. Based on the instruments and the identified evidence, we decided to estimate mean differences for each instrument and not using standardized mean differences to pool results across different instruments in the same outcome domain. Uncertainty was expressed

using 95% confidence intervals. Study heterogeneity was characterized using I^2, the size and direction of effect as well as the overlap of the confidence intervals. For statistical hypothesis testing, a significance level of 0.050 was used. Sensitivity analyses (i.e., high risk of bias vs. low risk of bias) was performed where studies with high risk of bias favoured the intervention over the comparator. If outcomes were only reported in one study, they were descriptively described. The analysis was performed in RStudio.

Table 3 Description of common instruments

Instrument	Short description of the instrument
Cognitive function	
ADAS-cog	The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) consists of 11 tasks that include both subject-completed tests and observer-based assessments. Together these tasks assess the cognitive domains of memory, orientation, attention, language, reasoning, and praxis. The ADAS-cog ranges from 0 to 70 with lower scores indicating lesser severity. The ADAS score is based on the number of errors made in each item.[84]
MMSE	The Mini-Mental State Exam (MMSE) is a widely used test of cognitive function among the elderly designed to screen the cognitive impairments seen in a variety of dementing conditions, although the content areas focus on those associated with AD. It includes tests of orientation, attention, memory, language, and visual-spatial skills. There are 21 different items in 11 different tests, with scores ranging from 0 to a perfect score of 30. Scores of 23 or less are typically seen as reflecting dementia and meriting more detailed assessment.[85]
SIB	The Severe Impairment Battery (SIB) scale consists of 40 items organized into nine subscales reflecting aspects of cognition that are sensitive to change over time in the later stages of AD, including social interaction, orientation, visual perception, construction, language, memory, praxis, attention and orienting to name. The possible scores range from 0 to 100, where higher scores reflect greater competence.[86]
Functional capacity	
ADCS-ADL(-sev)	The ADCS-ADL assesses the competence of patients with Alzheimer's Disease (AD) in basic and instrumental activities of daily living (ADL). It can be completed by a caregiver in questionnaire format or administered by a clinician/researcher as a structured interview with a caregiver. All responses should relate to the 4 weeks prior to the time of rating. Scores on the 24-item ADCS-ADL range from 0 to 78, where higher scores reflect greater competence. Adapted versions for people with moderate to severe AD (ADCS-ADL-sev) have also been developed. Scores on the 19-item ADCS-ADL-sev range from 0 to 54.[87]
DAD	The Disability Assessment for Dementia (DAD) evaluates the basic and instrumental activities in daily activities of elderly people with dementia. The proxy-respondent scale specifically measures daily living tasks in terms of executive functions. Thus, a 40-item scale addresses a range of functional domains: eating, meal preparation, telephoning, hygienic, dressing, medication, corresponding, finance, leisure, and housework. A total score is obtained by adding the rating for each question. The maximum score is 100. Higher scores represent less disability in ADL while lower scores indicate more dysfunction.[88]
Neuropsychiatric symptoms	
NPI (-10, -12)	The Neuropsychiatric Inventory (NPI) was developed to detect, quantify and track changes of psychiatric symptoms in a demented population. It uses a structured, caregiver-based interview format to assess 10 subdomains (NPI-10): delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor activity.[89] The NPI-12 has two more subdomains than NPI-10 which have been added since its development: night-time behavioral disturbances and appetite and eating abnormalities.[90] Neuropsychiatric symptoms are rated by the caregiver within a domain in terms of both frequency (1=rarely, less than once per week; 2=sometimes, about once per week; 3=often, several times per week; and 4=very often, once or more per day) and severity (1=mild; 2=moderate; 3=severe). This results in a composite symptom domain score (frequency × severity) ranging from 0 (absence of behavioral symptoms) to 120 points (144 points for NPI-12 respectively; maximum severity of behavioral symptoms). Frequency and severity rating scales have anchor points to enhance the reliability of caregiver responses. Caregiver distress is rated for each positive neuropsychiatric symptom domain on a scale from 0 to 5 points (0=no distress; 1=minimal distress; 2=mild distress; 3=moderate distress; 4=severe distress; and 5=very severe distress).[89]
Global	
ADCS-CGIC	Alzheimer's Disease Cooperative Study-Clinicians Global Impression of Change (ADCS-CGIC) is a systematic method for assessing clinically significant changes in clinical trials as it is viewed by an independent, skilled and experienced clinician. It relies on both direct examination of the patient and in-

	terview of informants (e.g. caregivers). Unlike a targeted symptom scale, it takes into account a subject's overall function in the cognitive, behavioral and functional activity domains through examination of 15 sub-domains. Generally, the relevant history such as recent relevant clinical events of the patient and observations/evaluations are being asked and noted at the beginning. Subdomains of the mental/cognitive state are arousal/alertness/attention/concentration, orientation, memory, language/speech, praxis, judgment/problem solving/insight. Subdomains of the behavioral state include thought content, hallucinations/delusions/ illusions, behavior/mood, sleep/appetite, neurological/psychomotor activity and lastly, subdomains of functioning contain basic and complex (instrumental) functional ability and social function.
CDR(-SB)	The Clinical Dementia Rating (CDR) is a global rating of patients with dementia of AD type. CDR is estimated based on an interview with both patient and caregiver and on the clinical judgment of the clinician. CDR is testing six different cognitive and behavioral domains such as memory, orientation, judgment and problem solving, community affairs, home and hobbies performance, and personal care. Each CDR domain is rated on a 5-point scale: no dementia (CDR = 0), questionable dementia (CDR = 0.5), mild cognitive impairment (CDR = 1), moderate cognitive impairment (CDR = 2), and severe cognitive impairment (CDR = 3) [91,92]. The six domains are often summed to create a 0 – 18 "sum of the boxes" score (higher scores indicate more impairment) which is also called the Clinical Dementia Rating-Sum of Boxes (CDR-SB).[88]
CIBIC-plus	The Clinician's Interview-Based Impression of Change is based only on patient interview. Thus, it measures disease severity at baseline, through the Clinician's Interview-Based Impression of Severity (CIBIS). However, CIBIC-plus (plus caregiver input) includes a caregiver interview to provide more complete information about the patient status. It measures the degree of change with a 7-point judgment-based rating scale in which 1 represents markedly improved; 4, no change; and 7, markedly worse. The CIBIC-plus evaluates cognition, behavior, and function, to yield written and numerical summaries from semi-structured interviews.[93]
GDS	The Global Deterioration Scale (GDS) provides an overview of the disease stages for those suffering from a primary degenerative dementia such as AD. It is broken down into 7 different stages. Each stage is numbered (1-7), given a short title followed by a brief listing of the characteristics for that stage. Stages 1-3 are the pre-dementia stages. Stages 4-7 are the dementia stages. In stage 5, an individual can no longer live without assistance. Caregivers can get a rough idea of where an individual is at in the disease process by observing that individual's behavioral characteristics and comparing them to the GDS.[94]

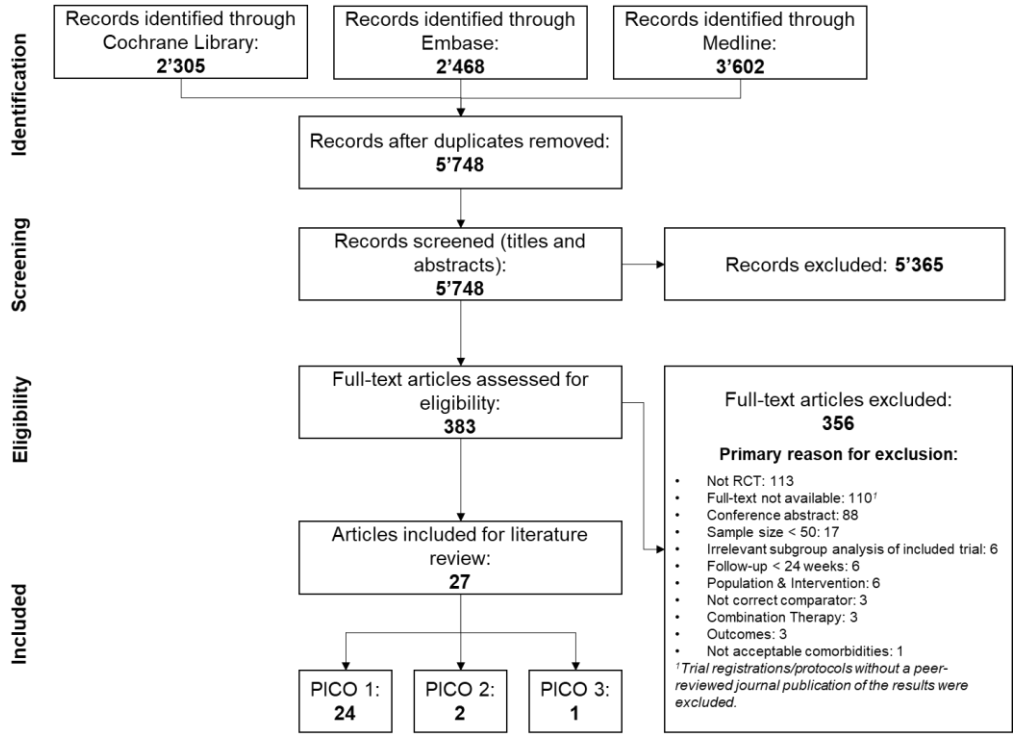
Abbreviations: ADAS-cog, Alzheimer's disease assessment scale–cognitive subscale; ADCS-ADL(-sev), Alzheimer's disease cooperative study activities of daily living inventory (for severe Alzheimer's disease); ADCS-CGIC, Alzheimer's disease cooperative study clinical global impression change; CDR(-SB), clinical dementia rating (sum of boxes); CIBIC-plus, clinician's interview-based impression of change plus caregiver input; GDS, global deterioration scale; DAD, disability assessment for dementia; MMSE, mini mental state examination; NPI, neuropsychiatric inventory; SIB, severe impairment battery

7.2 Results effectiveness, efficacy and safety

7.2.1 PRISMA flow diagram

5'748 unique hits were identified in the Cochrane Library, Embase and Medline. No additional trials were located in any of the SRs we used to develop the search strategy. Of the 5'748 unique hits, 5'365 were excluded during title-abstract screening (Figure 9). Of the remaining 383 articles whose full texts were screened, 356 were excluded, most frequently because they were not RCTs, no full-texts were available (trial registrations/protocols without a peer-reviewed journal publication of the results were excluded) or because they were conference abstracts/posters. Finally, 27 articles were retained for the HTA report, including 24 reporting on PICO 1, 2 reporting on PICO 2, and 1 reporting on PICO 3.

Figure 9 Prisma flow diagram



Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[95]

7.2.2 Evidence table

Overall, 11'527 dementia patients were included in our analysis. 10'384 patients were included for PICO 1 (Table 4), 602 patients for PICO 2 (Table 5) and 541 patients for PICO 3 (Table 6). By publication date, the two first RCTs were from 1998[96,97] and the most recent from 2016.[98] All included RCTs were multicenter studies. Most RCTs were multinational or were conducted in the United States. Two RCTs took place in Japan[99,100], one in the UK[101], one in Norway[102] and one in Italy.[103]

PICO 1

Interventions: In total, 24 RCTs were included for PICO 1. 15 RCTs used donepezil as a treatment. Usually, dosage started at 5mg/day and went up to 10mg/day. Galantamine was used in 3 RCTs. Two RCTs started dosage at 24mg/day and went up to 32mg/day[104,105] and the other RCT used galantamine prolonged-release capsules with an initial dosage of 16mg/day and went up to 24mg/day.[106] Lastly, rivastigmine was used in six RCTs. Some trials started with a dosage of 1mg/day and went up to 4mg/day while others started at 2mg/day and went up to 12mg/day.[96,100,101,107–109] Two of those RCTs used rivastigmine patches which were either 10cm^2 or 20cm^2 and were changed daily.[100,108]

Age: The mean age of the patients varied in the majority of RCTs from 70 to 76 years. Three RCTs had a higher mean age ranging between 80 and 86 years[101,102,110] and one RCT had a mean age below 70 years.[103]

Gender: All RCTs recruited both women and men. In most RCTs the proportion of women was about 50-70%. In three RCTs there were more than 70% women[101,110,111] and in one RCT the proportion of women was below 50% in the intervention group.[103]

Baseline MMSE: Most RCTs showed MMSE baseline means between 13 and 20. However, two RCTs indicated higher MMSE baseline means of 23 and 24, respectively.[102,112]

Follow-up time points: Our meta-analysis investigated follow-up at 24 to 26, and 52 weeks. 17 RCTs included the 24 weeks follow-up. 8 RCTs specified 26 weeks as follow-up time[96,101,104,106,107,109,113,114] and two RCTs 52 weeks.[102,115]

Outcome and instruments: Most RCTs used ADAS-cog or MMSE to measure cognitive function and CIBIC-plus as an instrument for global measure. GDS[96,107,109,115] and CDR-SB[97,99,110,116] are instruments for global measure and were reported in four RCTs. NPI-12 as an instrument for neuropsychiatric symptoms was also used in four RCTs.[106,108,110,117]. ADCS-ADL[106,108,118] and DAD-Score[100,105,117] are both instruments for functional capacity and were each reported in three RCTs. SIB (instrument for cognitive function)[101,117] was reported in two RCTs and the instruments for global measure J-CGIC[99] and ADCS-CGIC[108] were each reported in one RCT. Quality of life was also reported in two RCTs, however, the instrument used is not common.[97,116] In addition, safety outcomes such as adverse events, serious adverse events, and death as well as discontinuation due to any reason or due to adverse events were reported in most RCTs.

PICO 2

Interventions: Two RCTs examined patients who were treated with memantine (20mg/day).[119,120]

Age: The mean age of the patients in the intervention and control group varied from 75.5 to 78.3 years.

Gender: In both RCTs the proportion of women was between 65.5% and 72.5% in both, the intervention and control group.

Baseline MMSE: MMSE baseline means of both studies indicated moderate to severe dementia and the mean of the baseline MMSE ranged from 8 to 10.

Follow-up time points: One RCT specified 28 weeks[119] and the other 24 weeks[120] as follow-up time.

Outcome and instruments: Both RCTs investigating PICO 2 used CIBIC-plus as global measure, ADCS-ADL to assess functional capacity, SIB for cognitive function and NPI-12 for neuropsychiatric symptoms. Reisberg et al. 2003 also used the MMSE for cognitive function and GDS as global measure.[119] Safety outcomes and death as well as discontinuation due to any reason or due to adverse events were reported in both studies.

PICO 3

There was only one RCT included for PICO 3. This RCT examined rivastigmine as a treatment, which started with an initial dosage of 3mg/day and went up to 12mg/day.[121] Mean baseline MMSE was 19.4 in the intervention group and 19.2 in the control group respectively. The mean age of patients was 72.5 years. With 35%, the proportion of women was much lower than in the trials for PICO 1 and PICO 2. The follow-up time was 24 weeks for this RCT. Instruments used were ADCS-CGIC, ADAS-cog, ADCS-ADL, NPI-10 and MMSE. Regarding safety outcomes, AE, SAE and Death were reported. Discontinuation was either due to adverse events or due to any reason.

Table 4 Characteristics of included RCTs – PICO 1

First author, year	Publication source	Countries	Intervention (dosage)	Comparator	Sample size	Baseline MMSE (mean, sd)	Follow-up time points (in weeks)	Outcomes	Age (mean, sd)	Gender (%female)
Gault, 2016[98]	Biomedical Central (BMC) Alzheimer's Research & Therapy	Multinational	Donepezil (10mg/day)	Placebo	I: 76 C: 104	I: 18.4 (4.42) C: 19.1 (4.00)	4, 8, 12, 18, 24	MMSE, 13-item ADAS-Cog, AE, CIBIC-plus, Death, discontinuation due to adverse events, discontinuation due to any reason, SAE	I: 75.1 (+/- 7.75) C: 73.2 (+/- 7.39	I: 53% C: 63%
Maher-Edwards, 2015[118]	Alzheimer's & Dementia: Translational Research & Clinical Interventions (TRCI)	Multinational	Donepezil (5 to 10mg/day)	Placebo	I: 152 C: 145	I: 18.7 (3.75) C: 18.2 (3.88)	12, 24	ADAS-cog-11, CIBIC-plus, ADCS-ADL, MMSE, discontinuation due to any reason, discontinuation due to AE, Death, AE	I: 71.1 (7.49) C: 73.3 (6.80)	I: 65% C: 64%
Andersen, 2012[102]	BMC Neurology	Norway	Donepezil (5 to 10mg/day)	Placebo	I: 90 C: 90	I: 23.2 (4.2) C: 23.1 (4.1)	17, 35, 52	MMSE, ADAS-cog, AE, discontinuation due to adverse events	I: 80.80 (6.8) C: 80.85 (7.3)	I: 67% C: 54%
Maher-Edwards, 2011[114]	International Journal of Geriatric Psychiatry	Multinational	Donepezil (5mg/day with titration at week 4 to 10mg/day)	Placebo	I: 67 C: 63	I: 19.2 (3.20) C: 18.3 (3.36)	8, 16, 24, 26	ADAS-cog-11, CIBIC-plus, AE; SAE, severe AE, discontinuation due to AE, discontinuation due to any reason, Death	I: 71.1 (8.39) C: 71.6 (6.72)	I: 63% C: 70%

First author, year	Publication source	Countries	Intervention (dosage)	Comparator	Sample size	Baseline MMSE (mean, sd)	Follow-up time points (in weeks)	Outcomes	Age (mean, sd)	Gender (%female)
Nakamura, 2011[100]	Dementia and Geriatric Cognitive Disorders EXTRA	Japan	I1: Rivastigmine (5 cm2 Patch) I2: Rivastigmine (10 cm2 Patch)	Placebo	I1: 284 I2: 287 C: 288	I1: 16.8 ± 2.9 I2: 16.5 ± 3.1 C: 16.6 ± 2.9	8, 16, 24	ADAS-J cog, CIBIC plus-J, MMSE, DAD-J score, SAE, AE, Death, Discontinuation due to adverse events, Discontinuation due to any reason	I1: 74.3 ± 7.5 I2: 75.1 ± 6.9 C: 74.5 ± 7.4	I1: 69% I2: 68% C: 68%
Gold, 2010[113]	Dementia and Geriatric Cognitive Disorders	Multinational	Donepezil (5mg/day)	Placebo	I: 84 C:166	I: 19.4 (4.01) C: 19.6 (4.04	8, 16, 24, 26	ADAS-cog-11, AE, CIBIC-plus, Death, discontinuation due to any reason, discontinuation due to AE, severe AE, SAE	I: 72.9 (7.97) C: 72.5 (8.56)	I: 63% C: 60%
Feldmann, 2007[107]	Journal of Neurology, Neurosurgery, Psychiatry	Multinational	I1: Rivastigmine (TID 2 to 12mg (TID=three times daily)) I2: Rivastigmine (BID 2 to 12mg (BID=twice daily))	Placebo	I1: 227 I2: 229 C: 222	I1: 18.3 (4.5) I2: 18.8 (4.6) C: 18.7 (4.6)	12,18, 26	ADAS-cog-11, CIBIC-plus, ADAS-cogA (with an added item of attention), MMSE, GDS, AE, SAE, Death, Discontinuation due to any reason, Discontinuation due to adverse events	I1: 71.4 (7.9) I2: 71.0 (8.2) C: 71.7 (8.7)	I1: 60% I2: 57% C: 60%
Winblad, 2007[108]	International Journal of Geriatric Psychiatry	Multinational	I1: Rivastigmine (10 cm2 patch) I2: Rivastigmine (20 cm2 patch)	Placebo	I1: 293 I2: 303 I3: 297 C: 302	I1: 16.6 (3.1) I2: 16.6 (2.9) I3: 16.4 (3.1) C: 16.4 (3.0)	24	ADAS-cog-11, ADCS-CGIC, ADCS-ADL, NPI-12, MMSE, AE, SAE, Death,	I1: 73.6 (7.9) I2: 74.2 (7.7) I3: 72.8 (8.2) C: 73.9 (7.3)	I1: 68% I2: 66% I3: 66% C: 67%

First author, year	Publication source	Countries	Intervention (dosage)	Comparator	Sample size	Baseline MMSE (mean, sd)	Follow-up time points (in weeks)	Outcomes	Age (mean, sd)	Gender (%female)
			I3: Rivastigmine (12mg/day capsules)					Discontinuation due to adverse events, Discontinuation due to any reason		
Mazza, 2006[103]	European Journal of Neurology	Italy	Donepezil (5mg/day)	Placebo	I: 25 C: 26	I: 18.55 (3.47) C: 18.80 (3.63)	24	MMSE, AE, Discontinuation due to adverse events, Discontinuation due to any reason	I: 64.5 (6) C: 69.8 (3)	I: 48% C: 61%
Ballard, 2005[101]	British Medical Journal (BMJ)	UK	Rivastigmine (by week 12: 3 to 6mg twice a day, week 12 to 26: >=9mg daily)	Placebo	I: 31 C: 31	No information	6, 12, 26	Death, discontinuation due to serious adverse events, SIB	I: 84.3 (7.8) C: 83.0 (6.8)	I: 74% C: 77%
Brodaty, 2005[106]	Dementia and Geriatric Cognitive Disorders	Multinational	I1: Galantamine (prolonged-release capsule; PRC)* I2: Galantamine* *Subjects in both galantamine arms were titrated from an initial dosage of 8mg/day for the first 4 weeks up to a maximum daily dosage of 16 or 24mg/day.	Placebo	I1: 320 I2: 327 C: 324	I1: 17.96 (3.97) I2: 17.80 (4.14) C: 18.08 (4.08)	8, 12, 26	ADAS-cog-11, CIBIC-plus, ADCS-ADL, NPI-12, AE, Death, Discontinuation due to adverse events	I1: 76.6 (7.64) I2: 76.5 (7.77) C: 76.3 (8.03)	I1: 64% I2: 64% C: 64%
Seltzer, 2004[112]	JAMA Neurology	USA	Donepezil (5 to 10mg/day)	Placebo	I: 96 C: 57	I: 24.1 ± 1.7 (20-27) C: 24.3 ± 1.3 (22-27)	6, 12, 24	MMSE, Modified ADAS-cog- 13, AE, SAE, Discontinuation due to adverse events, Discontinuation	I: 73.3 ± 9.6 (50-90) C: 75.1 ± 8.8 (52-92)	I: 50% C: 60%

First author, year	Publication source	Countries	Intervention (dosage)	Comparator	Sample size	Baseline MMSE (mean, sd)	Follow-up time points (in weeks)	Outcomes	Age (mean, sd)	Gender (%female)
								due to any reason		
Krishnan, 2003[111]	American Journal of Psychiatry	USA	Donepezil (5 to 10mg/day)	Placebo	I: 34 C: 33	I: 19.5 (4.8) C: 19.0 (4.6)	24 or end-point	ADAS-cog-11, AE, Discontinuation due to any reason, Discontinuation due to AE	I: 74.4 (7.0) C: 72.4 (10.1)	I: 74% C:70%
Gauthier, 2002[117]	Current Medical Research and Opinion	Canada, Australia, France	Donepezil (5mg/day)	Placebo	I: 102 C: 105	I: 13.57 (2.93**) C: 13.86 (SE 2.66**)	4, 8, 12, 18, 24	AE, SAE, discontinuation due to AE, NPI-12, DAD-Score, SIB, MMSE, CIBIC-plus	I: 74.3 (range: 52-92) C: 74.3 (range 48-90)	I: 69% C: 57%
Mohs, 2001[122]	American Academy of Neurology Journal	USA	Donepezil (5mg/day for the first 28 days and 10mg/day thereafter)	Placebo	I: 214 C: 217	I: 17.1 (SE 2.93**) C: 17.1 (SE 2.95**)	6, 12, 18, 24, 30, 36, 42, 48, 54	AE, Death, discontinuation due to AE, discontinuation due to any reason, MMSE, SAE	I: 75.4 (8.78**) C: 75.3 (8.84**)	I: 61% C: 65%
Tariot, 2001[110]	Journal of the American Geriatrics Society	USA	Donepezil (5 to 10mg/day)	Placebo	I: 103 (76*) C: 105 (79*)	I: 14.4 ± 5.4 (5–25) C: 14.4 ± 5.8 (5–26)	4, 8, 12, 16, 20, 24	MMSE, NPI (nursing home version), CDR-SB (nursing home version), AE, SAE, Death, Discontinuation due to adverse events, Discontinuation due to any reason	I: 85.4 (64–98) C: 85.9 (65–102)	I: 83% C: 82%
Winblad, 2001[115]	American Academy of Neurology Journal	Multinational	Donepezil (5mg/day for 28 days, and then 10mg/day, as per the clinician's judgment)	Placebo	I: 142 C:144	I: 19.37 ± 4.37 C: 19.26 ± 4.54	12, 24, 36, 52	GDS, MMSE, AE, SAE Death, Discontinuation due to adverse events,	I: 72.1 ± 8.6 C: 72.9 ± 8.0	I: 70% C: 59%

First author, year	Publication source	Countries	Intervention (dosage)	Comparator	Sample size	Baseline MMSE (mean, sd)	Follow-up time points (in weeks)	Outcomes	Age (mean, sd)	Gender (%female)
								Discontinuation due to any reason		
Homma, 2000[99]	Dementia and Geriatric Cognitive Disorders	Japan	Donepezil (5mg/day)	Placebo	I: 116 C: 112	I: 17.8 (3.9) C: 16.6 (3.9)	4, 8, 12, 16, 20, 24, endpoint	ADAS-J cog, CDR-SB, AE, J-CGIC, Death, Discontinuation due to AE	I: 70.1 (7.6) C: 69.4 (8.8)	I: 68% C: 66%
Raskind, 2000[104]	American Academy of Neurology Journal	USA	I1: Galantamine (24mg/day) I2: Galantamine (32mg/day)	Placebo	I1: 212 I2: 211 C: 213	I1: 19.5±4.37** I2: 19.1 ±4.36** C: 19.2±4.38**	26	ADAS-cog-11, CIBIC-plus, AE, Discontinuation due to adverse events, Discontinuation due to any reason, SAE, Death	I1: 75.9 ± 7.28** I2: 75.0 ± 8.72** C: 75.3 ± 8.76**	I1: 66% I2: 59% C: 62%
Wilcock, 2000[105]	British Medical Journal (BMJ) Volume 321	Multinational	I1: Galantamine (24mg/day) I2: Galantamine (32mg/day)	Placebo	I1: 220 I2: 218 C: 215	I1: 19.5 (3.4) I2: 19.0 (3.8) C: 19.3 (3.5)	4, 8, 12, 16, 20, 24	ADAS-cog 11, DAD-Score, CIBIC-plus, AE, Discontinuation due to adverse events, Discontinuation due to any reason	I1: 71.9 (8.3) I2: 72.1 (8.6) C: 72.7 (7.6)	I1: 58%† I2: 58%† C: 63%†
Burns, 1999[116]	Dementia and Geriatric Cognitive Disorders	Multinational	I1: Donepezil (5mg/day) I2: Donepezil (10mg/day)	Placebo	I1: 271 I2: 273 C: 274	I1: 20 (4.94**) I2: 20 (3.30**) C: 20 (4.97**)	6, 12, 18, 24 and 30	Death, QoL, SAE, CIBIC-plus, CDR-SB, ADAS-cog-11	I1: 72 +/- 8.23**(51-91) I2: 72 +/- 8.26** (53-93) C: 71 +/- 8.28** (50-90)	I1: 61% I2: 57% C: 55%
Rosler, 1999[109]	British Medical Journal (BMJ) Volume 318	Multinational	I1: Rivastigmine (Higher dose (6 to 12mg/day)) I2: Rivastigmine	Placebo	I1: 243 I2: 243 C: 239	Total mean score at baseline: 19.9 (range 10-29)	12, 18, 26	MMSE, GDS, CIBIC, ADAS-cog-11, AE, SAE, Death,	Total: mean age 72 years (range 45-95 years)	Total: 59%

First author, year	Publication source	Countries	Intervention (dosage)	Comparator	Sample size	Baseline MMSE (mean, sd)	Follow-up time points (in weeks)	Outcomes	Age (mean, sd)	Gender (%female)
			(Lower dose (1 to 4mg/day))					Discontinuation due to adverse events, Discontinuation due to any reason		
Corey-Bloom, 1998[96]	International Journal of Geriatric Psychopharmacology	USA	I1: Rivastigmine (1 to 4mg/day) I2: Rivastigmine (6 to 12mg/day)	Placebo	I1: 233 I2: 231 C: 235	I1: 19.5 I2: 19.62 C: 20	12, 18, 26	CIBIC-plus, GDS, ADAS-cog, MMSE, AE, Discontinuation due to any reason, Discontinuation due to AE, Death	I1: 74.9 I2: 73.8 C: 74.8	I1: 57% I2: 68% C: 58%
Rogers, 1998[97]	American Academy of Neurology Journal	USA	I1: Donepezil (5mg/day) I2): Donepezil (10mg/day)	Placebo	I1: 154 I2: 157 C: 162	I1: 19.0 ± 4.96** I2: 18.9 ± 5.01** C: 19.2 ± 5.09**	6, 12, 18, 24, 30	ADAS-cog-11, CIBIC-plus, MMSE, CDR-SB, QoL, SAE, Death, discontinuations due to AE	I1: 72.9 ± 7.45** I2: 74.6 ± 7.52** C: 72.6 ± 7.64**	I1: 63% I2: 62% C: 61%

*Multinational means more than three countries; *Sample size of the population that fulfils the definition for PICO 1; C: comparator; I: intervention; I1: intervention 1; I2: intervention 2*

***Where standard error (SE) values were provided, we calculated the SD*

†Where absolute numbers were provided, we calculated percentages

Table 5 Characteristics of included RCTs – PICO 2

First author, year	Publication source	Countries	Intervention (dosage)	Comparator	Sample size	Baseline MMSE (mean, sd)	Follow-up time points (in weeks)	Outcomes	Age (mean, sd)	Gender (%female)
Reisberg, 2003[119]	The New England Journal of Medicine	USA	Memantine (20mg/day)	Placebo	I: 126 C: 126	I: 7.8±3.76 C: 8.1±3.60	12, 28	CIBIC-plus, ADCS-ADL, SIB, MMSE, NPI-12, GDS, AE, SAE, Death, Discontinuation due to adverse events, Discontinuation due to any reason	I: 75.5±8.16 C: 77.5±8.61	I: 72% C: 66%
van Dyck, 2007[120]	Alzheimer Disease & Associated Disorders – An International Journal	USA	Memantine (20mg/day)	Placebo	I: 178 C: 172	I: 10.0 (2.8) C: 10.3 (3.1)	4, 8, 12, 18, 24	SIB, ADCS-ADL, CIBIC-plus, NPI-12,AE, SAE, Death, Discontinuation due to adverse events, Discontinuation due to any reason	I: 78.1 (8.2) C: 78.3 (7.6)	I: 73% C: 70%

C: comparator; I: intervention

Table 6 Characteristics of included RCTs – PICO 3

First author, year	Publication source	Countries	Intervention (dosage)	Comparator	Sample size	Baseline MMSE (mean, sd)	Follow-up time points (in weeks)	Outcomes	Age (mean, sd)	Gender (%female)
Emre, 2004[123]	The New England Journal of Medicine	Multinational	Rivastigmine (3 to 12mg/day)	Placebo	I: 362 C: 179	I: 19.4±3.8 C: 19.2±4.1	24	ADCS-CGIC, ADAS-cog, ADCS-ADL, NPI-10, MMSE, AE, SAE, Death, Discontinuation due to adverse events, Discontinuation due to any reason	I: 72.8±6.7 C: 72.4±6.4	I: 35% C: 35%

Multinational means more than three countries; C: comparator; I: intervention

We identified 12 ongoing RCTs related to the PICOs investigated in this HTA on the WHO International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform) (Table 7). One of these RCTs (EUCTR2017-000569-61-FR) investigates donepezil, galantamine and rivastigmine against placebo.

Table 7 Ongoing RCTs

Main ID	Title	Date of registration	Current status
Donepezil			
ChiCTR2100044796	Clinical study on the effectiveness and mechanism of acupuncture combined with donepezil for mild Alzheimer's disease	2021-03-27	Recruiting
NCT04661280	Donepezil Versus Non-drug Treatment in Alzheimer's Disease	2020-12-03	Recruiting
ChiCTR2000037291	A Study on the Prevention and Treatment of Mild and Moderate Alzheimer's Disease from the Perspective of Phlegm and Deficiency	2020-08-27	Recruiting
NCT04308304	MK-1942/Donepezil Interactions in Participants With Alzheimer's Disease (MK-1942-005)	2020-03-11	Recruitment complete
IRCT20190317043079N1	A comparision between of Donepezil vs. Donepezil and Trazodonee efficacy in the cognitive impairment among elderly Patients with Dementia	2019-10-04	Recruitment complete
EUCTR2017-000569-61-FR	Comparison of therapeutic strategies with Cholinesterase Inhibitors: stop or still (SOS) trial	2017-10-30	Unknown
ACTRN12617001066370	An interventional study to evaluate the efficacy and safety of a donepezil transdermal patch compared to oral Aricept in Alzheimer's disease	2017-07-21	Recruiting
NCT03090516	Clinical Efficacy of Ginkgo Biloba Extract in the Treatment of Alzheimer's Disease	2017-03-04	Unknown
EUCTR2004-000016-10-FI	A 3-month, randomized, double-blind, placebo- controlled, multicenter, safety, tolerability, and efficacy study of 3 doses of sra-333 in outpatients with mild to moderate alzheimer’s disease with donepezil as active control	2004-08-23	Unknown
Galantamine			
EUCTR2017-000569-61-FR	Comparison of therapeutic strategies with Cholinesterase Inhibitors: stop or still (SOS) trial	2017-10-30	Unknown
Rivastigmine			
JPRN-UMIN000041148	Effects of rivastigmine on cognitive function and appetite	2020-07-20	Recruiting
EUCTR2017-000569-61-FR	Comparison of therapeutic strategies with Cholinesterase Inhibitors: stop or still (SOS) trial	2017-10-30	Unknown
Memantine			
EUCTR2005-005859-18-IT	Effect of memantine treatment on brain function and morphological structure in patients with moderate to severe patients with alzheimer s disease a structural mr and fmri study - nd	2006-11-10	Unknown
EUCTR2006-000860-10-FI	An Open-Label Study Investigating the Specific Effects of Memantine in Institutionalised Patients with Alzheimer’s Disease	2006-06-13	Prematurely Ended

7.2.3 Risk of bias assessment

Figure 10 shows the risk of bias across all included RCTs and outcomes. The item “selection of the reported result” was judged as having some concerns in most studies because no pre-specified analysis plan was available for the majority of the studies. The risk of bias concerning the item “measurement of the outcome” was assessed as low in all studies. For the items “missing outcome data”, “deviations from intended interventions” and “randomization process” low risk of bias resulted for most studies.

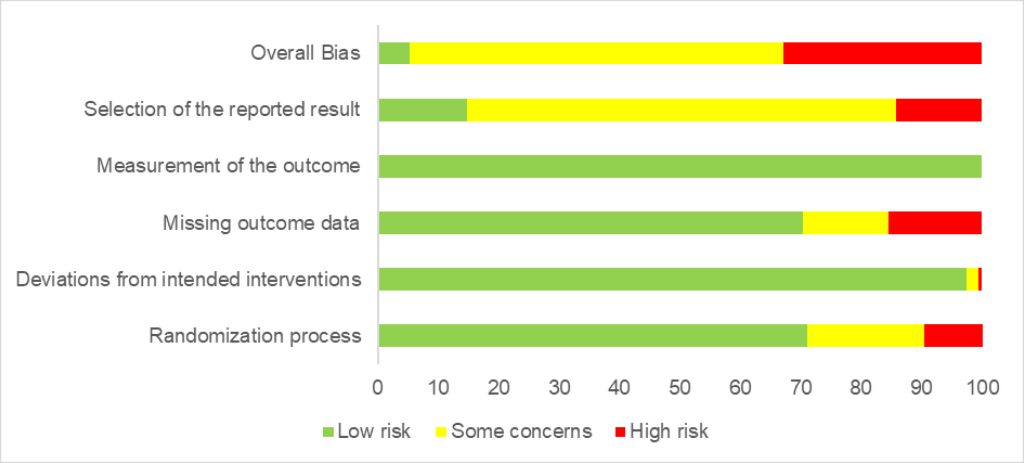
The detailed risk of bias assessments for each outcome of interest of the included RCTs are presented in the appendix in Table 31 to Table 37.

Regarding PICO 1, the overall bias for all efficacy outcomes (independent of the instrument used) was judged to be of “some concerns” or “high risk”. Especially the selection of the reported result resulted in “some concerns” or “high risk”. The main reason was that no pre-specified analysis was available for the included RCTs. For several trials “some concerns” or “high risk of bias” also arose from the randomization process or due to missing outcome data. The overall bias for safety outcomes was mostly judged as “some concerns”, few studies resulted at “high” or “low risk”. Safety outcomes also raised “some concerns” about selection of the reported results as no pre-specified analyses were available. In addition, some trials showed “some concern” or “high risk of bias” due to the randomization process and “some concerns” due to deviations from the intended interventions.

For PICO 2 we judged the overall risk of bias for all outcomes as “some concerns”. All outcomes resulted in having “some concerns” regarding the selection of the reported results. This is attributable to the same reason as described for PICO 1. In addition, several studies had “some concerns” due to the randomization process.

For PICO 3 only one RCT was included. The overall bias was rated as “high” for the efficacy outcomes and as “some concerns” for the safety outcomes. All outcomes had “some concerns” regarding the selection of the reported results due to the same facts as described for PICO 1. Furthermore, the efficacy outcomes were judged as “high risk of bias” due to missing outcome data.

Figure 10 Risk of bias across all studies and outcomes as percentage



7.2.4 GRADE Summary of Findings Table

We performed an assessment of quality of evidence using the GRADE tool. As per Table 8, a rating of "serious" resulted in downgrading by one level, a rating of "very serious" downgraded the quality of evidence by two levels, whereas a rating of "not serious" did not result in downgrading.

PICO 1

The certainty of evidence for ADAS-cog was rated as high; for CIBIC-plus and mortality as moderate; for MMSE, CDR, ADCS-ADL and SAE as low and for DAD and NPI-12 as very low (Table 8). Indirectness was downgraded for many outcomes as not all drugs could be included in the meta-analysis. Furthermore, imprecision was downgraded often as the confidence interval included the null effect.

PICO 2

The certainty of evidence for ADCS-ADL and CIBIC-plus was rated as moderate; for serious adverse events as low and for SBI and mortality as very low (Table 9). Downgrading was mainly due to imprecision and the suspected publication bias. Publication bias was suspected as we only identified two RCTs corresponding to our PICO although memantine was introduced about 20 years ago.

PICO 3

No GRADE Assessment is provided for PICO 3 as only one studied was included for the analysis of PICO 3.

Table 8 GRADE Assessment PICO 1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AChEI	placebo	Relative (95% CI)	Absolute (95% CI)		
Cognitive function measured with ADAS-cog-11 (follow-up: 24 and 26 weeks)												
13	randomised trials	not serious	not serious	not serious	not serious	none[a]	4'898	2'593	-	MD **2.15 lower** (2.56 lower to 1.73 lower)	⊕⊕⊕⊕ High	critical
Cognitive function measured with MMSE (follow-up: 24 and 26weeks)												
9	randomised trials	not serious	serious[c]	serious[b]	not serious	none	2'964	1'520	-	MD **0.85 higher** (0.49 higher to 1.22 higher)	⊕⊕◯◯ Low	critical
Functional capacity measured with ADCS-ADL (follow-up: 24 and 26 weeks)												
3	randomised trials	serious[m]	serious[c]	not serious	not serious	none[e]	1'591	771	-	MD **1.65 higher** (0.48 higher to 2.83 higher)	⊕⊕◯◯ Low	critical
Functional capacity measured with DAD (follow-up: 24 weeks)												
2	randomised trials	serious[f]	very serious[g]	serious[h]	serious[d]	none[i]	540	320	-	MD **6.08 higher** (0.08 lower to 12.24 higher)	⊕◯◯◯ Very low	critical
Neuropsychiatric symptoms measured with NPI-12 (follow-up: 24 weeks)												
2	randomised trials	not serious	very serious[g]	serious[b]	serious[d]	none[i]	995	407	-	MD **2.84 lower** (8.28 lower to 2.6 higher)	⊕◯◯◯ Very low	critical
Global measure CDR (follow-up: 24 weeks)												
2	randomised trials	serious[j]	not serious	serious[k]	not serious	none[i]	855	436	-	MD **0.45 lower** (0.66 lower to 0.23 lower)	⊕⊕◯◯ Low	critical
Global measure CIBIC-plus (follow-up: 24 and 26 weeks)												
13	randomised trials	serious[m]	not serious	not serious	not serious	none[a]	4'250	2'467	-	MD **0.39 lower** (0.48 lower to 0.29 lower)	⊕⊕⊕◯ Moderate	critical

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AChEI	placebo	Relative (95% CI)	Absolute (95% CI)		
SAE (follow-up: 24 and 26 weeks)												
11	randomised trials	not serious	not serious	serious[b]	serious[d]	none	381/3'584 (10.6%)	191/1'982 (9.6%)	**RR 1.03** (0.87 to 1.21)	**2 more per 1'000** (from 10 fewer to 16 more)	⊕⊕◯◯ Low	critical
Mortality (follow-up: 24 and 26 weeks)												
12	randomised trials	not serious	not serious	not serious	serious[l]	none	30/4'225 (0.7%)	12/2'333 (0.5%)	**RR 1.14** (0.60 to 2.18)	**1 more per 1'000** (from 3 fewer to 8 more)	⊕⊕⊕◯ Moderate	critical

CI: *confidence interval;* ***MD:*** *mean difference;* ***RR:*** *risk ratio*

Explanations

a. Some small studies included and showing non-significant differences

b. No study covered galantamine

c. I2 more than 50%, estimates different in direction, CI partially overlapping

d. >300 people but CI includes null effect

e. 2 studies, one reporting improvement another reporting not significant worsening

f. high risk of bias due to missing outcome data

g. I2 more than 50%, significant p value of heterogeneity, estimates different in size, CI partially overlapping

h. No studies cover rivastigmine

i. Too few studies in total to make a judgement

j. Out of two studies, a study with 66% of the weight had a high risk of bias

k. No studies cover rivastigmine or galantamine

l. CI includes null effect AND appreciable benefit or harm

m. More than 40% of the weight in the meta-analysis was contributed by studies with a high risk of bias

Table 9 GRADE Assessment PICO 2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study de-sign	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other consid-erations	Memantine	placebo	Relative (95% CI)	Absolute (95% CI)		
Cognitive function measured with SIB (follow-up: range 24 weeks to 28 weeks)												
2	randomised trials	not serious	very serious[a]	not serious	serious[b]	publication bias strongly sus-pected[c]	304	298	-	MD **3.26 higher** (2.23 lower to 8.75 higher)	⊕◯◯◯ Very low	critical
Functional capacity measured with ADCS-ADL (follow-up: range 24 weeks to 28 weeks)												
2	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly sus-pected[c]	304	298	-	MD **1.41 higher** (0.04 higher to 2.78 higher)	⊕⊕⊕◯ Moderate	critical
Global measure CIBIC-plus (follow-up: range 24 weeks to 28 weeks)												
2	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly sus-pected[c]	304	298	-	MD **0.3 lower** (0.47 lower to 0.13 lower)	⊕⊕⊕◯ Moderate	critical
SAE (follow-up: range 24 weeks to 28 weeks)												
2	randomised trials	not serious	not serious	not serious	serious[d]	publication bias strongly sus-pected[c]	42/304 (13.8%)	52/298 (17.4%)	**RR 0.79** (0.54 to 1.15)	**37 fewer per 1'000** (from 80 fewer to 26 more)	⊕⊕◯◯ Low	critical
Mortality (follow-up: range 24 weeks to 28 weeks)												
2	randomised trials	not serious	serious[e]	not serious	very serious[d]	publication bias strongly sus-pected[c]	7/304 (2.3%)	8/298 (2.7%)	**RR 0.85** (0.22 to 3.32)	**4 fewer per 1'000** (from 21 fewer to 62 more)	⊕◯◯◯ Very low	critical

CI: *confidence interval;* ***MD:*** *mean difference;* ***RR:*** *risk ratio*

Explanations

a. variation in size of effect, almost no overlap in CI, p value of heterogeneity is significant, I2 >50%

b. CI includes null effect

c. Only 2 studies fulfilled our PICO criteria (memantine monotherapy, moderate to severe dementia due to AD)

d. less than 300-400 events, CI includes null effect and appreciable benefit or harm

e. variation in direction of effect

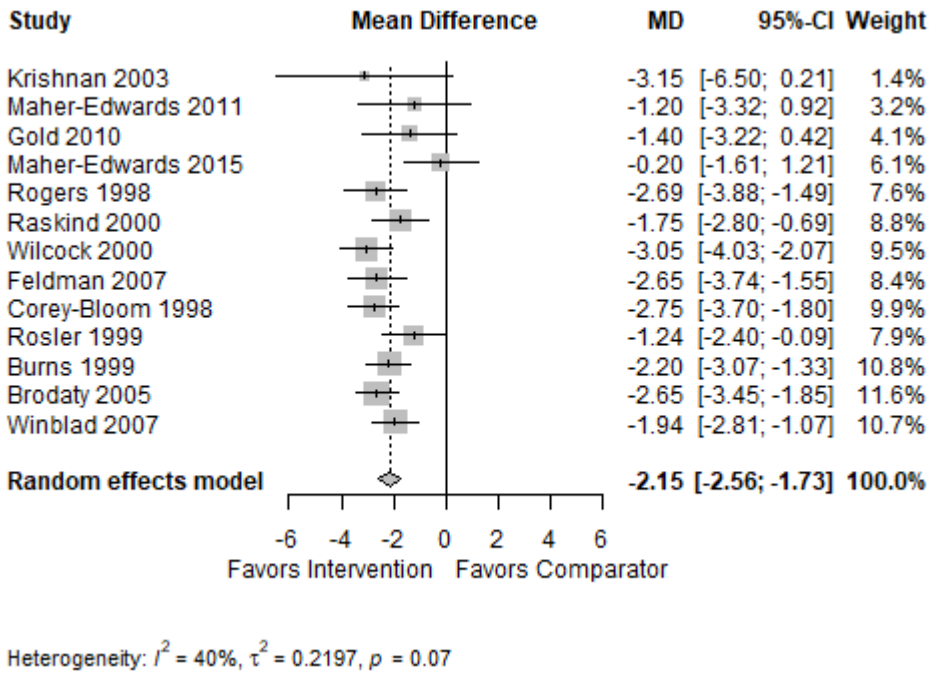
7.2.5 Findings efficacy

PICO 1

ADAS-cog (instrument for cognitive function)

Eight studies reported suitable input data for the meta-analysis of the instrument ADAS-cog for the 24 weeks follow-up[97,105,108,111,113,114,116,118], and five studies for the 26 weeks follow-up. [96,104,106,107,124] Combining results from studies with a follow-up of 24 and 26 weeks, the mean difference (MD) is estimated at -2.15 (p = < 0.001, 95%CI: -2.56 to -1.73, Figure 11), with no important heterogeneity (I^2 = 40%). Only looking at the 24 weeks follow-up, the meta-analysis yields a MD of -2.01 (p = < 0.001, 95%CI: -2.68 to -1.34, appendix Figure 38). At 26 weeks, the MD is estimated at -2.27 (p = < 0.001, 95%CI: -2.82 to -1.73, appendix Figure 39). When excluding studies with a high risk of bias at 24 and 26 weeks, the MD is estimated at -2.26 (p = < 0.001, 95%CI: -2.71 to -1.80**,** appendix Figure 40). Only one study reported results for the 52 weeks follow-up.[102] In this study, both arms contained 90 participants. The MD between the two arms is -1.02 (p = 0.235, 95%CI: -2.65 to 0.62).

Figure 11 Forest plot of ADAS-cog after 24 weeks and 26 weeks combined

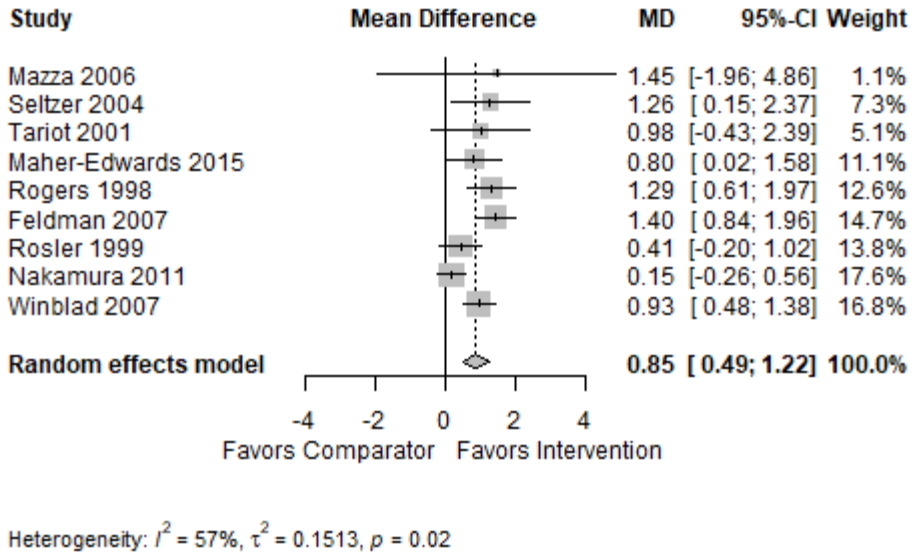


MMSE (instrument for cognitive function)

Seven studies reported suitable input data for the meta-analysis of the instrument MMSE for the 24 weeks[97,100,103,108,110,112,114], and two studies for the 26 weeks follow-up.[107,124] Combining results from studies with a follow-up of 24 and 26 weeks resulted in a MD of 0.85 (p = < 0.001, 95%CI: 0.49 to 1.22,

Figure 12), with moderate heterogeneity (I^2 = 57%). At the 24 weeks follow-up, the meta-analysis yields a MD of 0.82 (p = < 0.001, 95%CI: 0.40 to 1.24, appendix Figure 41). At 26 weeks, the MD is estimated at 0.91 (p = 0.065, 95%CI: -0.06 to 1.88, appendix Figure 42). When excluding studies with a high risk of bias at 24 weeks and 26 weeks, the MD is estimated at 1.03 (p = < 0.001, 95%CI: 0.66 to 1.39, appendix Figure 43). At 52 weeks (2 studies), the MD is estimated at 0.81 (p = 0.381, 95%CI: -1.00 to 2.61, appendix Figure 44).

Figure 12 Forest-plot of MMSE after 24 weeks and 26 weeks combined



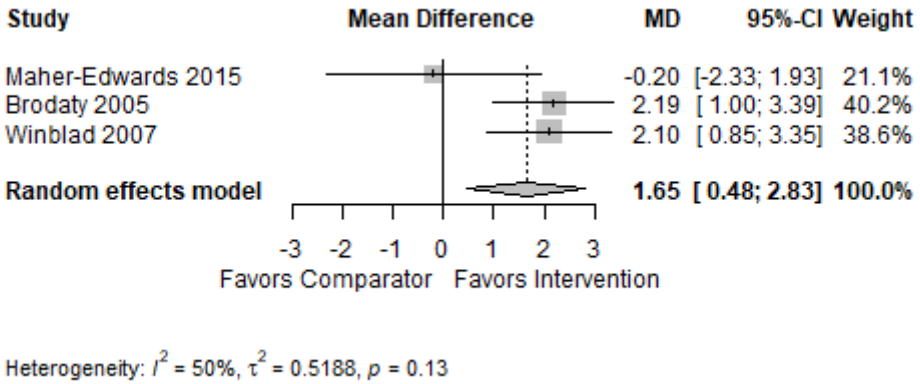
SIB (instrument for cognitive function)

Only one study reported results for the instrument SIB.[117] In this 24 weeks follow-up study, the intervention arm contained 102 participants, the comparator arm contained 105 participants. The MD between the two arms was 4.43 (p = 0.026, 95%CI: 1.25 to 7.61).

ADCS-ADL (instrument for functional capacity)

Two studies reported suitable input data for the meta-analysis of the instrument ADCS-ADL for the 24 weeks[108,118], and one for the 26 weeks follow-up.[106] Combining results from studies with a follow-up of 24 and 26 weeks resulted in a MD estimated at 1.65 (p = 0.006, 95%CI: 0.48 to 2.83, Figure 13), with moderate heterogeneity (I^2 = 50%). At the 24 weeks follow-up, the meta-analysis yields an MD of 1.12 (p = 0.326, 95%CI: -1.11 to 3.35, appendix Figure 45).

Figure 13 Forest-plot of ADCS-ADL after 24 weeks and 26 weeks combined

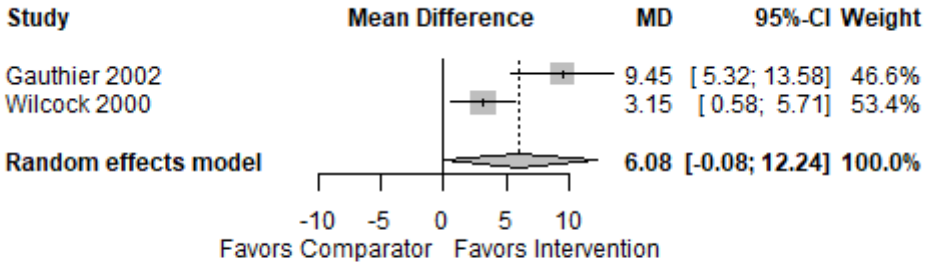


Heterogeneity: I^2 = 50%, τ^2 = 0.5188, p = 0.13

DAD (instrument for functional capacity)

Two studies reported suitable input data for the meta-analysis of the instrument DAD for the 24 weeks follow-up.[105,117] At the 24 weeks follow-up, the meta-analysis yields a MD of 6.08 (p = 0.053, 95%CI: -0.08 to 12.24, Figure 14) with considerable heterogeneity (I^2 = 84%).

Figure 14 Forest-plot of DAD after 24 weeks of treatment

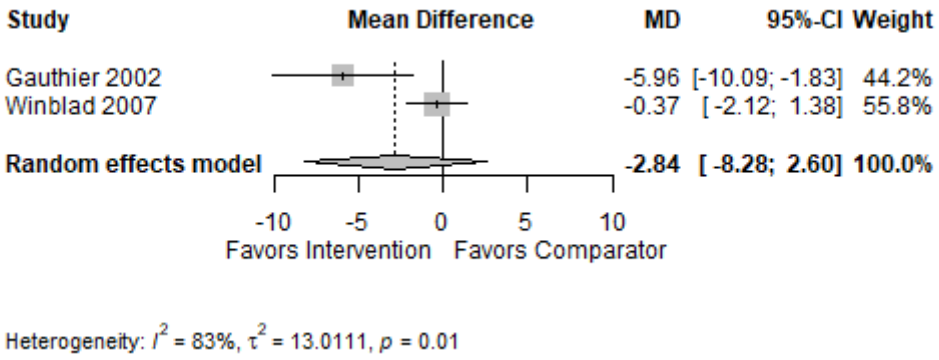


Heterogeneity: I^2 = 84%, τ^2 = 16.7592, p = 0.01

NPI-12 (instrument for neuropsychiatric symptoms)

Two studies reported suitable input data for the meta-analysis of the instrument NPI-12 for the 24 weeks follow-up.[108,117] At the 24 weeks follow-up, the meta-analysis yields a MD of -2.84 (p = 0.306, 95%CI: -8.28 to 2.60, Figure 15) with considerable heterogeneity (I^2 = 83%).

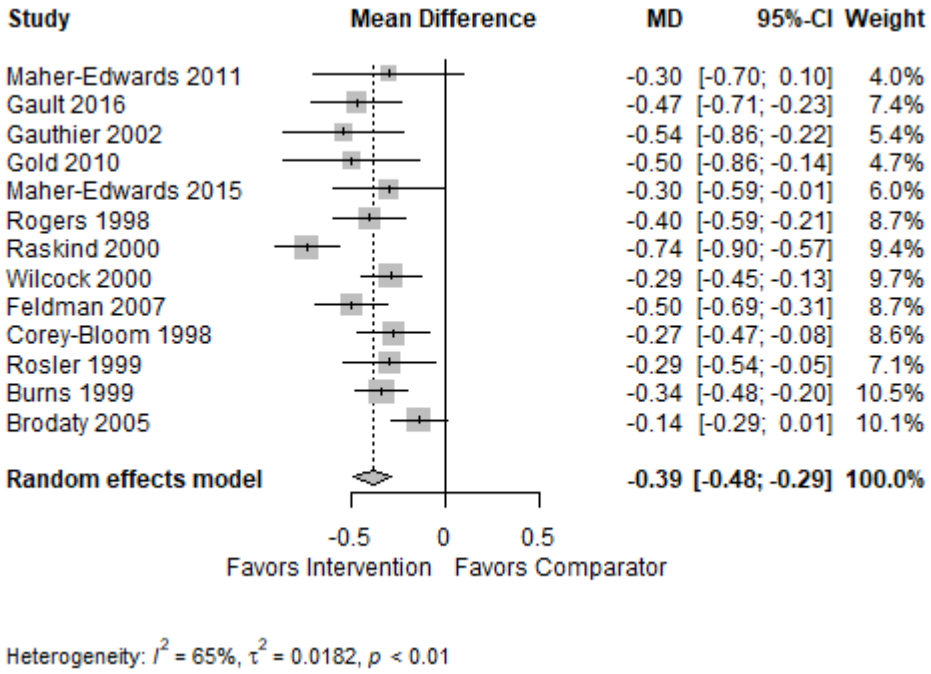
Figure 15 Forest-plot of NPI-12 after 24 weeks of treatment



CIBIC-plus (instrument for global measure)

Eight studies reported suitable input data for the meta-analysis of the instrument CIBIC-plus for the 24 weeks[97,98,105,113,114,116–118], and five for the 26 weeks follow-up.[96,104,106,107,124] Combining patient outcomes from studies with a follow-up of 24 and 26 weeks resulted in a MD estimated at -0.39 (p = < 0.001, 95%CI: -0.48 to -0.29, Figure 16), substantial heterogeneity (I^2 = 65%). At the 24 weeks follow-up, the meta-analysis yields a MD of -0.37 (p = < 0.001, 95%CI: -0.44 to -0.29, appendix Figure 46). At 26 weeks, the MD is estimated at -0.39 (p = < 0.001, 95%CI: -0.60 to -0.18, appendix Figure 47). When excluding studies with a high risk of bias at 24 weeks and 26 weeks, the MD is estimated at -0.46 (p = < 0.001, 95%CI: -0.61 to -0.31, appendix Figure 48). Longer follow-up evidence was not available for this instrument.

Figure 16 Forest-plot of CIBIC-plus after 24 weeks and 26 weeks combined



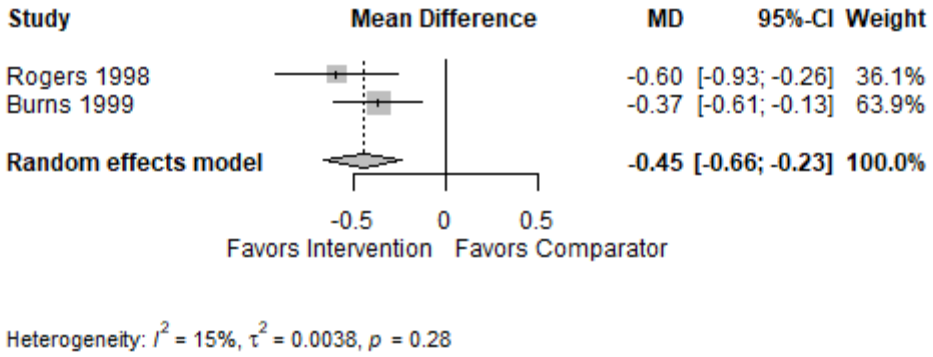
ADCS-CGIC (instrument for global measure)

Only one study reported results for the instrument ADCS-CGIC for 24 weeks of follow-up.[108] In this study, the intervention arm contained 893 participants, the comparator arm contained 302 participants. For the rivastigmine 10 cm^2 patch the MD was -0.30 (p = 0.004, 95%CI: -0.50 to -0.10), for the rivastigmine 20 cm^2 patch -0.20 (p = 0.059, 95%CI: -0.41 to -0.10) and for the rivastigmine capsules -0.20 (p = 0.060, 95%CI: -0.41 to -0.009).

CDR (instrument for global measure)

Two studies reported suitable input data for the meta-analysis of the instrument CDR for the 24 weeks follow-up.[97,116] At the 24 weeks follow-up, the meta-analysis yields an MD of -0.45 (p = < 0.001, 95%CI: -0.66 to -0.23, Figure 17) without important heterogeneity (I^2 = 15%).

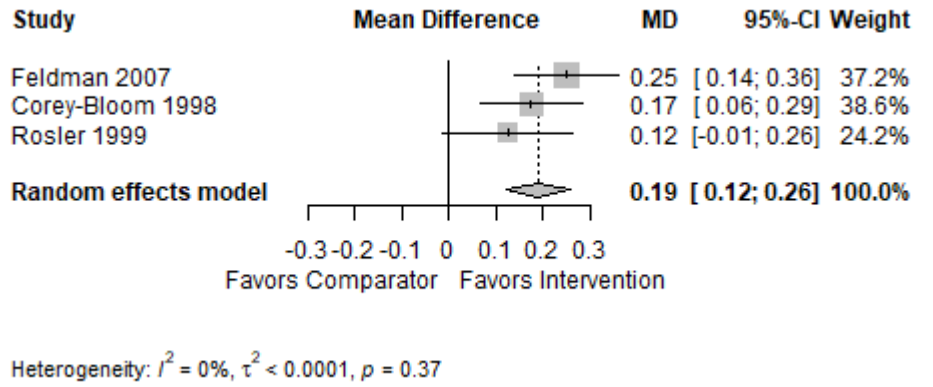
Figure 17 Forest-plot of CDR after 24 weeks of treatment



GDS (instrument for global measure)

Three studies reported suitable input data for the meta-analysis of the instrument GDS for the 26 weeks follow-up. [96,107,109] At the 26 weeks follow-up, the meta-analysis yields an MD of 0.19 (p = < 0.001, 95%CI: 0.12 to 0.26, Figure 18) without important heterogeneity (I^2 = 0%).

Figure 18 Forest-plot of GDS after 26 weeks of treatment



Quality of life

Only one study reported on quality of life for 24 weeks of follow-up.[97] In this study, the intervention arm contained 311 participants, the comparator arm contained 162 participants. For the donepezil 5mg/day intervention arm the MD was 12.79 (p = 0.104, 95%CI: -2.65 to 28.23) and for the donepezil 10mg/day arm 9.34 (p = 0.052, 95%CI: -0.08 to 18.76).

The quality of life measure used in this study is a seven item patient-rated scale derived from an originally ten item scale that evaluates the patient's feeling of well-being in measurable behavioural terms.[125] It is composed of social indicators of quality of life or its absence measured on a 5 score scale from 0, "non existent", to 50 "best possible". The maximum total score can reach 500, 450 when persons without children are assessed, or less if some items are excluded from assessment. An index of 350 or more means fairly successful conditions of living and quality of life. An index of 350-250 seems to suggest painful but adequate coping, and an index of 250-100 is found among persons suffering a lot and seeking immediate help. Institutionalized mental patients usually fall below 100. The assessment can be patient- or professional-rated.

PICO 2

None of the two identified trials for PICO 2 reported on ADAS-cog, DAD, CDR, ADCS-CGIC and quality of life.

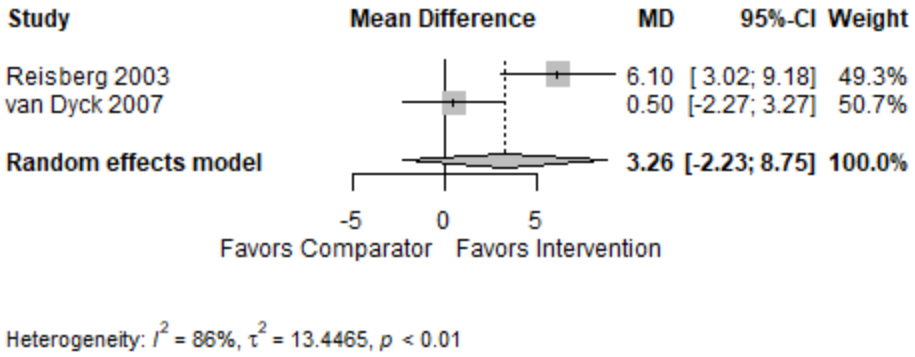
MMSE (instrument for cognitive function)

Only one study reported results for the instrument MMSE for 28 weeks of follow-up.[119] In this study, both arms contained 126 participants and the MD is estimated at 0.70 (p = 0.042, 95%CI: 0.02 to 1.38) in this trial.

SIB (instrument for cognitive function)

When SIB results from the studies looking at 24 and 28 weeks are combined, the MD is estimated at 3.26 (p = 0.245, 95%CI: -2.23 to 8.75, Figure 19) with considerable heterogeneity (I^2 = 86%).[119,120] Longer follow-up evidence was not available for this instrument.

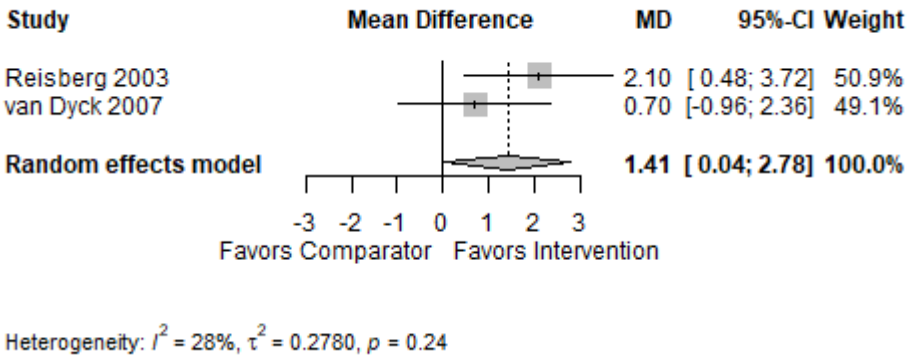
Figure 19 Forest-plot of SIB after 24 and 28 weeks of treatment



ADCS-ADL (instrument for functional capacity)

When results from ADCS-ADL from the studies looking at 24 and 28 weeks are combined, the MD is estimated at 1.41 (p = 0.044, 95%CI: 0.04 to 2.78, Figure 20) without important heterogeneity (I^2 = 28%).[119,120] Longer follow-up evidence was not available for this instrument.

Figure 20 Forest-plot of ADCS-ADL after 24 and 28 weeks of treatment



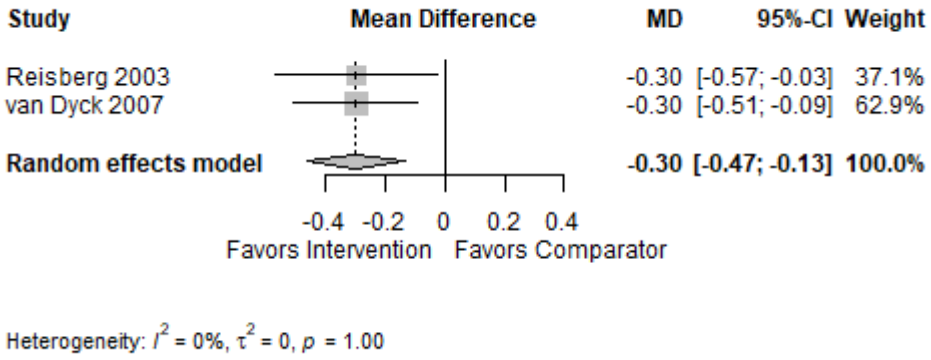
NPI (instrument for neuropsychiatric symptoms)

Only one study reported results for the instrument NPI for 24 weeks of follow-up.[120] In this study, the intervention arm contained 178 participants, the comparator arm contained 172 participants. The MD between the two arms was -0.10 (p = 0.963, 95%CI: -3.65 to 3.85).

CIBIC-plus (instrument for global measure)

When results regarding CIBIC-plus from the studies looking at 24 and 28 weeks are combined, the MD is estimated at -0.30 (p = < 0.001, 95%CI: -0.47 to -0.13, Figure 21) without important heterogeneity (I^2 = 0%).[119,120] Longer follow-up evidence was not available for this instrument.

Figure 21 Forest-plot of CIBIC-plus after 24 and 28 weeks of treatment



GDS (instrument for global measure)

Only one study reported results for the instrument GDS for 28 weeks of follow-up.[119] In this study, both arms contained 126 participants and the MD is estimated at -0.10 (p = 0.096, 95%CI: -0.22 to 0.02)..

PICO 3

The literature search rendered only one RCT that fulfilled the criteria for PICO 3.[123] In this study, the intervention arm contained 362 participants, the comparator arm contained 179 participants. Follow-up time was 24 weeks. On the ADAS-cog-11 scale the MD was -2.80 (p = 0.007, 95%CI: -4.23 to -1.37) and on the MMSE scale 1.00 (p = 0.03, 95%CI: 0.34 to 1.67). The MD for the ADCS-ADL was 2.50 (p = 0.02, 95%CI: 0.37 to 4.63). The NPI 10-item (NPI-10) scale showed a MD of -2.00 (p = 0.02, 95%CI: -3.82 to -0.18). The MD for the instrument ADCS-CGIC was -0.50 (p < 0.001, 95%CI: -0.76 to -0.24).

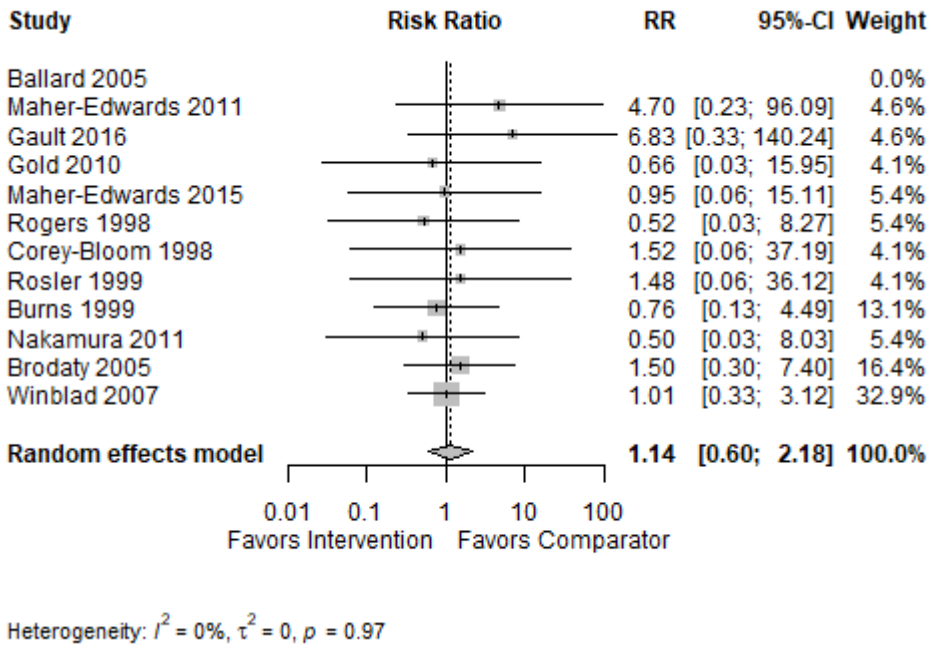
7.2.6 Findings safety

PICO 1

Mortality

For PICO 1, eight studies reported on mortality at 24 weeks follow-up[97,98,100,108,113,114,116,118], three at 26 weeks[96,106,124], one at 52 and one at 54 weeks of follow-up.[115,122] The proportion of patients who died was similar in the intervention and comparator arms. Combining patient outcomes from studies with a follow-up of 24 and 26 weeks resulted in a RR estimated at 1.14 (p = 0.685, 95%CI: 0.60-2.18, Figure 22), without important heterogeneity (I^2 = 0%). At all other follow up times, there was also no significant difference in the proportion of deaths between persons receiving AchE inhibitors and those receiving placebo (appendix Figure 49 to Figure 51).

Figure 22 Forest-plot for mortality after 24 weeks and 26 weeks combined

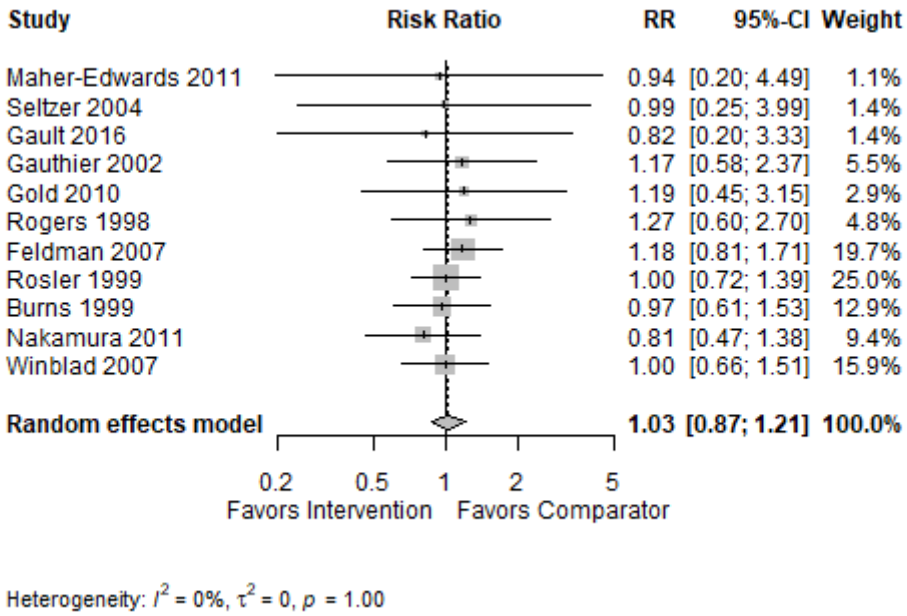


Serious adverse events

For PICO 1, nine studies reported on serious adverse events at 24 weeks follow-up [97,98,100,108,112–114,116,117], two at 26 weeks[107,124], one at 52 and one at 54 weeks of follow-up.[115,122] Combining patient outcomes from studies with a follow-up of 24 and 26 weeks resulted in a RR estimated at 1.03 (p = 0.732, 95%CI: 0.87 to 1.21, Figure 23), without important heterogeneity (I^2 = 0%). Only looking at the 24 weeks follow-up and 26 weeks follow-up, there was also no significant difference in the proportion of

serious adverse events between persons receiving AchE inhibitors and those receiving placebo (appendix Figure 52 and Figure 53). When information on serious adverse events from studies with a follow-up of 52 and 54 weeks, respectively, were combined, a significantly higher number of serious adverse events in the intervention arm was detected, RR 1.59 (95%CI: 1.10 to 2.31, appendix Figure 54).

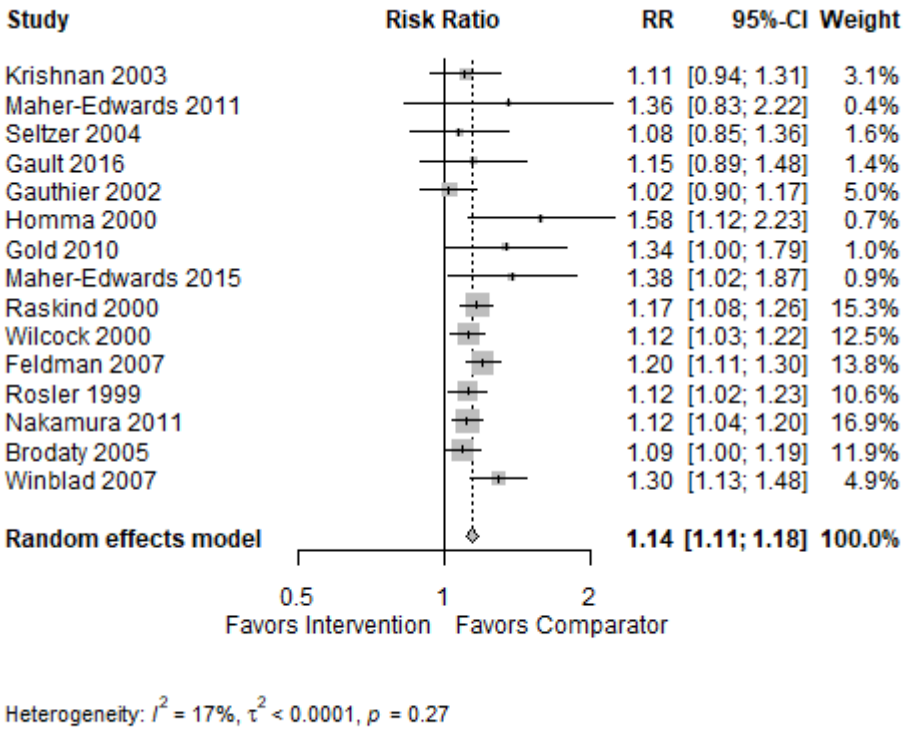
Figure 23 Forest-plot for serious adverse events after 24 weeks and 26 weeks combined



Adverse events

For PICO 1, eleven studies reported on adverse events at the 24 weeks follow-up [98–100,105,108,111–114,117,118], four at 26 weeks[104,106,107,124] and two at 52 weeks of follow-up.[102,115] Combining patient outcomes from studies with a follow-up of 24 and 26 weeks resulted in a RR estimated at 1.14 (p = < 0.001, 95%CI: 1.11 to 1.18, Figure 24), without important heterogeneity (I^2 = 17%). Looking at 24 weeks and 26 weeks separately, there was a statistically significant larger proportion of patients who had experienced an adverse event in the intervention arm compared to the comparator arm (appendix Figure 55 and Figure 56). However, this was not the case for the longer follow-up of 52 weeks (appendix Figure 57).

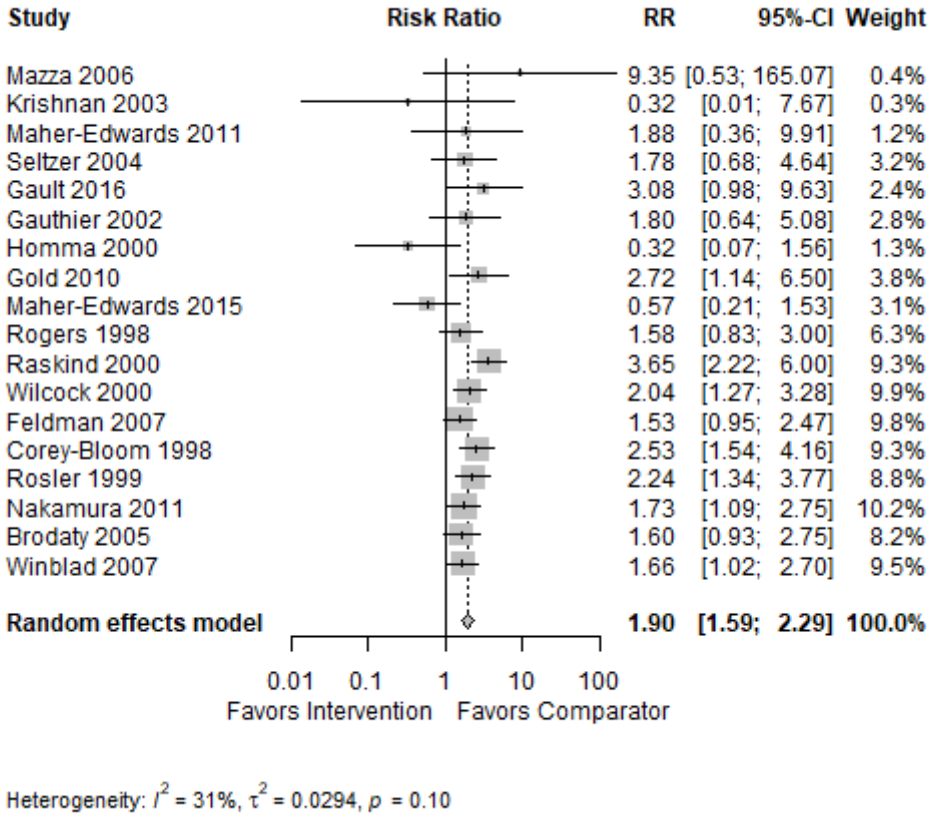
Figure 24 Forest-plot for adverse events after 24 weeks and 26 weeks combined



Treatment discontinuation due to adverse events

For PICO 1, thirteen studies reported on discontinuation due to adverse events at the 24 weeks follow-up [97–100,103,105,108,111–114,117,118], five at the 26 weeks follow-up,[96,104,106,107,124] and two at the 52 weeks follow-up.[102,115] Combining patient outcomes from studies with a follow-up of 24 and 26 weeks resulted in a RR estimated at 1.90 (p = < 0.001, 95%CI: 1.59 to 2.29, Figure 25), without important heterogeneity (I^2 = 31%). At the 24 weeks follow-up and the 26 weeks follow-up, the difference between the two arms was also statistically significant in favour of the comparator (appendix Figure 58 and Figure 59), but this was not the case for the longer follow-up of 52 weeks (appendix Figure 60).

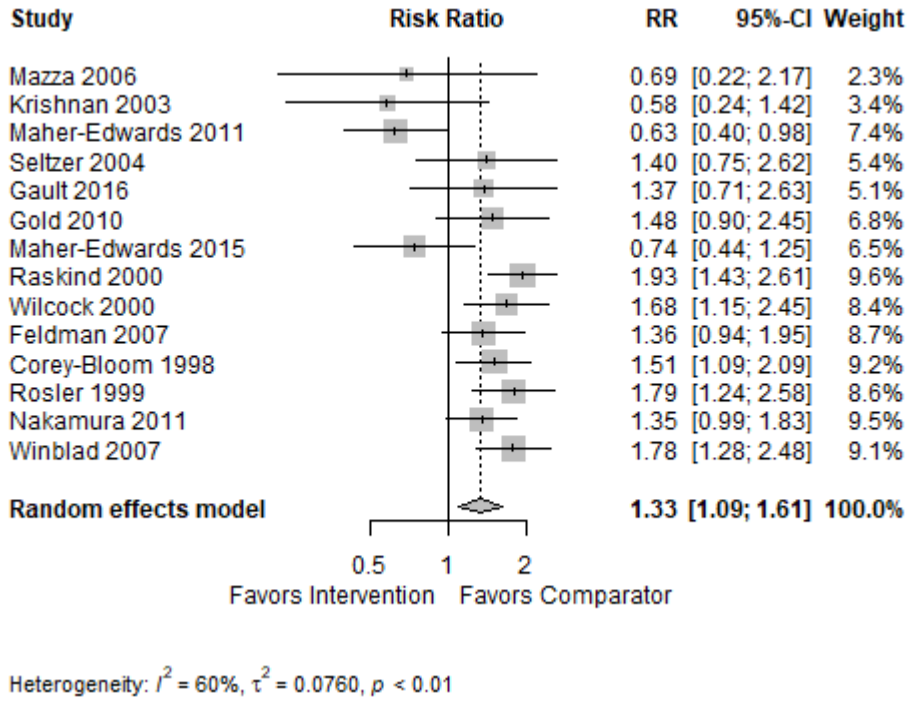
Figure 25 Forest-plot for treatment discontinuation due to adverse events after 24 weeks and 26 weeks combined



Treatment discontinuation due to any reason

For PICO 1, ten studies reported on trial discontinuation at the 24 weeks follow-up [98,100,103,105,108,111–114,118], four at the 26 weeks follow-up[96,104,107,124], one at the 52 weeks follow-up, and one at the 54 weeks follow-up.[115,122] Combining patient outcomes from studies with a follow-up of 24 and 26 weeks resulted in a RR estimated at 1.33 (p = 0.004, 95%CI: 1.09 to 1.61, Figure 26) with substantial heterogeneity (I^2 = 60%). The meta-analysis also revealed a statistically significant result in favour of the comparator group when only looking at the 24 weeks and the 26 weeks follow-up (appendix Figure 61 and Figure 62). When combined information from 52 and 54 weeks was used, no significant differences in discontinuation were identified between the two groups (appendix Figure 63).

Figure 26 Forest-plot for treatment discontinuation due to any reason after 24 weeks and 26 weeks combined

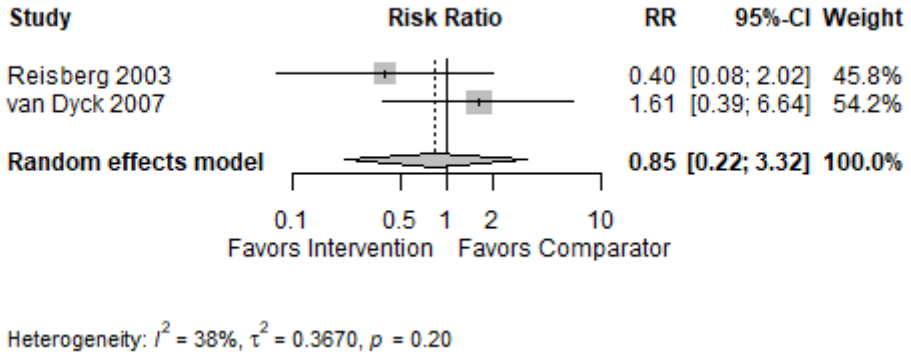


PICO 2

Mortality

For PICO 2, one study reported on mortality at the 24 weeks follow-up[120], and one at the 28 weeks follow-up.[119] When mortality data from 24 and 28 weeks was combined, the RR was 0.85 (p = 0.816, 95%CI: 0.22 to 3.32, Figure 27) without important heterogeneity (I^2 = 38%).

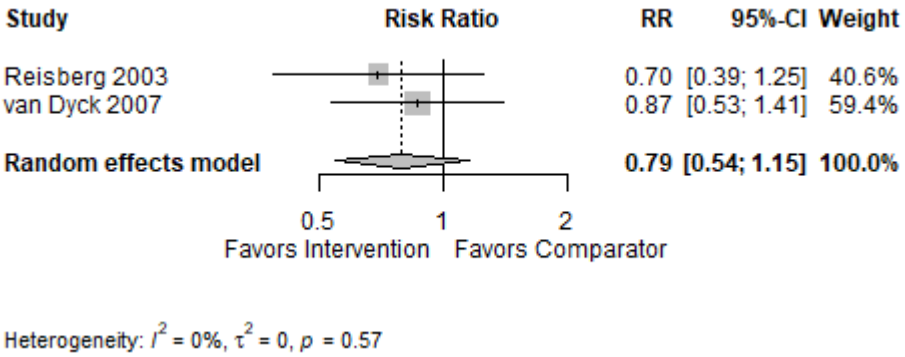
Figure 27 Forest-plot for mortality after 24 and 28 weeks of treatment



Serious adverse events

For PICO 2, one study reported on serious adverse events at the 24 weeks follow-up [120], and one at the 28 weeks follow-up.[119] The proportion of patients who had experienced serious adverse events was similar in the intervention and comparator arm. When serious adverse events data from 24 and 28 weeks was combined, the RR was 0.79 (p = 0.224, 95%CI: 0.54 to 1.15, Figure 28) without important heterogeneity (I^2 = 0%).

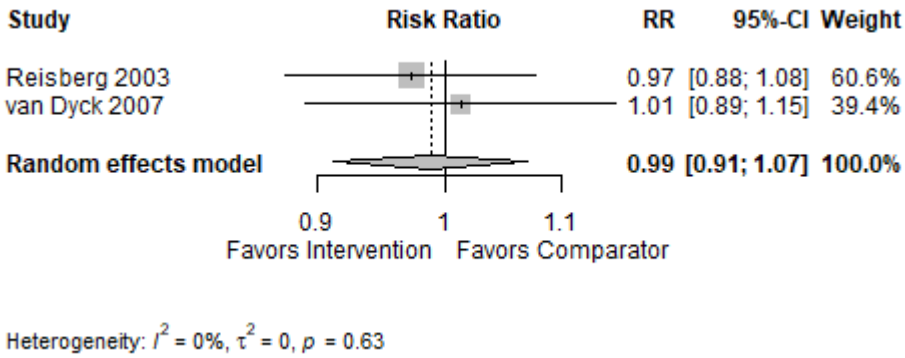
Figure 28 Forest-plot for serious adverse events after 24 and 28 weeks of treatment



Adverse events

For PICO 2, one study reported on adverse events at the 24 weeks follow-up [120], and one at the 28 weeks follow-up.[119] The proportion of patients who had experienced an adverse event was similar in the intervention and comparator arm. When adverse events data from 24 and 28 weeks was combined, the RR was 0.99 (p = 0.769, 95%CI: 0.91 to 1.07, Figure 29) without important heterogeneity (I^2 = 0%).

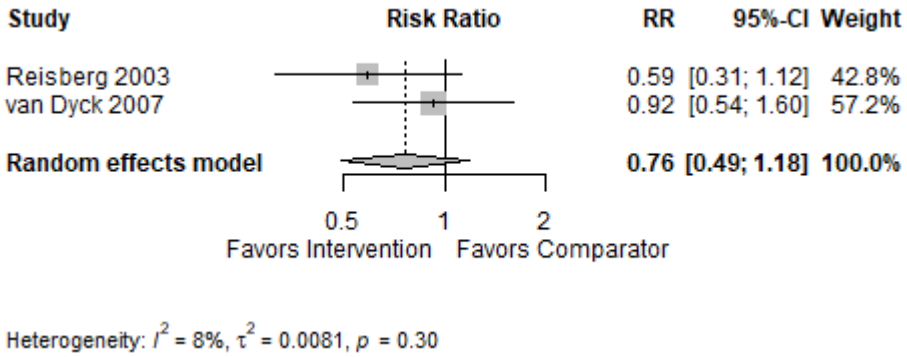
Figure 29 Forest-plot for adverse events after 24 and 28 weeks of treatment



Treatment discontinuation due to adverse events

For PICO 2, one study reported on treatment discontinuation due to adverse events at the 24 weeks follow-up [120], and one at the 28 weeks follow-up.[119] The proportion of patients who discontinued due to adverse events was similar in the intervention and comparator arm. When discontinuation due to adverse events data from 24 and 28 weeks was combined, the RR was 0.76 (p = 0.223, 95%CI: 0.49 to 1.18, Figure 30) without important heterogeneity (I^2 = 8%).

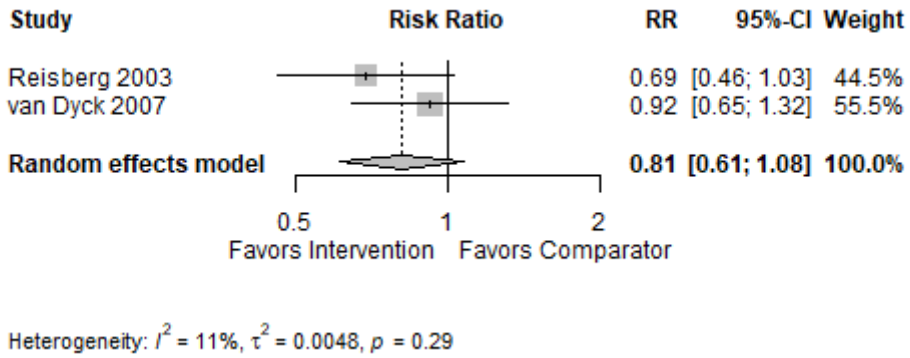
Figure 30 Forest-plot for treatment discontinuation due to adverse events after 24 and 28 weeks



Treatment discontinuation due to any reason

For PICO 2, one study reported on treatment discontinuation at the 24 weeks follow-up [120], and one at the 28 weeks follow-up.[119] The proportion of patients who discontinued due to any reason was similar in the intervention and comparator arm. When discontinuation data from 24 and 28 weeks was combined, the RR was 0.81 (p = 0.150, 95%CI: 0.61 to 1.08, Figure 31) without important heterogeneity (I^2 = 11%).

Figure 31 Forest-plot for treatment discontinuation due to any reason after 24 and 28 weeks



PICO 3

The literature search rendered only one RCT that fulfilled the criteria for PICO 3.[123] In that study, the intervention arm contained 362 participants, the comparator arm contained 179 participants. All safety results were reported at 24 weeks of follow-up. There were four (1.1%) deaths in the rivastigmine arm and seven (3.9%) in the placebo arm. RR was 0.28 (p = 0.042, 95%CI: 0.08 to 0.95). There were 99 (27.3%) and 32 (17.9%) treatment discontinuations in the rivastigmine and placebo arm, respectively, RR was 1.53 (p = 0.019, 95%CI: 1.07 to 2.18). Adverse events were more often reported in the rivastigmine 303 (83.7%) than in the placebo 127 (70.9%) group, RR was 1.18 (p = <0.001, 95%CI: 1.06 to 1.31), resulting in 62 (17.1%) and 14 (7.8%) treatment discontinuations, respectively. RR was 2.19 (p = 0.005, 95%CI: 1.26 to 3.80). The occurrence of serious adverse events was similar in both arms: 47 (13%) for rivastigmine and 26 (14.5%) for placebo, RR was 0.89 (p = 0.690, 95%CI: 0.57 to 1.39).

8 Health economic analysis

Summary statement regarding the health economic analysis

Based on a systematic review of health economic evaluations we retrieved 30 studies, 17 of which were considered transferable, based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) checklist, and were adapted for Switzerland to analyse the cost-effectiveness and cost-utility. Seven studies investigated PICO 1 and ten studies PICO 2. Only one study was identified regarding PICO 3 but was not considered transferable. Therefore, we did not conduct any health economic analysis regarding PICO 3. Of the seven studies investigating PICO 1, four were regarding donepezil, three galantamine and no study was considered transferable regarding rivastigmine.

Although these studies were considered transferable, their results should be interpreted with caution, as there is uncertainty related to their input parameters and assumptions. In most studies, the cost-effectiveness analysis was based on time spent in institutional care or full-time care (FTC). However, the direct treatment effect of the drugs under investigation on institutionalization or FTC has not been assessed in RCTs. Therefore, most economic analyses combined the clinical effects measured with MMSE, ADAS-cog, CDR or ADL from RCTs with several other sources (non-necessarily related to RCTs) to model the mid- and longer-term treatment effect on institutionalization or time spent in FTC (through AD severity and level of dependency). It is worth mentioning, that the clinical effect used as model input parameter was not always reported in these studies and when reported it was often more optimistic compared to the results of the efficacy part of this HTA. Moreover, most health economic evaluations made two main assumptions. First, they assumed that mortality is identical between treated and non-treated patients, which is in line with the results of the meta-analysis reported in the efficacy assessment of this HTA. Second, as most evidence from RCTs refer to a time horizon of up to one year, most identified health economic evaluations conservatively assumed that the duration of the effect was one year. After that the treatment would continue and the effect would be maintained, but no further slowing of the disease would occur. This conservative assumption might have influenced the cost-effectiveness and cost-utility results. Moreover, in many health economic evaluations, the utility values were based on the AD severity and the level of the patient's dependency based on ADL. Information on utility or quality of life in the RCTs included in the efficacy assessment of this HTA were extremely scarce and not comparable with assumptions undertaken in the economic literature. Finally, there was considerable heterogeneity across economic studies reporting information on institutionalization rates and utility values, which suggests a high level of uncertainty.

Regarding PICO 1, the adapted results from the identified health economic evaluations suggest that donepezil is not cost-effective over a time-horizon of up to 1.5 years, due to relatively high incremental costs compared to the QALYs gained. Over a time-horizon of 10 years, donepezil becomes dominant (cost saving and increased QALYs). Similarly, treatment with galantamine seems to be cost-effective over a time-horizon of 5 years. Regarding PICO 2, four out of the seven adapted studies indicate memantine to be dominant. The other three studies indicate that memantine is cost-effective lying below a hypothetical willingness-to-pay threshold of CHF 100,000 per QALY.

Furthermore, we calculated the budget impact from removing donepezil, rivastigmine, galantamine or memantine from the treatment of AD from a healthcare payer perspective for a time horizon of five years in Switzerland. This analysis was based on information on institutionalization and mortality rates of treated patients drawn from the CSS health insurance company, the assumption of no treatment effect on mortality and the assumption of a 10% reduction in the probability of being institutionalized over a period of 5 years. A total removal of the ACHE inhibitors or memantine would lead to a budget impact in 2021 of additional costs ranging from CHF 1.01 million for galantamine to CHF 12.42 million for rivastigmine for the healthcare payers. This corresponds to savings due to lower expenses for drugs, physician visits, and home care, ranging between CHF 0.88 million for galantamine and CHF 8.73 million for rivastigmine and to additional costs due to higher rates of institutionalization ranging between CHF 1.89 million for galantamine and CHF 21.15 million for rivastigmine. The assumption concerning the treatment effect on institutionalization rates showed the highest effect on the net budget impact. In the extreme assumption that there is no treatment effect on institutionalization, stopping AD treatment with one of the AChE inhibitors or memantine would lead to savings that vary from CHF 0.80 million for galantamine to CHF 7.87 million for rivastigmine in 2021.

8.1 Methodology costs, cost-utility, cost-effectiveness, and budget impact

In this section, we describe the approach we used to address the health economic research questions. We first conducted a systematic literature review of existing health economic evaluations. Based on the identified evidence we decided to assess the cost-utility and cost-effectiveness by transferring existing results to the Swiss setting. The budget impact was estimated for the Swiss setting with cost calculations using Swiss data sources.

8.1.1 Databases and search strategy

To identify health economic evaluations, we developed search strategies based on the PICO criteria in collaboration with a medical librarian and according to current best practice guidelines (see appendix section 13.1 for the detailed search strategy per database).[126–128] In addition to the search in Cochrane Library, Embase and Medline, we performed a search in EconLit, the international HTA database (INAHTA), the European Network for Health Technology Assessment (EUnetHTA) Planned and Ongoing Projects (POP) database and the NHS Economic Evaluation Database (NHS EED) and we also screened the references of the included health economic evaluations to identify additionally relevant evidence. The final search was conducted on 21 October 2021.

Inclusion and exclusion criteria were defined according to the PICO criteria (section 5) and were kept broad, without restricting the publication period or study quality. We included studies with adult populations, in line with the age of dementia onset. Studies with a published full text in English, French, German, or Italian were eligible. We included all outcomes related to cost-effectiveness or cost-utility. Inclusion/exclusion criteria for studies on health economic evaluations are listed in Table 10.

Table 10 Inclusion criteria for studies on health economic evaluations

Criterion	Inclusion	Exclusion
Publication period	No restrictions	—
Publication status	Published full text available	Published full text not available (including conference abstracts)
Language	English, French, German or Italian	Not English, French, German or Italian
Setting	No restrictions	—
Study design/type	Health economic evaluations, including within-trial or model-based cost minimization, -effectiveness, -utility, and -benefit analysis	Not health economic evaluations
Study population	• PICO 1: Adults (≥ 18 years) with mild to moderate dementia due to AD, diagnosed according to established criteria • PICO 2: Adults (≥ 18 years) with moderate to severe dementia due to AD, diagnosed according to established criteria • PICO 3: Adults (≥ 18 years) with mild to moderate dementia due to PD, diagnosed according to established criteria	• Animal studies • PICO 1: Adults (≥ 18 years) without mild to moderate dementia due to AD • PICO 2: Adults (≥ 18 years) without moderate to severe dementia due to AD • PICO 3: Adults (≥ 18 years) without mild to moderate dementia due to PD
Study intervention	• PICO 1: Donepezil, rivastigmine, galantamine as monotherapies according to the approved dosage • PICO 2: Memantine as monotherapy according to the approved dosage • PICO 3: Rivastigmine as monotherapy according to the approved dosage	• PICO 1: Other drugs than donepezil, rivastigmine, galantamine or combinations of these drugs with memantine • PICO 2: Other drugs than memantine or combinations of memantine with AChE inhibitors • PICO 3: Other drugs than rivastigmine or rivastigmine in combination with memantine
Study comparator	Treatment without drugs under investigation / placebo	Any other comparator
Study outcomes	Any related to cost-effectiveness or cost-utility	—

AChE: Acetylcholinesterase, AD: Alzheimer's disease, PD: Parkinson's disease, PICO: Population, intervention, comparator, outcome

In a first step, the studies were screened by title and abstract in duplicate according to the inclusion/exclusion criteria. In a second step, full texts of studies retained from the first step were reviewed in duplicate. Any disagreement was resolved by consensus. Where consensus could not be found, a third reviewer was consulted. To increase consistency between reviewers, prior training sessions were held.

8.1.2 Methodology data extraction

The reviewers extracted data into a predefined work sheet, which was pilot-tested with selected studies retained after full-text screening. Extracted data were checked by a second reviewer. Any disagreement was resolved by consensus.

The following data was extracted:

- Country
- Population
- Intervention
- Comparator
- Dosage
- Type of economic evaluation
- Type of model used (where applicable)
- Time horizon
- Perspective of cost assessment (e.g., societal, healthcare)
- Cost data used (currency and cost year)
- Discount rate
- Clinical data used
- Mean costs in intervention and control group
- Quality-adjusted life years (QALYs) in intervention and control group
- ICER in terms of QALYs
- Effectiveness outcomes in intervention and control group
- Key assumptions made for modelling, e.g., regarding the duration of treatment effect, discontinuation for intervention, mortality, further clinical, cost and utility assumptions
- Information of cost composition
- Information to assess the quality of studies and reporting including information on how uncertainty was handled (type of sensitivity analysis, scenario analysis etc.) and conflict of interest

8.1.3 Assessment of quality of reporting, transferability and quality of evidence

The quality of reporting of the included health economic evaluations was assessed using the updated Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) checklist [129]. The CHEERS 2022 statement consists of a 28-item checklist. For each item on the checklist, we judged whether the information was provided (Yes = 1 point), if it was not clearly provided (unclear = 0.5 point), or if it was not mentioned (No = 0 point). The percentage of the positively answered questions was calculated for each study.

Several studies have proposed procedures and unique criteria to assess geographic transferability. The methods vary substantially across these studies and there is no clear agreement on the procedure that should be followed.[130] We assessed the potential of transferring the existing evidence to the Swiss setting by first evaluating the eligibility of the studies. According to the ISPOR Task Force on Good Research Practices[131] that are based on Welte et al. 2004 [132], the eligibility was satisfied if the population, intervention and comparator were the same as in our HTA and the study's quality was acceptable. Based on previously described inclusion and exclusion criteria eligibility of the identified studies was by definition satisfied. The transferability of the studies to Switzerland was based on the CHEERS 2022 statement. The studies will need to fulfill CHEERS 2022 criteria 5, 7 and 11. Moreover, studies not meeting CHEERS 2022 criteria 6, 8, 9, 15, and 23 were regarded as not transferable due to lack of key information. In relation to criteria 23, the availability of costs and outcomes of interest for both the intervention and comparator strategies was considered fundamental. In addition, studies conducted for countries not comparable to Switzerland with respect to the healthcare system and the socio-economic characteristics were also regarded as not transferable. If transferability was considered possible, costs were converted to Swiss francs for the year 2019 following the method described in section 8.1.5.

To show the quality of the studies assessed as transferable we also described each study with respect to the methods applied, the associated main assumptions, the main input variables, and sources. In addition, we compared them with the results of the efficacy part of this HTA, whenever possible.

8.1.4 Cost approximation

For studies which did not calculate the costs from the healthcare payer perspective we approximated the costs based on information extracted from studies for which we could assess the costs from more than one perspective. In particular, we calculated the ratios of costs between the healthcare payer perspective, the societal perspective and the social care perspective. We then took the mean per ratio per study, if a study reported more than one ratio (e.g., for different time horizons) and then calculated the mean ratio over all studies. The respective costs were then multiplied with the respective ratios depending on the perspective.

8.1.5 Cost adaptation

The adaptation of cost data for Switzerland for the year 2019 was performed in three distinct steps including the correction for different levels of resource utilisation, for different prices of healthcare services, and for change in level of resource utilisation and prices over time (see Appendix 13.4).

1. *Resource utilisation:* The types and quantities of resource utilisation differ between countries. For the same disease, patients in Switzerland often receive more medical treatments than in

other countries (i.e., patients are treated more intensively for an equivalent diagnosis). Therefore a “quantity correction" is necessary. The quantity correction was based on the Organization for Economic Co-operation and Development (OECD) statistics of healthcare expenses per capita, corrected for purchasing power. A correction for differences in resource utilisation levels (unaffected by price levels) was thus achieved.[133]

2. *Prices of healthcare services:* The price for the same healthcare service or treatment is often different across countries. A currency conversion to Swiss Francs (CHF) including this “price of healthcare services correction” was achieved by applying purchasing power parities provided by the OECD. Such purchasing power parities represent the proportional costs for identical products in two countries.[134]
3. *Change in healthcare costs over time:* Healthcare costs change over time. For eligible studies performed in countries other than Switzerland, the two steps described above achieved an adaptation of reported costs. However, the resulting estimates are valid for the same cost year as in the original study. Additional correction for the development of costs over time was necessary. In the case of a specific disease and set of treatment strategies, costs may change over time due to mere price changes but no changes in resource utilisation, or resource utilisation for the treatment of the disease of interest may also change. In our 'base case' approach, we assumed the latter, and that changes in resource utilisation would occur with the same cost impact as at the level of total Swiss healthcare expenditures. The resulting correction was based on the yearly growth rates of total Swiss healthcare expenditures, as reported by the Swiss Federal Statistical Office.[135]

It is important to emphasize that this process cannot be interpreted as achieving fully realistic costs/ICERs for Switzerland but has intended to achieve a certain approximation of costs/cost-effectiveness levels to be expected for Switzerland. To fully adjust the costs of international studies it would be necessary to consider underlying costs differences between countries (e.g., physician visit costs or hospitalisation costs) as well as differences over time (including drug price changes over time due to patent expiry). Such approach was considered not feasible since for most identified studies the costs (and unit costs) were not reported in sufficient detail. Although such cost adaptation is subject to several limitations, it has certainly made the results of international studies, reported for different countries and in different currencies, more comparable.

8.1.6 Budget impact analysis

We built a budget impact model for the Swiss setting calculating the costs from withdrawing donepezil, rivastigmine, galantamine or memantine from the treatment of AD. We conducted the analysis from a healthcare payer perspective for a time horizon of five years. We calculated the budget impact based

on information on institutionalization and mortality rates of treated patients over a period of 5 years in Switzerland drawn from the CSS health insurance company. This analysis was also based on the assumption that there is no treatment effect on mortality and on one main assumption regarding the treatment effect on institutionalisation. As none of the identified RCTs in the clinical part of our HTA provided information on the direct effect of treatment on institutionalization, we assumed a reduction in institutionalization by 1.7 months based on other health economic evaluations. Based on this reduction we estimated a 10% reduction in the probability of being institutionalized over a period of 5 years.

Due to the lack of evidence regarding PD and not observing any patient that had used rivastigmine and an anti-Parkinson drug during the period 2016 and 2021 in the CSS health insurance claims data we did not conduct a budget impact analysis (BIA) for PICO 3.

Target population:

The target population for the BIA was AD patients in Switzerland. As reported in a recently published Ecoplan report, the number of newly diagnosed dementia patients in 2017 was 28'766.[3] Moreover, according to the previous Ecoplan report published in 2010, 63.5% of all dementia cases are attributable to AD.[136] Taking the ageing of the Swiss population into consideration, we estimated the number of new AD cases from 2017 to 2025.

Treatment:

Using CSS health insurance claims data, we extracted information on the treatment distribution (i.e., which percentage of AD patients receive a specific AD treatment), as well as on institutionalization and mortality rates over a period of 5 years (2017-2021). These rates were combined with the estimated number of new AD cases per year to estimate the total number of AD patients between 2017 and 2025. Among the individuals insured by CSS 0.19% were AD patients treated with an AChE inhibitor or memantine, which is lower compared to the share in the Swiss population, which we estimated at 0.26%. As the number of AD patients in Switzerland treated with an AChE inhibitor or memantine is not known, the latter share is based on the assumption that 63.5%[136] of dementia cases are due to AD and that 25%[137] of AD patients are treated with an AChE inhibitors or memantine. To make the budget impact estimations as representative as possible for the Swiss population we weighted the CSS sample based on the number of people by sex and age groups.

Concerning patient's institutionalization and mortality rates, the CSS data allowed us to estimate the percentages of patients being institutionalized or have died from the first year to the fifth year after treatment initiation. For example, it was estimated that 26.3% of the patients receiving donepezil was

expected to be institutionalized in the first year after treatment initiation, while 5.9% was expected to die. As consequence 67.8% of the donepezil patients in the first year of treatment was expected to be in a pre full-time care (pre-FTC) situation. Table 11 illustrates the progression of patients during the first 5 years after treatment initiation for patients receiving donepezil, rivastigmine, galantamine, or memantine. Unfortunately, CSS data did not allow an estimation of the patient's progression in the absence of AD treatment. Nevertheless, several health economic analyses identified in our systematic review of the literature provide useful information on the mean time of institutionalisation for treated versus untreated AD patients. For example, Migliaccio-Walle et al. 2003[138] estimated that the mean time in FTC over a time horizon of 10 years was 22.5 months without galantamine treatment and 19.4 months with galantamine treatment (difference 3.1 months in favour of AD treatment). Getsios et al. 2010[139] reported that the institutionalization time for patients treated with donepezil was shorter compared to placebo (1.9 to 2.6 months in favour of AD treatment, 10-year time horizon). Guo et al. 2010[140] has estimated that galantamine reduces the time spent in institutional care by about 2.4 months (10-year time horizon). Finally, Bond et al. 2012[141] estimated that treatment with the different AD drugs compared to best supportive care led to a delay to institutional care ranging between 1.4 and 1.7 months (20-year time horizon). Considering the time horizon of our analyses, the published results on the reduction of institutionalisation time and assuming no treatment effect on mortality (in line with the finding of the efficacy assessment), we assumed that the probability of being institutionalized for patients not receiving AD treatment in Switzerland is approximatively 10% higher if compared to treated patients (this would result in a mean increase of institutionalisation time of 1.7 months over a period of 5 years) (Table 12).

Concerning home care, the estimated number of spitex-clients suspected to have dementia in 2017 was 31'520 according to Ecoplan. Assuming again that 63.5% of all dementia cases are attributable to AD [136], leads to 20'015 patients with AD treated by spitex. According to these numbers, we assumed that 47% of the patients in pre-FTC received home care.

Furthermore, a special condition of treatment with AChE inhibitors and memantine in Switzerland is that patients using these drugs are required to go through a MMSE at the beginning of the treatment, 3 months after treatment initiation and every 6 months thereafter. As a result, treatment with AChE inhibitors and memantine is associated with additional physician visits. We accounted for this in the BIA by assuming three additional physician visits during the first year after treatment initiation and two additional visits for the following years.

Table 11 Progression of patients receiving Alzheimer disease treatment

Progression of patients receiving ANY AD treatment (weighted mean)					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Institutionalisation	32.4%	31.1%	28.5%	26.5%	25.6%
Pre-FTC	56.9%	50.8%	47.5%	45.8%	45.4%
Death	10.8%	18.2%	24.0%	27.7%	29.0%
Progression of patients receiving donepezil					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Institutionalisation	26.3%	27.6%	26.5%	24.2%	23.5%
Pre-FTC	67.8%	60.8%	57.2%	55.3%	54.5%
Death	5.9%	11.6%	16.2%	20.6%	22.0%
Progression of patients receiving rivastigmine					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Institutionalisation	31.6%	30.6%	28.2%	26.7%	25.6%
Pre-FTC	57.8%	51.5%	48.2%	46.4%	46.2%
Death	10.7%	17.9%	23.6%	27.0%	28.2%
Progression of patients receiving galantamine					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Institutionalisation	28.2%	31.7%	28.6%	28.6%	26.4%
Pre-FTC	65.4%	55.3%	52.5%	49.0%	49.0%
Death	6.4%	12.9%	18.9%	22.4%	24.6%
Progression of patients receiving memantine					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Institutionalisation	42.5%	36.5%	31.7%	29.1%	28.2%
Pre-FTC	39.4%	35.2%	32.4%	31.7%	31.3%
Death	18.1%	28.3%	35.8%	39.2%	40.5%

AD: Alzheimer disease, pre-FTC: pre full-time-care

Table 12 Progression of patients not receiving Alzheimer disease treatment

Progression of patients without treatment (110% institutionalization compared to treated)					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Institutionalisation	35.6%	34.2%	31.4%	29.1%	28.1%
Pre-FTC	53.6%	47.7%	44.7%	43.2%	42.8%
Death	10.8%	18.2%	24.0%	27.7%	29.0%
Progression of patients without donepezil (110% institutionalization compared to treated)					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Institutionalisation	28.9%	30.3%	29.2%	26.6%	25.9%
Pre-FTC	65.2%	58.0%	54.6%	52.8%	52.1%
Death	5.9%	11.6%	16.2%	20.6%	22.0%
Progression of patients without rivastigmine (110% institutionalization compared to treated)					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Institutionalisation	34.7%	33.6%	31.0%	29.3%	28.1%
Pre-FTC	54.6%	48.5%	45.4%	43.7%	43.6%
Death	10.7%	17.9%	23.6%	27.0%	28.2%
Progression of patients without galantamine (110% institutionalization compared to treated)					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Institutionalisation	31.0%	34.9%	31.5%	31.5%	29.0%
Pre-FTC	62.6%	52.2%	49.6%	46.1%	46.4%
Death	6.4%	12.9%	18.9%	22.4%	24.6%
Progression of patients without memantine (110% institutionalization compared to treated)					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Institutionalisation	46.7%	40.1%	34.9%	32.0%	31.1%
Pre-FTC	35.1%	31.6%	29.3%	28.7%	28.4%
Death	18.1%	28.3%	35.8%	39.2%	40.5%

AD: Alzheimer disease, pre-FTC: pre full-time-care

Cost per patient:

As in most of the economic analyses identified in the literature review, our analysis mainly focused on costs for medication, physician visits, institutionalisation, and support at home (“spitex”).

Time horizon:

The inclusion procedure of patients/costs into the analysis over the examined time horizon is represented schematically in Table 13. The analyses started in 2017 since a run-in period was required to achieve stable estimates based on a 5-year time horizon. For 2017, only the patients/costs in the first year after diagnosis were included. For 2018, patients diagnosed in 2017 who had not died were added to patients diagnosed in 2018. For 2019, patients diagnosed in 2017 and 2018 who had not died were added to the costs of patients diagnosed in 2019. For 2020, the patients of 2017, 2018, and 2019 were added to patients diagnosed in 2020. From year 2021 to 2025, the cumulative number of newly diagnosed cases as well as the number of patients diagnosed in the previous four years were included. This implies that the number of cases in the years 2017 to 2020 were clearly underestimated as they did not

include patients diagnosed before 2017. To avoid issues in the interpretation of the results, we only report results from 2021 onwards (i.e., from the first year in which a full 5-year follow-up for all patients can be included).

Table 13 Schematic representation of patients/costs included in the analyses

Year of diagnosis	2017	2018	2019	2020	2021	2022	2023	2024	2025
2017	Cases and costs in Y1	Cases and costs in Y2	Cases and costs in Y3	Cases and costs in Y4	Cases and costs in Y5				
2018		Cases and costs in Y1	Cases and costs in Y2	Cases and costs in Y3	Cases and costs in Y4	Cases and costs in Y5			
2019			Cases and costs in Y1	Cases and costs in Y2	Cases and costs in Y3	Cases and costs in Y4	Cases and costs in Y5		
2020				Cases and costs in Y1	Cases and costs in Y2	Cases and costs in Y3	Cases and costs in Y4	Cases and costs in Y5	
2021					Cases and costs in Y1	Cases and costs in Y2	Cases and costs in Y3	Cases and costs in Y4	Cases and costs in Y5
2022						Cases and costs in Y1	Cases and costs in Y2	Cases and costs in Y3	Cases and costs in Y4
2023							Cases and costs in Y1	Cases and costs in Y2	Cases and costs in Y3
2024								Cases and costs in Y1	Cases and costs in Y2
2025									Cases and costs in Y1
					Full 5-year follow-up estimations				

In the third step, unit costs for AD drugs, physician visits, institutionalisation, and home care were applied to the estimated resource use. Table 14 summarizes the adopted unit costs.

Table 14 Unit costs and sources of information for the cost calculations

Resource	Unit cost (CHF)	Source
Medication costs:		
donepezil	0.37 per gram	CSS
rivastigmine	0.50 per gram	CSS
galantamine	0.23 per gram	CSS
memantine	0.18 per gram	CSS
Physician visit	85.96 per visit	Ecoplan 2019[3]
Institutionalization	89'415 per year	Ecoplan 2019[3]
Home care (spitex)	7'791 per year	Ecoplan 2019[3]

Sensitivity analysis:

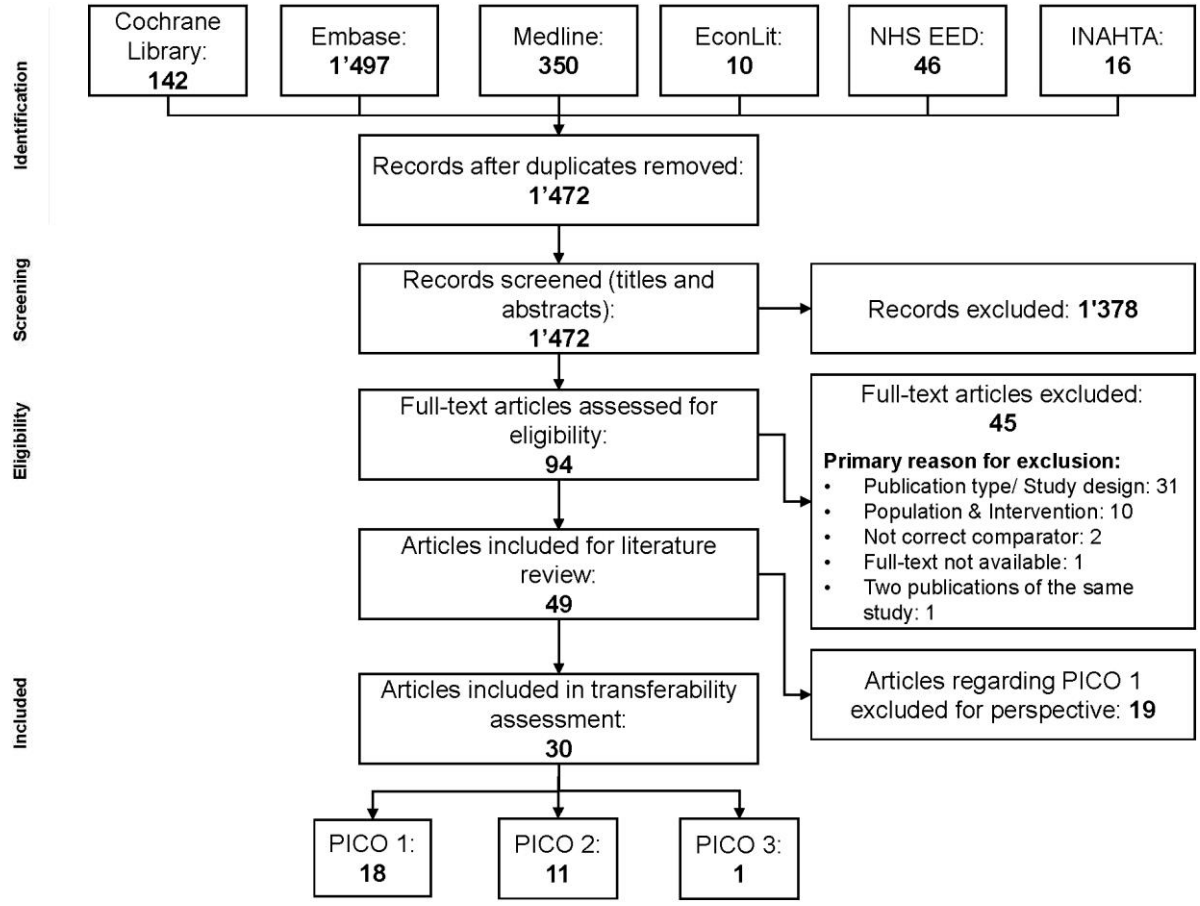
In the sensitivity analysis we varied the assumptions concerning percentages of dementia cases assumed to have AD (base case: 63.5%), the mean costs of institutionalization per year, the mean costs of home care per year, and the mean cost of a physician visit by ±30%. Moreover, the assumed effect of stopping AD treatment with one of the AChE inhibitors or memantine on institutionalization rates was varied from 0% and +5% to 15% (in the base case it was estimated that in the absence of AD drug treatment the institutionalisation rates for AD patients would increase by 10%).

8.2 Results cost, cost-utility cost-effectiveness and budget impact

8.2.1 PRISMA flow diagram

Figure 32 shows the PRISMA flow diagram. Of the 1'472 unique hits, 1'378 were excluded during title-abstract screening. Of the remaining 94 articles whose full texts were screened, 45 were excluded. The most frequent reasons were the publication type (e.g., conference abstract or letter to the editor) or the study design (e.g., review or systematic literature review instead of a health economic evaluation) or the population and intervention did not match the PICOs. As we identified many studies for PICO 1, we excluded another 19 studies that did not analyse the costs from a healthcare payer perspective. For PICO 2 and PICO 3 we included studies analysing the costs also from other perspectives due to the lower number of identified studies. This resulted to 30 studies for the transferability assessment: 18 for PICO 1[138–140,142–156], 11 for PICO 2[141,157–166] and 1 for PICO 3[167]. All 30 studies were health economic evaluations that did not include a budget impact analysis. No additional health economic evaluations were identified from screening the references of the included studies.

Figure 32 PRISMA flow diagram



8.2.2 Quality assessment and characteristics of included studies

Quality of reporting

Details on the CHEERS 2022 items and the reporting quality assessment for the selected studies are reported in the Appendix 13.5 and 13.6.

Overall, 74% of the CHEERS 2022 items were reported. However, there were considerable variations across different studies as well as across different CHEERS items. The reporting quality ranged from 43% to 91%: two studies[151,155] reported less than 60% of the questions, 19 studies answered between 60% and 80% of the questions, and nine studies[139–142,144,149,157,164,165] answered more than 80% of the questions. Although there were few exceptions, studies published more recently tended to have a better quality compared to older ones.

Concerning the CHEERS 2022 items that were judged as particularly important to consider a study transferable for Switzerland, most of them were answered by the great majority of the included studies (>90%). Only CHEERS 2022 Item 5 (i.e., “Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).”), CHEERS 2022 Item 15 (“Report the

dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.") and CHEERS 2022 Item 23 (i.e., "Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.") were reported less frequently (70%, 89%, and 75%, respectively).

The study population (Item 5) was insufficiently described in three studies[148,152,155] and was only partially described in nine studies[144,151,154,156,160,161,163–165]. Setting and location (Item 6) were not described in two studies[152,155], while price date (Item 15) was not reported in three studies[146,150,151]. Moreover, a total of seven studies[147,152,154–156,162,167] did not report the main results (item 23) for interventions and comparators separately.

In item 28 on the CHEERS 2022 checklist the authors have to declare whether a conflict of interest was present or not (if the presence/absence of conflict of interest was reported, the item was valued with 1 point). For the sake of transparency, we investigated more in detail whether a conflict of interest was present (see Appendix 13.7). In 12 studies the presence of a conflict of interest was declared, while in 6 studies the absence of a conflict of interest was stated. A total of 12 studies did not provide information concerning potential conflicts of interest. In 7 of them one or more authors were affiliated to a pharmaceutical industry. Considering that in most economic studies a conflict of interest was declared (or if not explicitly declared one of the co-authors was affiliated to a pharmaceutical company), a risk of bias in favour of the intervention should be considered.

Based on the CHEERS 2022 assessment, a total of 11 studies[146–148,150–152,154–156,162,167] were considered as non-transferable. In addition, according to the transferability criteria proposed by Welte et al. 2004[132], two studies conducted in Brazil[143] and Thailand[142] were also excluded from the cost adaptation as the healthcare system of both countries are not comparable to the Swiss context.

To summarize, a total of 17 studies were considered transferable to the Swiss setting. Seven of them were for PICO 1[138–140,144,145,149,153], out of which four were regarding donepezil[139,144,145,153] and three galantamine[138,140,149]. No study regarding rivastigmine was considered transferable. Ten of the transferable studies were for PICO 2[141,157–161,163–166]. The one study identified for PICO 3[167] was not considered transferable. As evidence regarding the effectiveness, efficacy and safety for PICO 3 (see section 7) is also scarce and therefore insufficient to build a de novo model, we did not conduct a health economic analysis for PICO 3.

Quality of evidence

PICO 1

In the discrete-event simulation model developed by Getsios et al. 2010[139], patient characteristics, disease progression, and treatment effects were based on registry data (CERAD) and donepezil clinical

trials spanning from mild to severe Alzheimer's disease [97,115,122,168–171]. The estimated treatment effect size on annualized rate of change was 6.16 in the first 20 weeks of treatment and 2.47 over weeks 20–52. After week 52, continued treatment was assumed to have no further effect on the predicted rate of disease progression, and as with all treatment effects in the model, it was assumed to serve to simply maintain previous gains (time horizon was set to 10 years). In case of treatment discontinuation, patients were assumed to lose all benefits over a 6-week period. Survival was assumed to be identical for both intervention and control groups. Probability of being institutionalized depended on the MMSE score (12.9% for MMSE >24, 25.6% for MMSE 20-24, 38.3% for MMSE 15-19, 51.0% for MMSE 10-14, and 70.0% for MMSE <10)[172]. Over a follow-up period of 10 years, the estimated time spent in institutionalization using donepezil decreased by 1.9-2.6 months if compared to no treatment. Utilities were based on a published regression equation and depended on MMSE score, NPI score, institutionalization, and caregiver's presence [Utility = 0.408 + 0.010*MMSE – 0.004*NPI - 0:159*Institutionalized + 0.051*Caregiver; [173]]. Comparing the treatment effect in Getsios et al. 2010[139] with the effects reported in the efficacy part of this HTA (e.g., MMSE after 24 weeks 0.82 higher than with placebo) is not possible since no mean MMSE reduction was reported. Similarly, information on institutionalization rates and utilities were generally not available in the RCTs identified in the efficacy part. As consequence, their validity may be questionable.

López-Bastida et al. 2009[145] developed a Markov model simulating the natural history of a cohort of AD patients. Health states were based on the Clinical Dementia Rating (CDR) scale, and transition probabilities were derived from two studies published by Neumann et al. 2001 and 1999[174,175] based on the CERAD registry. To measure the effects of donepezil against placebo, data from a RCT published by Rogers et al. 1998[97] was used. According to the reported estimations, donepezil and placebo group had different monthly probabilities to stay in a mild state (98.0% vs. 96.3%), to switch from mild to moderate state (1.5% vs. 3.2%), to stay in moderate state (95.3% vs 95.8%), and to switch from moderate to mild state (0.9% vs. 0.4%). In contrast, probabilities to reach a severe state or die were identical for both groups. The duration of the effect of the medication was not clearly described. To assess QALYs, utilities from a Spanish study[176] conducted by the same author including a sample of 237 patients were used. Utilities over a period of one year were estimated at 0.5249 for mild state, 0.1818 for moderate state, and -0.2014 for severe state. The costs were also drawn from Lopez-Bastida et al. 2006[176] and included costs for donepezil and other drugs, medical visits, hospital admissions, emergency, visits, orthopedic devices and others, without mentioning any further information or related assumptions. Two RCTs identified in the efficacy part of this HTA suggested that the mean difference in CDR was -0.45 in favour of donepezil [97,116]. López-Bastida et al. 2009[145] did not clearly report the mean CDR changes in their analyses, however they used as source of information one of the RCTs included in the efficacy assessment. Considering that the other RCT identified in the efficacy assessment showed a smaller effect in favour

of the intervention (-0.37 vs. -0.60 in Rogers et al. 1998[97]), it may be argued that the positive effects of donepezil may have been overestimated. Concerning quality of life, it could be argued whether applying negative utility values for severe AD is realistic or not.

Happich et al. 2005[149] created a Markov model including mild, mild-moderate, moderate, and severe AD (based on the MMSE score). Transition probabilities for the placebo group were based on a cost-effectiveness study by Jönsson et al. 2005[163] (study included in PICO 2). For placebo, the probability to remain in the same health state was 76.44% for mild state, 84.90% for mild-moderate state, 76.34% for moderate state, and 77.16% for severe state. The probability to switch to the next stage was 5.61% for mild state, 6.11 for mild-moderate state, and 7.34% for moderate state, while probability of dying increased from 7.19% in mild state to 22.84% in severe state. The effects of galantamine were based on a Cochrane systematic review published by Loy et al. 2004[177] and a RCT published by Raskind et al. 2004[178]. In short, it was assumed that probability to progress to the following stage for patients receiving galantamine was 50% lower than in patients using placebo. Treatment effect was up to 1 year (afterwards transition probabilities of placebo used). According to a study published by Hux et al. 1998[179], different institutionalisation rates were assumed depending on disease severity: 0% for mild state, 17% for mild-moderate state, 50% for moderate state, and 86% for severe state. Utilities were based on a cross-sectional study published by Neumann et al. 1999[180]. Following values were adopted: 0.69 for mild state, 0.53 for mild-moderate state, 0.38 for moderate state, and 0.27 for severe state. Since Happich et al. 2005[149] did not report the mean MMSE reduction in their model, it is not possible to compare their assumptions with the efficacy part of this HTA. If compared with Getsios et al. 2010[139], institutionalization rates in Happich et al. 2005[149] were lower for mild and mild-moderate states, but higher for moderate and severe states. Compared to the previous two studies, the model of Happich et al. 2005[149] did not allow a swich to less severe AD states (e.g., from moderate to mild states). This may lead to an underestimation of the treatment effects. Utilities were generally higher if compared to López-Bastida et al. 2009[145] (especially for the severe state).

The cost-effectiveness analysis published by Hartz et al. 2012[144] was based on the above-mentioned model developed by Getsios et al. 2010[139]. As consequence, model assumptions were identical and most of the information was extracted from the same donepezil clinical trials[115,122,169] and from the CERAD registry. The estimated MMSE changes compared to placebo were 1.16 for donepezil and 0.48 for memantine. The reduction in time patients spent institutionalized was not reported separately for donepezil, memantine, and no treatment (it was only reported that institutionalization with donepezil was 10 days shorter than with memantine). If compared to the results of the efficacy part of this HTA (MMSE after 24 weeks 0.82 higher than with placebo), MMSE reduction assumption in Hartz et al. 2012[144] (and presumably also in Getsios et al. 2010[139]) was slightly more optimistic (1.16). As already mentioned,

information on institutionalization rates and utilities were generally not available in the RCTs identified in the efficacy part. As consequence, their validity may be questionable.

Guo et al. 2010[140] developed a discrete event simulation in which disease progression was influenced by baseline disease severity and treatment received over a period of 10 years. Efficacy assumptions were based on galantamine RCTs[104–106,181–183]. As in other cost-effectiveness analyses, the duration of treatment effect was 1 year (afterwards gains were maintained but no further slowing of the disease occurred). For patients responding to treatment (59.5%), the mean change in ADAS-cog score over 6-months was -4.7, while for non-responders the ADAS-cog score was assumed to increase by 3.2. Combining this information, it can be estimated that over 6 months the mean change in ADAS-cog score using galantamine was -1.5. It was assumed that patients in mild and mild-moderate state did not require institutionalization, while patients in moderate, moderate-severe, and severe states needed it (14%, 29%, 50%, respectively). Utilities and QALYs were not considered in the model. Over the follow-up period of 10 years, patients treated with galantamine stayed on average 3.57 months longer with ADAS-cog scores below 47 (i.e., not in severe stage of the disease), if compared to patients receiving no-drug treatment. Moreover, it was estimated that galantamine reduced time spent in an institution by 2.34 months.

According to the results of the efficacy assessment, the ADAS-cog score among treated patients was 2.01 lower than with placebo after 24 weeks follow-up. This estimate is comparable with the data published by Guo et al. Nevertheless, such effects concerned ADAS-cog score changes over 6 months (or 24 weeks), while in Guo et al. 2010[140] the treatment effect was assumed to last for an entire year (it is not clear how the results after 6 months were extrapolated to one year). If compared to other analyses included in this systematic review, the institutionalization rates used in Guo et al. 2010[140] were generally lower.

Migliaccio-Walle et al. 2003[138] used a model simulating the experience of a cohort of patients in 3 states: pre full time care (pre-FTC), FTC, and death. In pre-FTC patients were assumed to live at home, while in FTC they were in a nursing home (59%) or received FTC at home (41%).[184] The model used predictive equations including patients' characteristics (e.g., duration of illness, age, sex, ADAS-cog score, NPI, symptoms) to estimate the probability of FTC and death after 6 months of treatment with galantamine vs. no treatment (time horizon of the analysis: 10 years). Treatment effects were based on 2 RCTs[104,181]. Concerning survival, it was assumed that galantamine provided no benefit. After 6 months of treatment, it was estimated that the ADAS-cog score decreased by 0.6-1.1 points, while with no treatment it increased by 1.2 points (difference 1.8-2.3 in favour of galantamine). The costs included costs for galantamine, nursing home, hospitalization, physician visits, nursing care and emergency department visits and were based on the resource use shown in the RCT by Raskind et al. 2000[104]. Utilities and QALYs

were not considered in the model. For patients with no treatment, the mean time spent in FTC was 22.5 months, while for patients receiving galantamine it ranged between 19.4 and 19.9 months.

The estimated treatment effect in terms of ADAS-cog score in Migliaccio-Walle et al. 2003[138] is comparable with the results in the efficacy results of this report (ADAS-cog 2.01 lower in the treatment group). The idea to use predictive equations to provide the hazard of requiring FTC based on many patients' characteristics is valid. It is however unclear how this equation was combined with the percentage of patients requiring institutionalization (59%) that was fixed a priori.

In contrast with the cost-effectiveness analyses mentioned above that were based on models, the analysis by Wimo et al. 2003[153] was conducted as part of a RCT comparing donepezil with placebo [clinical results published by Winblad et al. 2001[115]]. As a consequence, effectiveness assumptions based on other studies were not necessary. Along with the efficacy measures, Wimo et al. 2003[153] collected information on resource utilization using the Resource Utilization in Dementia (RUD) questionnaire and including medication, hospitalization, visits to healthcare professionals, living accommodation and use of social services. In terms of MMSE score, the results of Winblad et al. 2001[115] (0.92 in favour of the intervention) were in line with the results of the meta-analysis conducted in the efficacy assessment (0.82 in favour of the intervention). Since resource use and unit costs were not clearly reported it is impossible to estimate whether for example time in institutionalization or FTC was comparable to the assumptions used in other economic evaluations.

To summarize, most studies included for PICO 1 modelled disease progression based on MMSE or ADAS-cog score and depending on AD severity they applied different institutionalization rates (and utilities). In most cases, treatment effect was estimated to last for 1 year. Thereafter, disease progression was identical to the no treatment group. Mortality was considered identical for both intervention and no treatment groups.

PICO 2

Similar to the study by Wimo et al. 2003[153] for PICO 1, the cost analysis of memantine vs. placebo by Wimo et al. 2003[166] was conducted as part of a RCT. This RCT including patients with moderate to severe AD investigated changes in terms of function and cognition, as well as resource utilization over a period of 28 weeks. Efficacy on function and cognition was measured through ADCS-ADL, FAST, SIB, and CIBIC-Plus. Resource utilization was measured in days spent in nursing homes, hospitals or emergency rooms, as well as with caregiver time. At week 28, Wimo et al. 2003[166] found a statistically significant advantage for the memantine-treated patients in terms of moving from a community to an institutional setting, as well as in terms of time to institutionalization. The estimated treatment effects in terms of CIBIC-Plus, SIB and ADL are more optimistic in Wimo et al. 2003[166] compared to the efficacy results

of this report (CIBIC-Plus: -0.36 at 28 weeks vs. -0.30 at 24 and 28 weeks, SIB: 5.7 at 28 weeks vs. 3.26 at 24/28 weeks; ADL: 3.37 at 28 weeks vs. 1.41 at 24/28 weeks). On the other hand, in line with the efficacy results, Wimo et al. 2003[166] did not find significant differences with respect to NPI and MMSE scores. Information on FAST was not available in the RCTs identified in the efficacy part.

Yunusa et al. 2021[157] developed a Markov model simulating the costs and effectiveness of treatment with memantine over the lifetime of patients with moderate to severe AD. The health states were mild AD, moderate AD, severe AD (based on the CDR), and death. The transition probabilities were calculated based on information extracted from 29 Alzheimer's Disease Centers (ADCs) in the US. Memantine and best supportive care had different yearly probabilities to stay in the mild state (95.5% vs. 95.4%), to switch from mild to death (0.4% vs. 0.5%), to switch from moderate to mild (4.2% vs. 4.6%), to switch from moderate to death (9.6% vs. 9.2%), to stay in the severe state (68.7% vs 70.1%), and to switch from severe to death (31.3% vs. 29.9%). The probabilities to reach the moderate state, to switch from mild or moderate to severe, and to switch from severe to mild or moderate were identical for both groups. The effect of memantine versus best supportive care (non-pharmacological treatment) was extracted from a Bayesian network meta-analysis by Tricco et al. 2018[75] including 142 studies. The duration of the effect of the medication was not clearly described. The effect on mortality was estimated with an OR of 1.05 (95%CI 0.63-1.70). Cost of care and utility estimates by health states to calculate the QALYs were drawn from a cost-utility analysis by Saint-Laurent Thibault et al. (2015)[185]. The utilities over a period of one year were estimated at 0.54 for the moderate and 0.37 for the severe state. Comparing the treatment effect with the effects reported in the efficacy part of this HTA is not possible, as the treatment effect in Yunusa et al. 2021[157] was reflected through the differences in the transition probabilities between the two groups that were observed in the ADC data, while no information on CDR was identified in the efficacy part. Similarly to PICO 1, information on utilities were generally not available in the RCTs identified in the efficacy part.

The cost-effectiveness analysis by Knapp et al. 2017[158] is based on a 52-week RCT (DOMINO-AD) comparing memantine with placebo. The patients had moderate or severe AD, had been prescribed donepezil for at least 3 months, and were living in the community together with a caregiver or the caregiver visited the patient at least daily. Along with the outcomes on cognition and functioning, the RCT collected information on the generic health-related quality of life rated with the EQ-5D-3L, which was used to calculate QALYs. In addition, information on healthcare service use including inpatient and outpatient care (e.g., psychologists, psychiatrists, GPs, nurses, social workers, occupational therapists, home care) was recorded on the Client Service Receipt Inventory (CSRI). The respective unit costs were drawn from Curtis 2014[186] and from the Department of Health in 2014. Out of 295 recruited participants 39 died over the trial period, one was lost to follow-up and 29 withdrew. The estimated treatment

effect of memantine in terms of sMMSE in Knapp et al. 2017[158], after adjusting for baseline characteristics, is slightly higher than the effect identified in the efficacy results of this report by Reisberg et al. 2003[119] (0.9 vs 0.7). However, both effects are not statistically significant. Furthermore, Knapp et al. 2017[158] did not find significant differences with respect to QALYs and the Bristol Activities of Daily Living Scale (BADLS), while no information was available on these indicators in the studies on PICO 2 identified in the efficacy part.

Bond et al. 2012[141] conducted an health economic evaluation as part of an health technology assessment by adjusting a three-state Markov model for UK (named after the Peninsula Technology Assessment Group PenTAG), that was previously developed by the Southampton Health Technology Assessment Centre (SHTAC-AHEAD). The time horizon was 20 years and the health states of this model are pre-institutionalization, institutionalization, and death. Institutionalization is defined as 'Living in a residential home or a nursing home (not as short respite care) or in hospital on a long-term or permanent basis' and is assumed to be equivalent to severe AD.[187] After each successive cycle, patients can move to the institutionalized or deceased state, or remain in the non-institutionalized state. Transition to death from either of the alive states can occur at any cycle. The model, however, does not allow for any backward transitions assuming that a patient cannot return to the pre-institutionalized state once institutionalized. Disease progression and cost estimates were drawn from the UK-based retrospective cohort study by Wolstenholme et al. 2002[187], as it represent the target population better than a RCT. However, the cohort of this study is living in the community, and thus does not fully represent patients living in the community and in institutionalized care. Therefore, it was assumed that 60% of the patients start in the pre-institutionalization state and 40% in the institutionalization state based on the LASER-AD study[188]. The participants in the study by Wolstenholme et al. 2002[187] were recruited in the Oxfordshire area during 1988–1989 and were followed for up to 11 years. At study entry, the individuals had the AD diagnosis for a mean of 4.9 years, which might indicate that the study population is not as ill as the general population.[187] The effectiveness estimate with regard to MMSE was obtained from Reisberg et al. 2003[119], which is the same study identified in the efficacy part of this HTA (0.70). The effectiveness estimate with regard to ADCS-ADL was obtained from a meta-analysis of the study by Reisberg et al. 2003[119] and the study by Van Dyck et al. 2007[120], which are the same studies we identified in the efficacy part (MD: 1.41). These treatment effects are assumed to delay institutionalization but not survival, as there is no evidence based on RCTs or epidemiological data that shows that treatment affects survival. The mean time to institutionalization and mean time to death were predicted based on an exponential regression model with age, MMSE and Barthel ADL Index as covariates, which was fitted to the cohort of the study by Wolstenholme et al. 2002[187]. Due to lack of effectiveness data beyond the 6-month time period, it was assumed that the rate of decline in the treated and untreated groups is the same after the first 6 months. Moreover, using the treatment paths and outcomes of the cohort from Wolstenholme et

al. 2002[187], Bond et al. 2012[141] developed a multivariate regression model to predict time to institutionalization. As a result, they adjusted the SHTAC-AHEAD model such that it would allow for disease severity (based on MMSE) to increase as patients approach the time when they become institutionalized. This allows for the gradual increase of costs and reduction in health-related quality of life during the pre-institutionalization state. The utility weights by MMSE were drawn from Jönsson et al.[173]. The costs considered included costs for drugs, hospitalizations and respite care, outpatient visits, day care, home attendances by district nurses, community psychiatric nurses, other care assistants, GP or practice nurse based on the healthcare utilization recorded by Wolstenholme et al. 2002[187]. It was further assumed that 4% of the total cohort discontinue treatment each month leading to no individuals receiving treatment after 2 years, based on a mixture of evidence from RCTs and clinical opinions on the time patients would spend on treatment.

Jones et al. 2004[189] developed a Markov model to simulate progression through a range of health stages defined by severity, dependency, and institutionalization with a time horizon of 2 years for the UK setting. The initial distribution of patients, costs per dependency stage and residential setting data were drawn from the LASER study[190]. For institutionalized patients only costs for institutionalization and hospitalization were considered. Over a period of three months the mean hospitalization length was 12 days for independent patients and 32 days for dependent patients. Transition probabilities and the treatment effect were mainly based on the RCT of Reisberg et al. 2003[119]. Similarly to other health economic evaluations, Jones et al. 2004[189] limited the efficacy of memantine to 12 months. Utility values were derived from a Danish epidemiological study.[191] In this study dependency was the main factor influencing the utilities. Therefore, the mean utility values were calculated per dependency level (dependent: 0.3207 and independent: 0.6511). Probability of being institutionalized depended on the MMSE score. The institutionalization probabilities for the non-pharmacological treatment arm were taken from the non-treated patients of the LASER study[190] (MMSE>14: 7.4%, MMSE<=14: 12.5%). Clinical trial data was not used, because institutionalization is country related. For the memantine arm, an odds ratio (OR) was estimated based on the resource utilization trial-based study by Wimo et al. 2003[166], that is described above and that was computed alongside the RCT by Reisberg et al. 2003[119] (OR to remain independent=0.147). The OR was then applied to the probabilities of the non-pharmacological treatment arm. Nevertheless, the rate of institutionalization was not significant between the two arms. Memantine was assumed to have no direct impact on survival, and thus the death probabilities were similar in the treatment arms.

Jönsson 2005[163] developed a Markov model that considered the effect of memantine on cognitive function, dependence in terms of ADL, QALYs, and institutionalization, over a period of 5 years. Costs of care and mortality rates were based on an observational study[192]. Memantine was assumed to have no

direct impact on survival. Jönsson used the same utility weights as Jones et al. 2004[189] (see above). For the first year, the transition probabilities between cognitive levels were calculated based on the RCT by Reisberg et al. 2003[119]. After the first year the transition probabilities of an observational study[192] which could be extrapolated over a longer time period were used. Memantine was assumed to have an effect over 12 months. The transition probabilities between levels of dependence were also calculated based on Reisberg et al. 2003[119]. The institutionalization probabilities were calculated with a Weibull survival model using observational data of 65 patients. All patients with severe dementia resulted as being institutionalized after 5 years while 48% of patients with moderate to moderately severe cognitive impairment (MMSE score between 10 and 20) resulted as living in the community after 5 years.

Antonanzas et al. 2006[161] adapted the Markov model used by Jones et al. 2004[189] and Francois et al. [164] to the Spanish setting. As in Spain patients get mainly treated in the community, the model focused on community-based patients, while institutionalization was not considered [161]. Similarly to most of the previous health economic evaluations on PICO 2, dependency and severity transition probabilities were derived from the RCT of Reisberg et al. 2003[119] included in the clinical part of this HTA. The time horizon was 2 years, and the duration of the treatment effect was 1 year.[193] After the first year, the standard care transition probabilities were used for both arms [161]. The same drug-specific input data as in the previous models was used, while for mortality, cost and epidemiological input data from Spanish studies [194–196] were used. The resource utilization in dementia questionnaire [197] was used to estimate resource utilization. The same death probabilities from Saz et al. 1999[196] were considered for the two arms. As the model does not take into account the delay in institutionalization as an outcome, the resulted benefit is rather conservative [161].

In the Markov model of Francois et al. 2004[164] a time horizon of 5 years was applied. They simulated patient's progression through a range of health states defined by cognitive function, dependency, and institutionalization. They also used the probabilities and resources use differences between treatment and no treatment arms from the RCT of Reisberg et al. 2003 [119]. Based on Reisberg et al. 2003[119] and its extension study[198], a duration of the effect of memantine of one year was considered. Initial distribution was based on the a Finnish population-based health survey of dementia and functional capacity.[199] Based on the results of a regression model, Francois et al. 2004[164] assumed that dependency transition probabilities depended on treatment, severity of disease, and level of dependency at the beginning of the cycle. The OR for dependency and severity adjusted was calculated at 3.03. Francois et al. 2004[164] used the same institutionalization probabilities as Jones et al. 2004[189] (see above). As memantine was assumed to not provide benefit concerning survival, death probabilities were similar for both treatment arms. Costs were based on the study of Rahkonen et al. 2003[199]. The cost of one day in institution was multiplied by 180 to obtain the costs for institutionalized patients.

Comparing the treatment effects estimated in Reisberg et al. 2003[119], that was used in Jones et al. 2004[189], Jönsson 2005[163], Antonanzas et al. 2006[161] and Francois et al. 2004[164], with the treatment effect identified in the efficacy part of the present HTA suggests that the positive effects of memantine might have been overestimated in published health economic studies. In the efficacy part of the present HTA the studies of Reisberg et al. 2003[119] and van Dyck et al. 2007[120] were included. Reisberg et al. 2003[119] found a bigger effect in favor of memantine than van Dyck et al. 2007[120] in terms of SIB and ADCS-ADL, while both studies observed the same mean CIBIC-plus changes in favor of memantine.

Gagnon et al. 2007[160] adapted the Markov model developed by Jones et al. [189], that is described above, for Canada for a time horizon of 2 years. Compared to the Markov model by Jones et al. [189], the health states in the Markov model by Gagnon et al. 2007[160] were based only on severity and dependency on the basis of ADL[200]: moderate not completely dependent, moderate dependent, severe not completely dependent, severe dependent, and death. The initial distribution of patients among the health states was based on a Canadian population-based survey conducted in 1991–1992 with subsequent survey waves in 1996–1997 and 2001–2002.[201] The transition probabilities were estimated based data pooled from four 24-week RCTs [119,202–204] and an 6-month extension study[205]. Due to lack of data on MMSE after the first 6 months, Gagnon et al. 2007[160] mapped the Severe Impairment Battery or the Alzheimer's Disease Assessment Scale–Cognitive subscale to the MMSE using linear regression.[184] The treatment effectiveness of memantine in terms of severity progression and progression in dependence within severity level was based on the same studies [119,202,203,205] and was assumed to last for one year. The OR regarding having moderately severe AD adjusted on initial severity was calculated at 1.384 (95%CI 0.916 to 2.092), and regarding being not completely dependent adjusted for initial severity and dependence was calculated at 1.557 (95%CI 1.057 to 2.292). The death probability was assumed to be the same among the health states and treatment arms and was computed based on the Canadian Study of Health and Aging (CSHA)[206] considering that patients with AD have 2.5 times higher mortality than age-adjusted individuals without AD. Utility values were based on a UK cohort study[188] and, similarly to the utilities values used by Jones et al. 2004[189] and Jönsson 2005[163], they were found to be most affected by the dependency state (complete dependent: 0.598, not completely dependent: 0.254,). However, the utilities seem to be reversed, with the values being higher for the complete dependent state than the independent state, which does not seem to be very plausible. Costs and healthcare utilization were drawn from the CSHA[179] considering also treatment guidelines and clinical expert opinion. The services included medication, nursing care, physiotherapy, occupational therapy, podiatry, chiropractic, day centre, respite stay in nursing home, and physician visits due to treatment with memantine.

Hoogveldt et al. 2011[159] used the adapted Markov model by Gagnon et al. 2007[160] and further adapted it to compare treatment with memantine with no pharmacological treatment among patients with moderate to severe AD in the Netherlands in terms of additional time living independently, additional time in a moderate state, QALYs, and societal costs over a period of 5 years. The health states were moderate independent, moderate dependent, severe independent, severe dependent, and death. The initial distribution of patients among the health states was based on a Dutch study by Breteler et al. 1992[207]. The transition probabilities were estimated based on data pooled from four RCTs [119,120,202,203]. For all treatment arms and health states the same probability of death over each 6 month cycle (7.55%) was used based on Dutch data [208]. Hoogveldt et al. 2011[159] assumed that 2/3 of the independent patients live in a home for elderly and 1/3 live in a nursing home, while half of the dependent patients live in a home for elderly and half in nursing homes. The healthcare services used per health state were derived from a Dutch study[209] and the costs per unit of care were based on Dutch guidelines[210]. To estimate the total costs per stage a prevalence of 66% of female with AD was used based on the Dutch study by Breteler et al. 1992[207]. The following utility values from the LASER-AD study[211] from UK were considered: dependent in institution: 0.169, dependent in community: 0.340, independent in institution: 0.543 and independent in community: 0.608.

Summary

While the general assumption that mortality is identical between treated and non-treated patients is perfectly in line with the results of the meta-analysis reported in the efficacy assessment, comparing all other assumptions used in the economic studies with the results reported in the efficacy assessment is difficult or impossible. Most economic analyses were based on a combination of several sources (non-necessarily related to RCTs). How these sources were combined to define a treatment effect was generally unclear. The modelled treatment effect in terms of mean MMSE, ADAS-cog score or CDR reduction was rarely reported. In the few cases where it was reported, the impression is that the authors tended to use more optimistic assumptions if compared to the results of our efficacy assessment (i.e., the change in score in favour of the intervention was higher than in our meta-analyses). In several studies one of the main economic outcomes was institutionalization (or time spent in FTC). This variable was unfortunately not reported in the RCTs included in the efficacy assessment. Nevertheless, the considerable heterogeneity across economic studies reporting information on institutionalization rates suggest a high level of uncertainty. Similarly, information on utility or quality of life in the RCTs included in the efficacy assessment were extremely scarce and not comparable with assumptions undertaken in the economic literature. Again, the large variation in utility assumptions suggest a high level of uncertainty.

8.2.3 Cost approximation and cost adaptation

All transferable studies regarding PICO 1 could be used directly to assess the costs from a healthcare payer perspective. One study[166] regarding PICO 2 and the single study regarding PICO 3[167] distinguish the direct medical costs from the other types of costs and could thus also be used directly to assess the costs from the healthcare payer perspective. The direct medical costs in the other PICO 2 studies[141,157–161,163–165] were shown together with the direct non-medical or indirect costs. For these studies the costs from the healthcare payer perspective were approximated as described in section 8.1.4. The ratio of costs from the healthcare payer perspective to the costs from the societal perspective is 0.33 and the ratio of costs from healthcare payer perspective to the costs from the social care perspective is 0.71.

The costs reported in the identified health economic evaluations that were considered transferable were adapted for Switzerland and are presented in Table 18. The adaptation included a correction for different levels of resource utilisation, for different prices of healthcare services, and for change in healthcare costs over time. As mentioned in section 8.1.5, this process cannot be interpreted as achieving realistic costs/ICERs for Switzerland but intends to achieve a certain approximation and improve the comparability of studies from different countries. In this section, only adapted costs are illustrated. The costs originally reported in the identified studies (after the approximation) are reported in the Appendix 13.8.

It is worth mentioning that both the expenditure in health as well as the purchasing power parity in Switzerland are generally much higher than in other countries. Among the countries in which the identified studies were performed, only the US have a higher expenditure on health per capita and only Sweden had a higher purchasing power parity. In addition, most of the identified studies have been conducted many years ago: although the costing year ranged between 1999 and 2020, in two thirds of the studies the costing year ranged between 1999 and 2006. Considering that the healthcare costs in Switzerland constantly increased from 1999 to 2019 (with slightly stronger increases in the first decade), the correction factor for older cost results was much higher than for recent studies. As consequence, the cost adaptation for most studies included in this report led to a conspicuous increase of the costs. For example, López-Bastida et al. 2009[145] reported mean intervention costs of EUR 1,136 for the year 2006 (0.5-year time horizon). This cost estimate was multiplied by 1.769 for the “resource utilisation” correction, by 2.174 for the “price of healthcare service” correction, and by 1.555 for “the change of healthcare cost over time” correction. The resulting adjusted cost for Switzerland in year 2019 was CHF 6,791.

8.2.4 Study characteristics and evidence table

The main characteristics of the identified health economic studies are summarized in Table 15.

Countries: Three studies regarding PICO 1 were performed for Germany[140,144,149], one for the UK[139], one for Spain[145] and one for five Northern European countries (Denmark, Finland, Netherlands, Norway and

Sweden)[153]. Three studies regarding PICO 2 were performed for the UK[141,158,165] two for the US[157,166], one for Netherlands[159], one for Spain[161], one for Sweden[163], one for Finland[164], and one for Canada[160].

Time horizon: The time horizon ranged from 0.5 to 10 years in the studies regarding PICO 1 and from 0.5 to 20 years in the studies regarding PICO 2.

Perspective: Most studies for PICO 1 reported results from both healthcare and social/societal perspectives. Among studies included for PICO 2, only one[166] reported results from a healthcare perspective, while all other used a social/societal perspective. Finally, the study identified for PICO 3[167] used both healthcare and societal perspectives.

Modelling approach: Markov models were most adopted approaches (10 studies), followed by discrete event simulations (3 studies), trial-based analyses (3 studies), and calculations based on predictive equations (1 study).

Cost year and discounting: Cost years ranged from 1999 in Wimo et al. 2003[153] to 2020 in Yanusa et al. 2021[157]. Studies adopting a short time horizon (i.e., may one year) generally reported no discounting. In studies with longer horizons the most used discount rates for both costs and outcomes were 3% (5 studies), 3.5% (3 studies) and 5% (4 studies). One study adopted a 6% discount rate for costs and outcomes [161], while Hoogveldt et al. 2011[159] discounted the costs by 4% and the outcomes by 1.5% [159].

Table 15 Main characteristics of the identified health economic literature

Authors, year	Country	Population	Intervention	Comparator	PICO	Time horizon(s)	Perspective	Modelling approach	Cost year and discount rate
Getsios et al. 2010	UK	Mild to moderately severe AD	donepezil	Placebo	1	10	Healthcare and Societal	DES	2007, 3.5%
López-Bastida et al. 2009	ES	Mild to moderately severe AD	donepezil	Placebo	1	0.5, 1, 1.5, 2, 2.5	Healthcare and Societal	Markov	2006, 3%
Happich et al. 2005	DE	Mild to moderately severe AD	galantamine	Placebo	1	5	Healthcare and Societal	Markov	2004, 5%
Hartz et al. 2012	DE	Mild to moderately severe AD	donepezil	Placebo	1	10	Healthcare and Societal	DES	2008, 3%
Guo et al. 2010	DE	Mild to moderately severe AD	galantamine	Placebo	1	10	Healthcare and Societal	DES	2009, 5%
Migliaccio-Walle et al. 2003	US	Mild to moderately severe AD	galantamine	Placebo	1	10	Healthcare	Predictive equations	2000,3%
Wimo et al. 2003 (donezepil)	Mixed (SE)	Mild to moderately severe AD	donepezil	Placebo	1	1	Healthcare, Societal, Social care	Trial-based	1999, 0%
Wimo et al. 2003 (memantine)	US	Moderate to severe AD	memantine	Placebo	2	0.5	Healthcare, Societal, Social care	Trial-based	1999, 0%
Yunusa et al. 2021	US	Moderate to severe AD	memantine	NPT	2	20	Societal	Markov	2020, 3%
Knapp et al. 2017	UK	Moderate to severe AD	memantine	Placebo	2	1	Social care	Trial-based	2013/2014, NR
Bond et al. 2012	UK	Moderate to severe AD	memantine	NPT	2	20	Social care	Markov	2009, 3.5%
Hoogveldt et al. 2011	NL	Moderate to severe AD	memantine	NPT	2	5	Societal	Markov	2006, 4% (costs) and 1.5% (outcomes)
Gagnon et al. 2007	CA	Moderate to severe AD	memantine	NPT	2	2	Societal	Markov	2005, 5%
Antonanzas et al. 2006	ES	Moderate to severe AD	memantine	NPT	2	2	Societal	Markov	2005, 6%
Jönsson 2005	SE	Moderate to severe AD	memantine	NPT	2	5	Social care	Markov	2004, 3%
Francois et al. 2004	FI	Moderate to severe AD	memantine	NPT	2	5	Societal	Markov	2001, 5%
Jones et al. 2004	UK	Moderate to severe AD	memantine	NPT	2	2	Social care	Markov	2003, 3.5%
Willian et al. 2006	CA	Mild to moderately severe PD	rivastigmine	Placebo	3	0.5	Healthcare and Societal	Trial-based	2004, 0%
Willian et al. 2006	UK	Mild to moderately severe PD	rivastigmine	Placebo	3	0.5	Healthcare and Societal	Trial-based	2004, 0%

CA: Canada, DE: Germany, DES: Discrete event simulation, ES: Spain, FI: Finland, NL: Netherlands, NPT: Non-pharmacological treatment, NR: not reported, PD: Parkinson disease, SE: Sweden, UK: United Kingdom, US: United States

Treatment effectiveness and main effectiveness sources

Treatment effectiveness was mainly assessed in terms of disease progression according to changes in MMSE scores (7 studies) or ADAS-cog scores (2 studies), according to published transition probabilities (8 studies), institutionalisation rates/patient's dependency status (11 studies). In most cases, the treatment effect was limited to one year (Table 16). Thereafter, patient's deterioration was generally considered equal to the deterioration of those who did not receive a treatment (placebo). As most evidence from RCTs is up to one year, most identified health economic evaluations conservatively assumed that the duration of the effect was one year. After that the treatment would continue and the effect would be maintained, but no further slowing of the disease would occur. Therefore, the deterioration would be the same between the two groups but not the absolute value of the cognitive/functional function. This conservative assumption might have influenced the cost-effectiveness and cost-utility results.

The sources of information varied considerably across the different health economic analyses. For PICO 2 it can be noticed that the RCT conducted by Reisberg et al. 2003[119] was mentioned particularly frequently.

In almost all studies it was assumed that treatment did not have an effect on mortality (i.e., intervention and comparators had identical mortality rates).

Table 16 Main treatment effect measurement and sources of information

Authors, year	Main treatment effect measurement	Main sources of information
Getsios et al. 2010	Based on disease progression (MMSE score) and institutionalization rates by disease severity. Treatment effect for 1 year. After week 52, continued treatment was assumed to have no further effect on the predicted rate of disease progression and was assumed to serve to simply maintain previous gains.	RWE: CERAD registry[212] RCT: Mohs et al. 2001[122] RCT: Winblad et al. 2001[115] and 2006[168] RCT: Feldman et al. 2001[169] RCT: Rogers et al. 1998[97] RCT: Black et al. 2007[171] RWE: Macdonald et al. 2007[172]
López-Bastida et al. 2009	Based on transition probabilities. The duration of the treatment effects of the medication is uncertain, because the longest reviewed RCT only lasted for 24 weeks.	RCT: Rogers, 1998[97] RWE: Neumann et al. 1999[175] and Neumann et al. 2001[174] based on the CERAD registry
Happich et al. 2005	Based on transition probabilities and institutionalization rates by disease severity. Treatment effect for 1 year (afterwards transition probabilities of placebo used)	RCT: Loy et al. 2004[177] RCT: Raskind et al. 2004[178] RWE: Neumann et al. 1999[180] Hux et al. 1998[179]
Hartz et al. 2012	Based on disease progression (MMSE score). Treatment effect for 1 year (afterwards gains are maintained but no further slowing of the disease occurs)	HE: Simulated using Getsios et al. 2010[139] RCT: Mohs et al. 2001[122] RCT: Winblad et al. 2001[115] RCT: Feldman et al. 2001[169] RCT: Rogers et al. 1998[97] RCT: Rogers et al. 1998[170] RCT: Black et al. 2007[171] Extension study: Doody et al. 2001[213] Extension study: Winblad et al. 2006[214] RWE: CERAD registry[212]
Guo et al. 2010	Based on disease progression (ADAS-cog) and institutionalization rates by disease severity. Treatment effect for 1 year (afterwards gains are maintained but no further slowing of the disease occurs)	RCT: Raskind et al. 2000[104] RCT: Tariot et al. 2000[181] RCT: Wilcock et al. 2000[105] RCT: Wilkinson et al. 2001[182] RCT: Rockwood et al. 2001[183] RCT: Brodaty et al. 2005[106]
Migliaccio-Walle et al. 2003	Based on disease progression (ADAS-cog) and institutionalization rates by disease severity. After the first 6 months of treatment, no further benefit (patients deteriorate at the same rates as if they had received no treatment).	AHEAD model based on data from Stern et al. 1997[184] RCT: Raskind et al. 2000[104] RCT: Tariot et al. 2000[181]
Wimo et al. 2003 (donezepil)	Based on disease progression (MMSE score)	Trial itself: Winblad et al. 2001[115]
Wimo et al. 2003 (memantine)	Based on disease progression (MMSE score)	Trial itself
Yunusa et al. 2021	Based on transition probabilities. Duration of treatment effect unclear.	RWE: Data from 29 Alzheimer's Disease Centers (ADCs) between 2005–2015 from the National Alzheimer's Coordinating Center (NACC) database[215,216] Meta-analysis of 142 studies: Tricco et al. 2018[75]
Knapp et al. 2017	Based on the trial itself. Treatment effect for 1 year.	Trial itself (DOMINO-AD trial)

Bond et al. 2012	Based on disease progression (MMSE score) and time to institutionalisation. 0.5 year treatment effect duration (afterwards gains are maintained but rate of disease parallels comparator arm)	RWE: Wolstenholme et al. 2002[187] RCT: Reisberg et al. 2003[119] RCT: Van Dyck et al. 2007[120]
Hoogveldt et al. 2011	Based on transition probabilities and patient's dependency status. Treatment effect for 1 year (afterwards gains are maintained but no further slowing of the disease occurs)	RCT: Reisberg et al. 2003[119] RCT: Peskind et al. 2006[202] RCT: Bakchine et al. 2005[203] RCT: Van Dyck et al. 2007[120] Extension study : Reisberg et al. 2006[217]
Gagnon et al. 2007	Based on transition probabilities and patient's dependency status. Treatment effect for 1 year.	RWE: Canadian Study of Health and Aging Working Group[201] RCT: Reisberg et al. 2003[119] RCT: Peskind et al. 2006[202] RCT: Bakchine et al. 2005[203] Extension study: Reisberg et al. 2002[205] RCT: Forest Laboratories Clinical Trial Registry. Study No. MEM-MD-01[204]
Antonanzas et al. 2006	Based on transition probabilities and patient's dependency status. Treatment effect for 1 year.	RCT: Reisberg et al., 2003[119] Extension study: Reisberg et al. 2000[193]
Jönsson 2005	Based on transition probabilities and patient's dependency status. Treatment effect for 1 year.	RCT: Reisberg et al. 2003[119] RWE: Fratiglioni et al. 1992[192]
Francois et al. 2004	Based on transition probabilities and patient's dependency status. Treatment effect for 1 year.	RCT: Reisberg et al. 2003[119] Extension study: Ferris et al. 2001[198]
Jones et al. 2004	Based on disease progression (MMSE score), transition probabilities, and institutionalization rates by disease severity.	RCT: Reisberg et al. 2003[119]
Willian et al. 2006	Based on disease progression (changes in MMSE score)	Trial itself

RWE: real word evidence, RCT: randomized controlled trial, HE: health economic

Costs

Table 17 illustrates the cost variables considered in the identified literature as well as the main sources for unit costs. As expected, all studies investigated the costs of the drugs of interest. Also physician visits costs were included in all studies except one (Jönsson et al. 2005[163]). Almost all studies included either inpatients or institutionalization costs (and the difference between the two of them was not always clearly defined nor stated). Since all studies for PICO 1 were conducted using a healthcare perspective, no costs related to informal care or productivity loss were included. In contrast, most studies for PICO 2 were conducted using a social/societal perspective: in six of them informal care costs were clearly stated, while two studies reported details on productivity loss.

Table 17 Costs variables included in the identified health economic analyses and sources of information

Authors, year	Drugs	Inpatient	Institutionalization (nursing home)	Physician visits	Informal care	Productivity loss	Main data sources
Getsios et al. 2010	YES	NO	YES	YES	NO	NO	Curtis 2007[218] Knapp et al. 2007[219] Macdonald and Cooper 2007[172]
López-Bastida et al. 2009	YES	YES	UNCLEAR	YES	NO	NO	Lopez-Bastida, 2006[176]
Happich et al. 2005	YES	NO	YES	YES	NO	NO	Hallauer et al. 2000[220]
Hartz et al. 2012	YES	NO	YES	YES	NO	NO	Teipel et al. 2007[148] Hallauer et al. 2000[220]
Guo et al. 2010	YES	NO	YES	YES	NO	NO	IMS Health 2008[221] Lauer-Taxe et al. 2009[222] Kulp et al. 2002[223] Bundesministerium fur Gesundheit[224]
Migliaccio-Walle et al. 2003	YES	YES	YES	YES	NO	NO	Raskind et al. 2000[104] Stern et al. 1997[184] US Department of Labor, Health Care Financing Review Medicare and Medicaid Statistial Supplement[1] National Association for Home Care. Homecare Salary and Benefits Report[225] Freedman and Reschovsky 1997[226]
Wimo et al. 2003 (donezepil)	YES	YES	No information	YES	NO	NO	Resource Utilization in Dementia (RUD) questionnaire: Wimo et al. 1998[227]
Wimo et al. 2003 (memantine)	YES	YES	No information	YES	NO	NO	Resource Utilization in Dementia (RUD) questionnaire: Wimo et al. 1988[228]
Yunusa et al. 2021	YES	NO	NO	YES	NO	NO	CMS[229], RED BOOK[230], Saint Laurent Thibault et al. 2015[185]
Knapp et al. 2017	YES	YES	NO	YES	YES	YES	Curtis (2014)[186] NHS Reference Costs (Department of Health, 2014)[231] DOMINO-AD trial
Bond et al. 2012	YES	YES	YES	YES	NO	NO	Wolstenholme et al. 2002[187] BNF 58[232] NHS Reference Costs 2008–9[233]
Hoogveldt et al. 2011	YES	YES	YES	YES	YES	NO	Oostenbrink, 2000[210] Van der Roer, 2000[209]

Gagnon et al. 2007	YES	No information	YES	YES	YES	No information	CSHA Canadian Study of Health and Aging Working Group (Canadian population-based survey) 1994[201]
Antonanzas et al. 2006	YES	No information	No information	YES	YES	YES	Spanish cohort (Lopez-Pousa et al., 2004)[195] Resource Utilisation in Dementia (RUD) question-naire (Winblad et al 1997)[197]
Jönsson 2005	YES	YES	YES	No information	NO	No information	Katz et al. 1970[234] Wimo et al. 1999[235] Järfälla et al. 1999[236] National DRG prices 1999[237] FASS Pharmaceutical specialities in Sweden 2002[238]
Francois et al. 2004	YES	YES	YES	YES	YES	NO	Heikkinen et al. 2000[239] A. Kumpulainen 2002[240] Kansanela¨kelaitoksen tilastollinen vuosikirja 2001[241]
Jones et al. 2004	YES	YES	UNCLEAR	YES	YES	No information	LASER study: Paton et al. 2004[190]
Willian et al. 2006	YES	YES	YES	YES	YES	YES	The EXPRESS trial[123]

Costs in PICO 1

A total of seven studies included for PICO 1 reported mean costs for intervention and comparator [138–140,144,145,149,153]. Among them, four[139,144,145,153] were comparing donepezil with placebo, while three[138,140,149] compared galantamine with placebo.

In general, a large cost variation can be noticed across the selected studies: mean intervention costs ranged between CHF 6'791 in Lopez-Bastida et al. 2009[145] (0.5-year time horizon) and CHF 426'556 in Getsios et al. 2010[139] (10-year time horizon), while mean comparator costs ranged between CHF 3'240 in Lopez-Bastida et al. 2009[145] (0.5-year time horizon) and CHF 437'772 in Getsios et al. 2010[139] (10-year time horizon).

The estimated costs seemed to be strictly related to the adopted time horizon, with lower costs for short time horizons (up to 2 years) and higher costs for long time horizons (10 years). This was particularly evident in the study published by Lopez-Bastida et al. 2009[145], who reported costs for five different time horizons: the mean intervention costs increased almost linearly from CHF 6'791 using a 0.5-year time horizon to CHF 33'861 using a 2.5-year time horizon. At the same time, the mean comparator costs increased from CHF 3'240 to CHF 27'159.

Although the mean costs of interventions and comparators differed considerably across the selected studies, the incremental costs (i.e., the cost difference between interventions and comparators) showed a much smaller variation. In three studies[145,149,153] the mean intervention costs were higher than the mean comparator costs, while in four studies[138–140,144] it was the opposite. Among the studies comparing donezepil with placebo, two reported that the intervention was less expensive than the comparator (CHF -11'216 in Getsios et al. 2010[139], CHF -22'237 in Hartz et al. 2012 [144]), while the other two suggested that it was more expensive (CHF 3'551-12'214 in López-Bastida et al. 2009[145], CHF 7'750 in Wimo et al. 2003[153]). Among the studies comparing galantamine with placebo, one reported higher costs for galantamine (CHF 427 in Happich et al. 2005[149]), while two concluded that the intervention was less expensive than placebo (CHF -6'307 in Migliaccio-Walle et al. 2003[138], CHF -9'942 in Guo et al. 2010[140]).

In general, the cost difference was in favour of the intervention when long time horizons (10-year) were adopted. In contrast, analyses conducted using a shorter time horizon suggested that the intervention was more expensive than the comparator.

Costs in PICO 2

Mean intervention costs and mean comparator costs were reported for ten studies included according to PICO 2 [141,157–161,163–166]. Among them, two compared memantine with placebo, one compared it with standard care, and seven compared it with non-pharmacological treatment.

As in PICO 1, studies included for PICO 2 showed a large cost variation: mean intervention costs ranged between CHF 7'438 (0.5-year time horizon in Wimo et al. 2003[166]) and CHF 283'885 (5-year time horizon in Jönsson et al. 2005[163]), while mean comparator costs ranged between CHF 2'263 (0.5-year time horizon in Wimo et al. 2003[166]) and CHF 314'895 (5-year time horizon in Jönsson et al. 2005[163]).

In six out of ten studies[159–161,163–165] the intervention was less expensive than the comparator, with incremental costs ranging between CHF -1'156 in Gagnon et al. 2007[160] and CHF -31'011 in Jönsson et al. 2005[163]. The remaining four studies[141,157,158,166] reported an opposite situation, with incremental costs ranging between CHF 1'249 in Bond et al. 2012[141] and CHF 5'157 in Wimo et al. 2003[166].

In contrast to PICO 1, the results of the studies selected for PICO 2 did not suggest that the incremental costs depend on the adopted time horizon. Among the studies suggesting that the intervention is less expensive than the comparator, three studies[160,161,165] used a time horizon of 2 years, and three studies[159,163,164] used a time horizon of 5 years. Two studies[158,166] suggesting that the intervention is more expensive than the comparator had a time horizon of 1 year or below, while the other two studies[141,157] used a 20-year time horizon.

Costs in PICO 3

Only one study was identified for PICO 3[167], which was not considered transferable to the Swiss setting. In this study, costs of rivastigmine compared to placebo were calculated in parallel for two different countries (Canada and UK). Unfortunately, the authors reported information on the incremental costs, but details on mean intervention costs and mean comparator costs were not reported. The intervention resulted to be more expensive than the comparator, with incremental costs of CHF 2'090 in the Canadian estimation and CHF 2'674 in the British estimation. No further health economic analysis could be conducted for PICO 3 due to lack of evidence.

Table 18 Costs reported in the identified health economic studies after adaptation to Swiss Francs in 2019 (healthcare perspective).

Authors, year	Country	Intervention	Comparator	PICO	Time horizon in years	Mean intervention costs (CHF)	Mean control costs (CHF)	Incremental costs (CHF)
Getsios et al. 2010	UK	donepezil	Placebo	1	10	426'556	437'772	-11'216
López-Bastida et al. 2009	ES	donepezil	Placebo	1	0.5	6'791	3'240	3'551
López-Bastida et al. 2009	ES	donepezil	Placebo	1	1	13'762	6'791	6'971
López-Bastida et al. 2009	ES	donepezil	Placebo	1	1.5	20'499	13'762	6'737
López-Bastida et al. 2009	ES	donepezil	Placebo	1	2	27'159	20'499	6'660
López-Bastida et al. 2009	ES	donepezil	Placebo	1	2.5	33'861	27'159	6'702
Happich et al. 2005	DE	galantamine	Placebo	1	5	41'865	41'438	427
Hartz et al. 2012	DE	donepezil	Placebo	1	10	380'371	402'609	-22'237
Guo et al. 2010	DE	galantamine	Placebo	1	10	119'305	129'247	-9'942
Migliaccio-Walle et al. 2003 [a]	US	galantamine	Placebo	1	10	168'233	174'540	-6'307
Migliaccio-Walle et al. 2003 [b]	US	galantamine	Placebo	1	10	165'113	174'540	-9'427
Wimo et al. 2003	Mixed (SE)	donepezil	Placebo	1	1	12'366	4'616	7'750
Wimo et al. 2003	US	memantine	Placebo	2	0.5	7'438	2'263	5'175
Yunusa et al. 2021	US	memantine	NPT	2	lifetime (4-20)[c]	11'968	9'449	2'519
Knapp et al. 2017	UK	memantine	Placebo	2	1	23'819	20'772	3'046
Bond et al. 2012	UK	memantine	NPT	2	20	242'144	240'895	1'249
Hoogveldt et al. 2011	NL	memantine	SC	2	5	114'749	118'741	-3'992
Gagnon et al. 2007	CA	memantine	NPT	2	2	68'143	69'299	-1'156
Antonanzas et al. 2006	ES	memantine	NPT	2	2	50'978	52'389	-1'411
Jönsson 2005	SE	memantine	NPT	2	5	283'885	314'895	-31'011
Francois et al. 2004	FI	memantine	NPT	2	5	165'185	168'374	-3'189
Jones et al. 2004	UK	memantine	NPT	2	2	281'559	290'692	-9'133
Willian et al. 2006	CA	rivastigmine	Placebo	3	0.5	NA	NA	2'090
Willian et al. 2006	UK	rivastigmine	Placebo	3	0.5	NA	NA	2'674

[a]: Galantamine dosage 16 mg/day; [b]: Galantamine dosage 24 mg/day. [c]: not defined in the study

8.2.5 Findings cost-utility

Eleven transferable studies reported cost-utility results; four studies[139,144,145,149] for PICO 1 and seven studies[141,157–160,163,165] for PICO 2. Figure 33 shows the cost-effectiveness plane with the adapted costs of the transferable studies for PICO 1 and Figure 34 for PICO 2. Regarding PICO 1 three studies[139,144,145] reported results on donepezil and one study[149] on galantamine.

Regarding PICO 1, donepezil does not seem to be cost-effective over a time-horizon of up to 1.5 years, due to relatively high incremental costs compared to the QALYs gained [145]. Over a time-horizon of 10 years, donepezil becomes dominant (cost saving and increased QALYs) with savings ranging between approximately CHF 11'000 [139] and CHF 22'000 [144] and QALYs gained ranging between 0.109 [139] and 0.131 [144]. In line with the results regarding donepezil, treatment with galantamine seems to be cost-effective with low incremental costs of CHF 427 and incremental QALYs of 1.43 over a time-horizon of 5 years.

Regarding PICO 2, four[159,160,163,165] out of the seven adapted studies indicate memantine to be dominant. The other three studies[141,157,158] indicate that memantine is cost-effective assuming a hypothetical willingness-to-pay threshold of CHF 100’000 per QALY gained. This was also the case in Knapp et al. [158] who used a time-horizon of only one year and found that the adjusted differences in costs and clinical outcomes were not statistically significant. The study by Bond et al.[141] found the smallest increase in QALYs (only 0.013) over a time horizon of 20 years. Considering that patients with AD have a life expectancy ranging between 3 and 10 years[242], the appropriateness of such a time horizon is questionable.

Figure 33 Cost-utility results for PICO 1

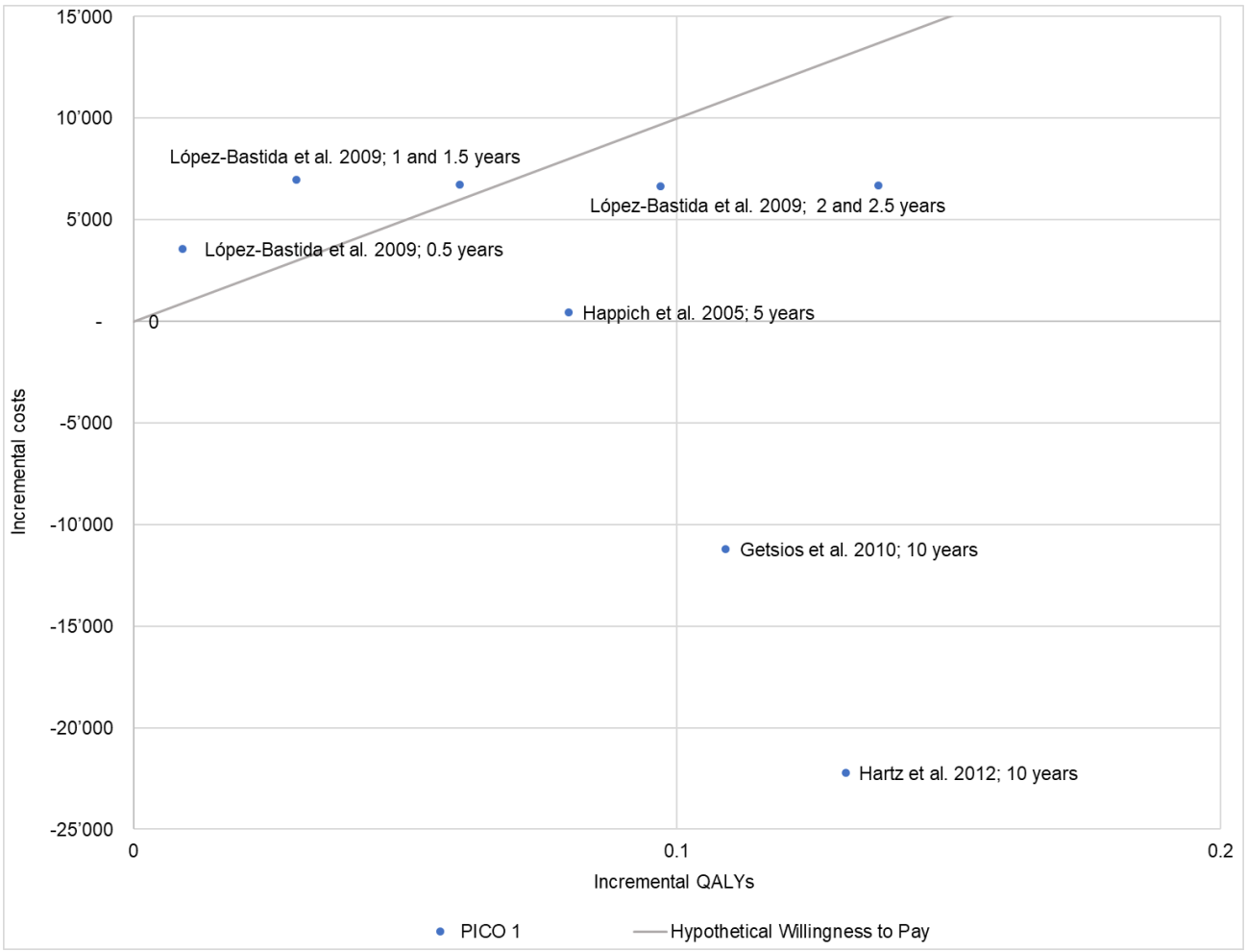
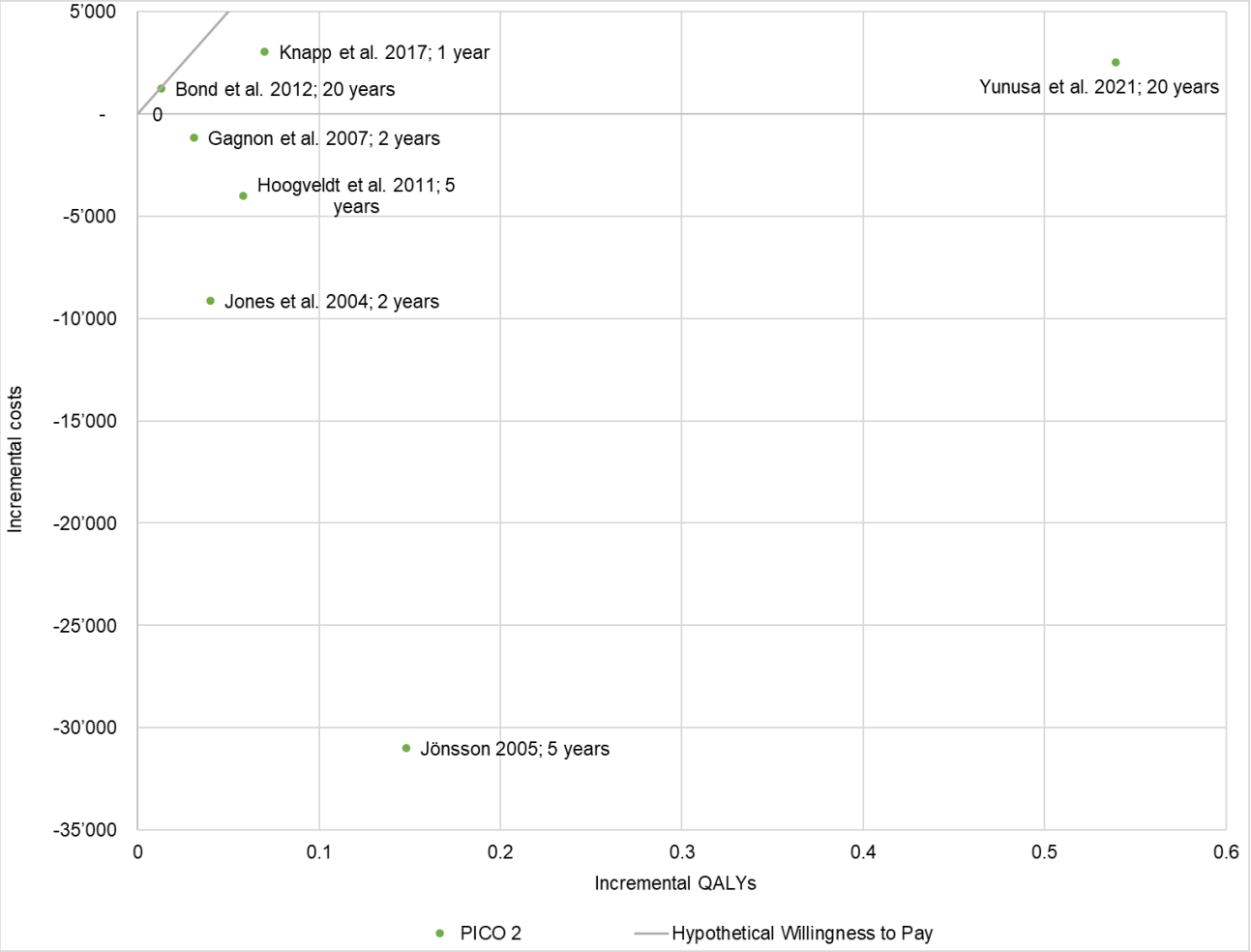


Figure 34 Cost-utility results for PICO 2



8.2.6 Findings cost-effectiveness

The effectiveness and adapted costs of the transferable studies from a healthcare payer perspective, which are mainly model based, are presented in Table 19 and Table 20. Fifteen transferable studies reported cost and effectiveness results. Regarding PICO 1 three studies[139,144,153] reported results on donepezil and three studies[138,140,149] on galantamine. Regarding PICO 2 nine studies[141,153,158–161,163,164,243] were included.

In most studies, the intervention was cost saving and more effective than the comparator. The adapted costs are described in section 8.2.3. Except for one effectiveness indicator (Bristol Activities of Daily Living Scale BADLS in Knapp et al. 2017[158]) all effectiveness results were in favor of the intervention. However, the clinical meaningfulness of these differences was not further assessed.

Concerning PICO 1 the identified health economic evaluations showed based on models that intervention resulted in more life years gained, less time in full-time care and institutional care, less total care and caregiving time, less time in a severe state (MMSE > 10, NPI > 28), more time in a not severe state

(ADAS-cog < 47, NPI < 29, NPI < 28), and more time with better function in terms of activities of daily living (ADL < 50, IADL <50). Migliaccio-Walle et al. 2003[138] also showed that an intervention with higher dosage (24mg versus 16mg) can lead to more life years gained (incremental effectiveness of 0.10 versus 0.12 life years) and less time in full-time care (incremental effectiveness of -2.6 versus -3.1 months). Incremental time in institutional care was equal for galantamine and donepezil and no remarkable differences between the three studies[139,140,144] were identified. Getsios et al. 2010[139] showed that severity at treatment initiation has an impact on the size of the effect: for time in institutional care they reported a smaller effect for the group initiating treatment when the disease was advanced to the moderate stage compared to the group initiating treatment when disease was in the mild stage. Also for time with NPI > 28 (i.e. time in a not severe state), Getsios et al. 2010[139] found a slightly smaller effect in the group initiating treatment when the diseases was advanced to the moderate stage. On the other hand, regarding the time with MMSE > 10 (i.e., time not in a severe state) a greater effect was observed in the group initiating treatment when the disease was advanced to the moderate stage. In terms of caregiving time Wimo et al. 2003[153] observed a greater incremental caregiving time for donepezil than Guo et al. 2010[140] for galantamine.

Regarding PICO 2 the identified health economic evaluations showed that treatment with memantine resulted in greater functional impairment (BADLS), better cognition (standardized MMSE), more time in a moderate severity state and in community. However, in the studies reporting a precision estimate (i.e., the 95% CI or the standard deviation) these effects were not statistically significant. In addition, the identified health economic evaluations showed that treatment with memantine resulted in more time in independence, not in complete dependence, as well as less caregiving time and time in full-time care/institutional care. Incremental time in independence ranged from 0.11 years[243] to 0.47 years[163], while incremental time in community ranged from 0.07 years[243] to 0.13 years[163].

Table 19 Effectiveness and adapted costs for PICO 1

Authors, year	Country	Intervention	Dosage	Comparator	Time horizon (years)	Adjusted mean intervention costs	Adjusted mean control costs	Adjusted incremental costs	Mean intervention effectiveness	Mean control effectiveness	Incremental effectiveness
											Life years gained (years)
Happich et al. 2005	DE	Galantamine	24 mg/day	Placebo	5	41'865	41'438	427	2.97	2.89	0.08
Migliaccio et al. 2003	US	Galantamine	16 mg/day	Placebo	10	168'233	174'540	-6'307			0.10
Migliaccio et al. 2003	US	Galantamine	24 mg/day	Placebo	10	165'113	174'540	-9'427			0.12
											Time in full time care (months)
Migliaccio et al. 2003	US	Galantamine	16 mg/day	Placebo	10	168'233	174'540	-6'307	19.90	22.50	-2.60
Migliaccio et al. 2003	US	Galantamine	24 mg/day	Placebo	10	165'113	174'540	-9'427	19.40	22.50	-3.10
											Time in institutional care (years)
Guo et al. 2010	DE	Galantamine	83%16 mg/day, 17%=24 mg/day	Placebo	10	119'305	129'247	-9'942	0.94	1.14	-0.20
Getsios et al. 2010	GB	Donepezil[a]	10 mg/day	Placebo	10	426'556	437'772	-11'216			-0.22
Getsios et al. 2010	GB	Donepezil[b]	10 mg/day	Placebo	10	426'556	437'772	-11'216			-0.16
Hartz et al. 2012	DE	Donepezil	10 mg/day	Placebo	10	380'371	402'609	-22'237	1.46	1.66	-0.21
											Total care time (years)
Hartz et al. 2012	DE	Donepezil	10 mg/day	Placebo	10	380'371	402'609	-22'237	1.845	1.908	-0.06
											Caregiving time (years)
Guo et al. 2010	DE	Galantamine	83% 16 mg/day, 17% 24 mg/day	Placebo	10	119'305	129'247	-9'942	0.23	0.24	-0.01
Wimo et al. 2003	Mixed	Donepezil	20 mg/day	Placebo	1	12'366	4'616	7'750	0.41	0.46	-0.05
											Time with MMSE >10 (years)
Getsios et al. 2010	GB	Donepezil[a]	10 mg/day	Placebo	10	426'556	437'772	-11'216			0.28
Getsios et al. 2010	GB	Donepezil[b]	10 mg/day	Placebo	10	426'556	437'772	-11'216			0.50
Hartz et al. 2012	DE	Donepezil	10 mg/day	Placebo	10	380'371	402'609	-22'237	2.44	1.97	0.46
											Time not in severe state (years), ADAS-cog<47
Guo et al. 2010	DE	Galantamine	83% 16 mg/day, 17% 24 mg/day	Placebo	10	119'305	129'247	-9'942	2.15	1.85	0.30
											Time not in severe state (years), NPI<29
Guo et al. 2010	DE	Galantamine	83% 16 mg/day, 17% 24 mg/day	Placebo	10	119'305	129'247	-9'942	2.17	2.03	0.14
											Time with NPI < 28
Hartz et al. 2012	DE	Donepezil	10 mg/day	Placebo	10	380'371	402'609	-22'237	2.79	2.68	0.11
											Time with NPI >28 (years)
Getsios et al. 2010	GB	Donepezil[a]	10 mg/day	Placebo	10	426'556	437'772	-11'216			-0.10
Getsios et al. 2010	GB	Donepezil[b]	10 mg/day	Placebo	10	426'556	437'772	-11'216			-0.08
											ADL < 50 (years)
Hartz et al. 2012	DE	Donepezil	10 mg/day	Placebo	10	380'371	402'609	-22'237	2.036	1.896	0.14
											IADL<50 (years)
Hartz et al. 2012	DE	Donepezil	10 mg/day	Placebo	10	380'371	402'609	-22'237	0.303	0.241	0.06

[a] initiating treatment when disease is in the mild stages, [b] initiating treatment when disease has advanced to the moderate stages

ADAS-cog: Alzheimer disease assessment scale-cognitive subscale, ADL: activities of daily living, IADL: instrumental activities of daily living, MMSE: mini-mental state examination, NPI: neuropsychiatric inventory

Table 20 Effectiveness and adapted costs for PICO 2

Authors, year	Country	Intervention	Dosage	Comparator	Time horizon (years)	Adjusted mean intervention costs	Adjusted mean control costs	Adjusted incremental costs	Mean intervention effectiveness	Mean control effectiveness	Incremental effectiveness
											BADLS
Knapp et al. 2017	UK	Memantine	20 mg/day	Placebo	1	23'819	20'772	3'046			1.90
											sMMSE
Knapp et al. 2017	UK	Memantine	20 mg/day	Placebo	1	23'819	20'772	3'046			0.90
											Time in a moderate severity state (years)
Hoogveldt et al. 2011	NL	Memantine	20 mg/day	SC	5	114'749	118'741	-3'992	2.14	2.05	0.09
											Time in independence (years)
Hoogveldt et al. 2011	NL	Memantine	20 mg/day	SC	5	114'749	118'741	-3'992	1.75	1.60	0.15
Antonanzas et al. 2006	ES	Memantine	20 mg/day	NPT	2	50'978	52'389	-1'411	0.72	0.51	0.20
Jönsson 2005	SE	Memantine	20 mg/day	NPT	5	283'885	314'895	-31'011	1.54	1.07	0.47
Francois et al. 2004	FI	Memantine	20 mg/day	NPT	5	165'185	168'374	-3'189	1.21	0.87	0.34
Jones et al. 2004	UK	Memantine	20 mg/day	NPT	2	281'559	290'692	-9'133	0.37	0.26	0.11
											Time not in complete dependence (years)
Gagnon et al. 2007	CA	Memantine	No information	NPT	2	68'143	69'299	-1'156	0.89	0.80	0.09
											Time in community (years)
Jönsson 2005	SE	Memantine	20 mg/day	NPT	5	283'885	314'895	-31'011	2.40	2.27	0.13
Francois et al. 2004	FI	Memantine	20 mg/day	NPT	5	165'185	168'374	-3'189	0.69	0.61	0.08
Jones et al. 2004	UK	Memantine	20 mg/day	NPT	2	281'559	290'692	-9'133	0.54	0.47	0.07
											Caregiver time (hours)
Wimo et al. 2003	US	Memantine	20 mg/day	Placebo	0.5	7'438	2'263	5'175			-51.52
											Time in full time care/institutional care
Bond et al. 2012	UK	Memantine	20% 15 mg/day, 80% 20 mg/day	NPT	20	242'144	240'895	1'249	1.966	2.032	-0.065

BADLS: Bristol Activities of Daily Living Scale, CI: confidence interval, NPT: non-pharmacological treatment, SC: standard of care, SD: standard deviation, sMMSE: standardised Mini-Mental State Examination

8.2.7 Findings budget impact

We estimated that the number of newly diagnosed AD cases will increase from approximatively 20'000 in 2021 to almost 22'000 in 2025. Assuming that only 25% of the AD patients are treated with donepezil, rivastigmine, galantamine, or memantine, the estimated number of prevalent cases adopting a 5-year time horizon (i.e., excluding patients with a disease duration above 5 years) was 23'723 in 2021 and 26'055 in 2025.

Table 21 summarizes the estimated number of new AD cases from 2021 to 2025, the estimated number of prevalent cases (using a 5-year time horizon), and the treatment distribution from 2021 to 2025.

Table 21 Estimated number of new AD cases from 2021 to 2025, the estimated number of prevalent cases (using a 5-year time horizon), and the treatment distribution

	Year 1	Year 2	Year 3	Year 4	Year 5
Incident cases of dementia	31'375	32'066	32'780	33'547	34'355
Incident cases due to AD	19'923	20'362	20'815	21'303	21'815
Total number of AD cases treated (5-year time horizon)	23'723	24'247	24'805	25'401	26'055
donepezil	8'569	8'759	8'960	9'175	9'412
rivastigmine	8'279	8'462	8'656	8'864	9'092
galantamine	735	751	769	787	807
memantine	6'140	6'276	6'420	6'574	6'743

Abbreviation: AD = Alzheimer disease

Treatment duration and medication costs

We estimated that the mean duration with an AChE inhibitor or memantine is two years with very few patients changing from one AChE inhibitor to another. The mean number of grams bought within the first year of treatment ranges from 1'560 for rivastigmine to 4'480 for memantine (Table 22). Considering the mean cost per gram shown in Table 14 we estimated mean medication costs that ranged from CHF 632 for donepezil to CHF 829 for galantamine for the first year of treatment. By multiplying the cost per patient with the estimated number of patients (Table 21) we estimated that in 2021 the costs for donepezil were CHF 5.42 million, for rivastigmine CHF 5.74 million, for galantamine CHF 0.61 million and for memantine CHF 4.18 million (Table 23).

Table 22 Estimated number of grams and costs per drug per year of treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Mean number of grams					
donepezil	1'965.88	2'259.22	2'208.11	2'055.95	1'624.52
rivastigmine	1'559.94	2'077.17	1'949.49	2'012.83	1'578.32
galantamine	3'930.62	4'341.64	3'822.68	4'193.46	3'310.22
memantine	4'479.60	4'750.48	4'327.89	4'505.96	5'416.25
Mean costs (in CHF)					
donepezil	632.27	644.56	607.15	551.28	452.70
rivastigmine	693.15	723.44	594.88	562.27	375.07
galantamine	829.41	748.79	648.81	688.64	463.01
memantine	681.52	671.45	598.71	626.79	548.52

Table 23 Estimated medication costs according to the current treatment situation between 2021 and 2025 (in mio CHF)

	2021	2022	2023	2024	2025
donepezil	5.42	5.65	5.44	5.06	4.26
rivastigmine	5.74	6.12	5.15	4.98	3.41
galantamine	0.61	0.56	0.50	0.54	0.37
memantine	4.18	4.21	3.84	4.12	3.70

Costs for physician visits

Additional costs for physician visits were assumed for the treatment with one of the AChE inhibitors or memantine. This was because in Switzerland it is mandatory to regularly perform a MMSE test during medication treatment. Considering that MMSE test should be performed 3 months after treatment initiation and then every six months, we assumed three additional physician visits during the first year after treatment initiation and two additional visits for the following years. For the conduct of a visit including a MMSE test we assumed a unit costs of CHF 85.96 (30-minute consultation). The estimated costs for the additional physician visits in 2021 were CHF 2.2 million due to treatment with donepezil, CHF 2.13 million due to treatment with rivastigmine, CHF 0.19 million due to treatment with galantamine and CHF 1.58 million due to treatment with memantine (Table 24). In the absence of medication treatment of AD these costs would be saved.

Table 24 Estimated physician costs per drug treatment between 2021 and 2025 (in mio CHF)

	2021	2022	2023	2024	2025
donepezil	2.21	1.51	1.54	1.58	1.62
rivastigmine	2.13	1.45	1.49	1.52	1.56
galantamine	0.19	0.13	0.13	0.14	0.14
memantine	1.58	1.08	1.10	1.13	1.16

Institutionalisation and non-hospital care and support at home ("spitex") costs

We estimated that the number of institutionalized cases among patients treated for AD with one of the AChE inhibitors or memantine was 6'849 in 2021. At the same time, among the 11'720 patients in a pre-FTC situation, 5'548 patients were expected to require home care (spitex).

Table 25 illustrates the estimated number of institutionalized AD patients as well as the estimated number of AD patients in pre-FTC requiring home care between 2021 and 2025 according to the current treatment situation and for scenarios in which it was assumed that patients treated with a specific drug would not be treated. For example, in the absence of donepezil treatment, the total number of institutionalizations in 2021 would increase to 7'069 (+3.2% compared to the current situation), while the number of AD patients requiring home care would decrease to 5'355 (-3.5% compared to the current situation). In the total absence of AD treatment with an AChE inhibitor or memantine, we estimated that the number of institutionalized AD patients would increase by 685 patients, reaching 7,534 institutionalizations (+10.0%). At the same time, the expected number of AD cases requiring home care was expected to decrease from 5'458 with AD treatment to 5'139 without AD treatment (-5.6%). Table 26 illustrates the incremental number of patients requiring institutionalization or home care compared to current treatment situation between 2021 and 2025.

Table 25 Estimated number of institutionalized AD patients and estimated number of AD patients in pre-FTC requiring home care between 2021 and 2025

Current situation	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	6'849	7'003	7'166	7'337	7'524
Pre-FTC with spitex	5'458	5'580	5'708	5'845	5'994
No donepezil treatment scenario	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	7'069	7'228	7'396	7'573	7'766
Pre-FTC with spitex	5'355	5'475	5'601	5'735	5'882
No rivastigmine treatment scenario	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	7'086	7'245	7'413	7'591	7'784
Pre-FTC with spitex	5'347	5'467	5'593	5'727	5'873
No galantamine treatment scenario	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	6'870	7'025	7'188	7'360	7'547
Pre-FTC with spitex	5'448	5'570	5'698	5'834	5'984
No memantine treatment scenario	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	7'057	7'215	7'383	7'560	7'752
Pre-FTC with spitex	5'361	5'481	5'607	5'742	5'888
No AD treatment scenario	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	7'534	7'704	7'882	8'071	8'277
Pre-FTC with spitex	5'139	5'253	5'375	5'503	5'644

Table 26 Incremental number of patients requiring institutionalization or home care compared to current treatment situation between 2021 and 2025

Current situation	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	6'849	7'003	7'166	7'337	7'524
Pre-FTC with spitex	5'458	5'580	5'708	5'845	5'994
No donepezil treatment scenario	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	+220	+225	+230	+236	+242
Pre-FTC with spitex	-103	-105	-107	-110	-112
No rivastigmine treatment scenario	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	+237	+242	+247	+254	+260
Pre-FTC with spitex	-111	-113	-115	-118	-121
No galantamine treatment scenario	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	+21	+22	+22	+23	+23
Pre-FTC with spitex	-10	-10	-10	-11	-10
No memantine treatment scenario	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	+208	+212	+217	223	+228
Pre-FTC with spitex	-97	-99	-101	-103	-106
No AD treatment scenario	**2021**	**2022**	**2023**	**2024**	**2025**
Institutionalized	+685	+701	+716	+734	+753
Pre-FTC with spitex	-319	-327	-333	-342	-350

Assuming mean costs of CHF 89'415 per institutionalized AD patients and CHF 7'791 per patients requiring home care, we estimated that in 2021 the costs of institutionalization and home care were CHF 612.42 million and CHF 42.52 million, respectively (Table 27). In the total absence of AD treatment with one of the AChE inhibitors or memantine, we estimated that the institutionalization costs would increase to CHF 673.66 million (i.e., +61.24 million), while the costs related to home care would decrease to CHF 40.04 million (i.e., -2.48 million). If a single AD treatment was excluded, the increase in institutionalization costs ranged between CHF 1.89 million for galantamine and CHF 21.15 million for rivastigmine, while the decrease in home care costs ranged between CHF -0.08 million for galantamine and CHF -0.86 million for rivastigmine. The estimated costs according to the current treatment of AD patients compared to a scenario in which AD patients are not treated with one of the AChE inhibitors or memantine are reported in Table 28.

Table 27 Estimated institutionalization and home care costs according to the current treatment situation and the no treatment scenario between 2021 and 2025 (in mio CHF)

Institutionalisation costs (mio CHF)	2021	2022	2023	2024	2025
Current situation	612.42	626.20	640.72	656.07	672.78
No donepezil treatment	632.08	646.30	661.28	677.13	694.38
No rivastigmine treatment	633.57	647.83	662.84	678.73	696.01
No galantamine treatment	614.31	628.13	642.69	658.09	674.85
No memantine treatment	630.96	645.17	660.12	675.93	693.15
No AD treatment	673.66	688.82	704.79	721.68	740.06
Home care costs (mio CHF)	**2021**	**2022**	**2023**	**2024**	**2025**
Current situation	42.52	43.47	44.47	45.54	46.70
No donepezil treatment	41.72	42.65	43.64	44.68	45.83
No rivastigmine treatment	41.66	42.59	43.57	44.62	45.76
No galantamine treatment	42.44	43.39	44.39	45.46	46.62
No memantine treatment	41.77	42.70	43.69	44.73	45.88
No AD treatment	40.04	40.93	41.87	42.88	43.97

Table 28 Incremental costs of institutionalization and home care costs compared to the current treatment situation between 2021 and 2025 (in mio CHF)

Institutionalisation costs (mio CHF)	2021	2022	2023	2024	2025
Current situation	612.42	626.20	640.72	656.07	672.78
No donepezil treatment	+19.66	+20.10	+20.57	+21.06	+21.60
No rivastigmine treatment	+21.15	+21.63	+22.13	+22.66	+23.24
No galantamine treatment	+1.89	+1.93	+1.98	+2.02	+2.07
No memantine treatment	+18.54	+18.96	+19.40	+19.87	+20.37
No AD treatment	+61.24	+62.62	+64.07	+65.61	+67.28
Home care costs (mio CHF)	**2021**	**2022**	**2023**	**2024**	**2025**
Current situation	42.52	43.47	44.47	45.54	46.70
No donepezil treatment	-0.80	-0.82	-0.83	-0.85	-0.88
No rivastigmine treatment	-0.86	-0.88	-0.90	-0.92	-0.94
No galantamine treatment	-0.08	-0.08	-0.08	-0.08	-0.08
No memantine treatment	-0.75	-0.77	-0.79	-0.81	-0.83
No AD treatment	-2.48	-2.54	-2.60	-2.66	-2.73

Budget Impact

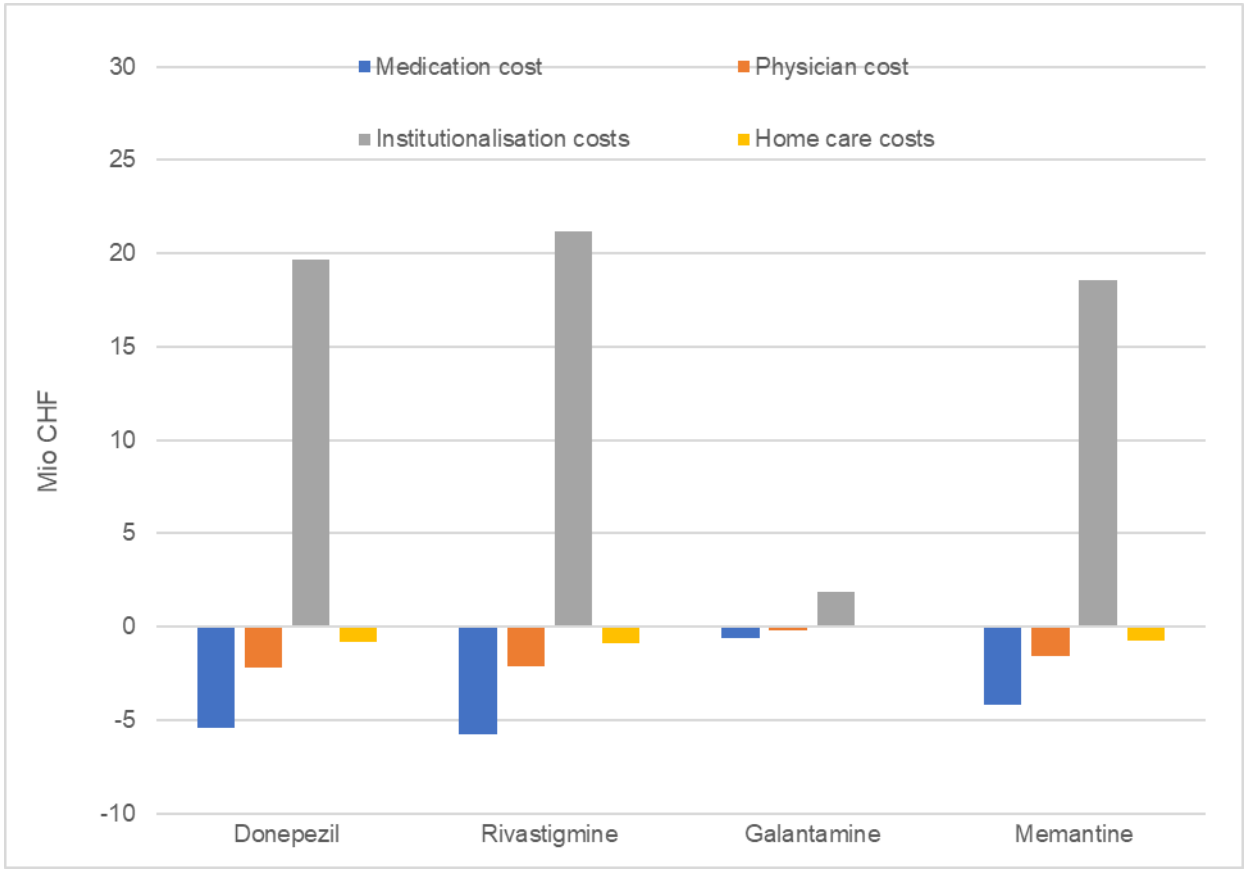
Table 29 shows the net budget impact of a complete removal of donepezil, rivastigmine, galantamine or memantine. In 2021 a complete removal of treatment with one of the AChE inhibitors or memantine

leads to savings ranging between CHF 0.88 million for galantamine and CHF 8.73 million for rivastigmine due to lower expenses for drugs, physician visits, and home care (Figure 35). However, at the same time, the increase in the number of institutionalizations would lead to additional institutionalization costs ranging between CHF 1.89 million for galantamine and CHF 21.15 million for rivastigmine. As a result, AD treatment without one of the AChE inhibitors or memantine in 2021 would lead to a net budget impact of CHF 11.23 million for donepezil, CHF 12.42 million for rivastigmine, CHF 1.01 million for galantamine, and CHF 12.02 million for memantine. This indicates that a removal of one of the AChE inhibitors or memantine would lead to additional costs and not to savings.

Table 29 Net budget impact analysis (in mio CHF)

	2021	2022	2023	2024	2025
donepezil					
Medication cost	-5.42	-5.65	-5.44	-5.06	-4.26
Physician cost	-2.21	-1.51	-1.54	-1.58	-1.62
Institutionalisation costs	19.66	20.10	20.57	21.06	21.60
Home care costs	-0.80	-0.82	-0.83	-0.85	-0.88
Net costs	**11.23**	**12.13**	**12.75**	**13.57**	**14.84**
rivastigmine					
Medication cost	-5.74	-6.12	-5.15	-4.98	-3.41
Physician cost	-2.13	-1.45	-1.49	-1.52	-1.56
Institutionalisation costs	21.15	21.63	22.13	22.66	23.24
Home care costs	-0.86	-0.88	-0.90	-0.92	-0.94
Net costs	**12.42**	**13.17**	**14.59**	**15.23**	**17.32**
galantamine					
Medication cost	-0.61	-0.56	-0.50	-0.54	-0.37
Physician cost	-0.19	-0.13	-0.13	-0.14	-0.14
Institutionalisation costs	1.89	1.93	1.98	2.02	2.07
Home care costs	-0.08	-0.08	-0.08	-0.08	-0.08
Net costs	**1.01**	**1.16**	**1.26**	**1.26**	**1.48**
memantine					
Medication cost	-4.18	-4.21	-3.84	-4.12	-3.70
Physician cost	-1.58	-1.08	-1.10	-1.13	-1.16
Institutionalisation costs	18.54	18.96	19.40	19.87	20.37
Home care costs	-0.75	-0.77	-0.79	-0.81	-0.83
Net costs	**12.02**	**12.90**	**13.67**	**13.81**	**14.69**

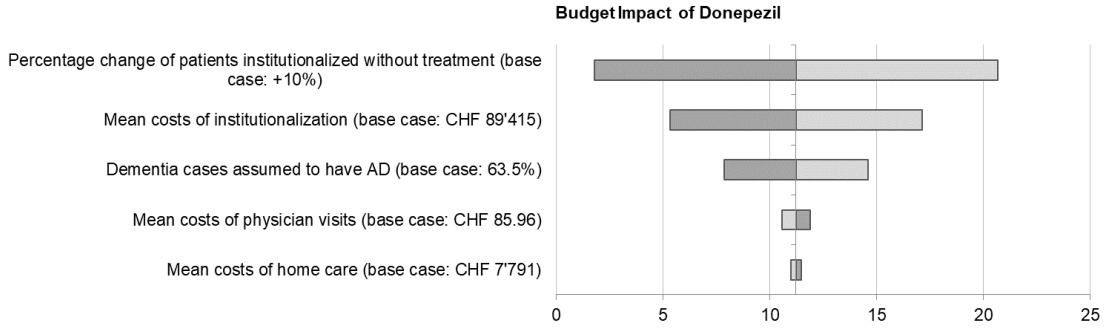
Figure 35 Economic impact of removing one AD treatment in 2021 (in mio CHF)

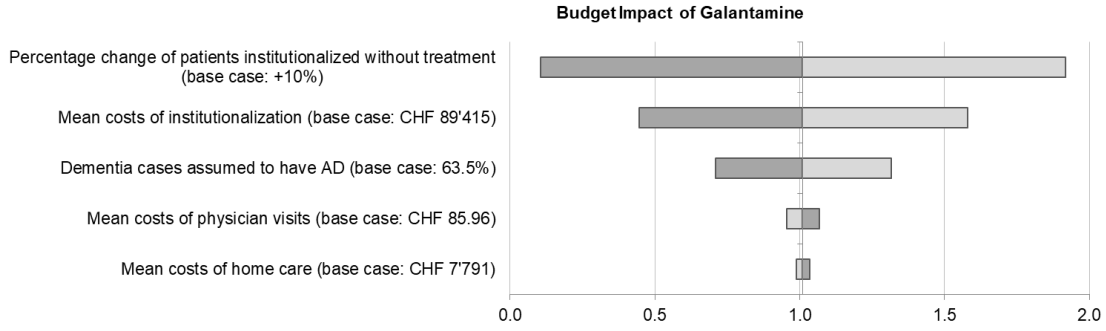


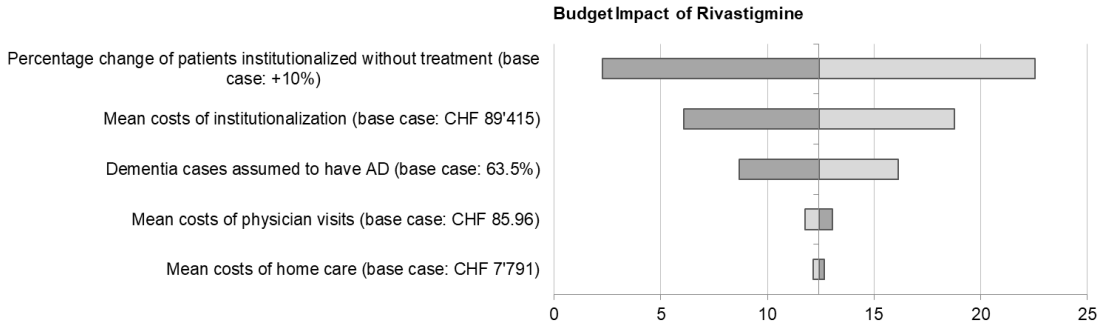
Sensitivity analysis

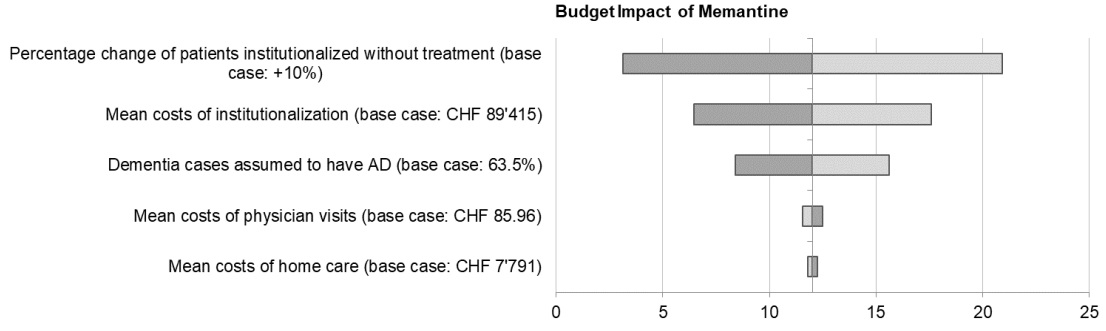
In the sensitivity analysis we tested the effect of the main parameters on the variation of the net budget impact in 2021. Figure 36 illustrates this graphically for each AChE inhibitor and memantine. The results are comparable across the different treatment options. The assumption concerning the effect of stopping AD treatment on institutionalization rates was varied from +5% to +15% and showed the highest effect on the net budget impact (percentage change between ±74% and ±89%). If we assumed that there is no treatment effect on institutionalization, stopping AD treatment with one of the AChE inhibitors or memantine would lead to savings that vary from CHE 0.80 million for galantamine to CHF 7.87 million for rivastigmine in 2021. This corresponds to a change in the net budget impact of -148% for memantine to -179% for galantamine. A ±30% variation of the mean cost of institutionalization also showed a high impact leading to a percentage change of the net budget impact of ±46% to ±56%. A ±30% variation of the share of dementia cases due to AD has the third strongest effect leading to a ±30% percentage change of the net budget impact. The same was also observed for the share of AD cases treated with an AChE inhibitor or memantine. The mean costs of home care and of physician visits do not seem to have a remarkable effect on the net budget impact.

Figure 36 Univariate sensitivity analysis









9 Ethical, legal, social and organisational issues

Summary statement ethical, legal, social and organisational issues

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The ethical challenges delineated in this report are, from our perspective, centred on issues of patient autonomy, social arrangements, and choice of endpoints. As a consequence, we see relevant ethical questions in the decision-making process: As patients' cognitive abilities are already reduced in mild to moderate dementia and will continue to decline, it is vital to discuss how the decision is made in order to respect patient autonomy and what the consequences are for the proxies in case they are involved in the decision-making process. Another crucial ethical issue is the focus on cognitive and global outcomes in the trials that might leave out many much more relevant signs and symptoms, such as alterations of mood, anxiety, psychotic symptoms, and insomnia. Of utmost relevance to the decision-maker should be the lack of data on health-related quality of life and the delay of need of being transferred to institutionalized care, and overall activities of daily life based on RCTs.

From a legal perspective, a decision by the competent authorities must consider various fundamental and human rights guarantees. Of particular importance here are guarantees for the protection of people with disabilities and elderly persons. In this regard, persons suffering from dementia must be protected from abuse, remain integrated in society and they are entitled to have their wishes and interests respected. Furthermore, the capacity of judgment should be considered for the decision whether to use antidementia drugs or not.

Social issues identified are patients who currently do not have good access to antidementia drugs, the high burden on caregivers and how the treatment choices are explained to patients. In regard to the last aspect, shared decision making seems to be a promising approach in the case of mild to moderate symptoms.

Organisational issues discussed in the identified literature were diverse: national dementia strategies, innovative care models, drug coverage, monetary incentives, problems related to co-medications and variations in antidementia treatment between different regions, patients living in rural areas versus patients living in urban areas, nursing home residents versus community-dwelling patients, and patients treated in outpatient psychiatric settings versus those treated by general practitioners. In addition, the regulation of the dementia severity in the SL by the MMSE was identified as an organisational issue as the performance of the MMSE can be seen as cumbersome and even humiliating and as other tools like

the Montreal Cognitive Assessment (MoCA) are used more often in current daily clinical practice.

9.1 Methodology ethical, legal, social and organisational issues

9.1.1 Databases and search strategy

To address the ethical, legal, social and organizational (ELSO) issues, we conducted a targeted literature search in Medline (see appendix section 13.9 for the detailed search strategy). The final search was conducted on 5 January 2022. Inclusion and exclusion criteria are presented in Table 30 and were developed in accordance with those of the efficacy, safety, effectiveness, and health economic search (see Table 2 and Table 10). We imposed no study design restrictions as we expected discussions of ELSO outcomes to be presented in a variety of study designs. A single researcher screened and reviewed the literature and identified studies relevant to the ELSO domains. Note that this review was not systematic. However, we consider this to be an appropriate approach as the primary purpose was to identify key aspects relevant to ELSO outcomes but not to provide an exhaustive or systematic review of the literature on these domains.

Table 30 Inclusion criteria for studies on ethical, legal, social and organizational outcomes

Criterion	Inclusion	Exclusion
Publication period	As for Table 2 and Table 10	
Publication status		
Language		
Setting	As for Table 2 and Table 10	
Study design/type	No restrictions	—
Study quality	As for Table 2 and Table 10	
Study population	No restrictions	—
Study intervention and comparator	Discussion of antidementia drugs (any symptomatic antidementia drug)	No discussion of antidementia drugs
Study outcomes	Discussion of ethical, legal, social, or organizational aspects	No discussion of ethical, legal, social, or organizational aspects

9.1.2 Assessment of quality of evidence

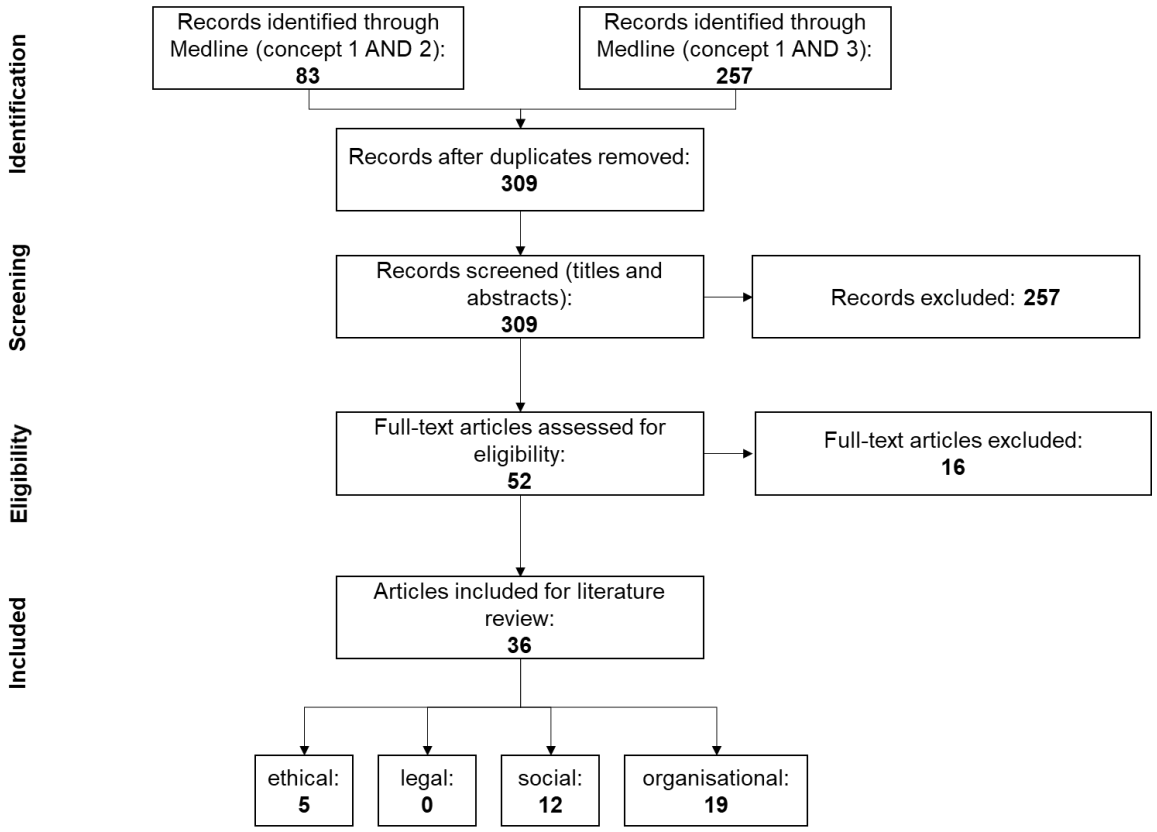
The quality of evidence for ELSO outcomes was not formally assessed.

9.2 Results ethical, legal, social and organisational issues

9.2.1 PRISMA flow diagram

Of the 309 unique hits, 257 were excluded during title-abstract screening (Figure 37). Of the remaining 52 articles whose full texts were screened, 16 were excluded, because they were considered as not relevant. Finally, 36 articles were retained for the HTA report, including 19 reporting on organisational issues, 12 reporting on social issues, and 5 reporting on ethical issues. No studies were identified regarding legal issues.

Figure 37 Prisma flow diagram ELSO search



Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[95]

9.2.2 Findings ethical issues

In the opinion of Abrishami et al., 2017[244] "'meaningfulness and relevance' to the needs of the population must be the prime criteria for determining the extent of HTA and for 'sufficiency' of analyses. … . A fit-for-purpose HTA is neither reductionistic nor unnecessarily exhaustive in terms of types of disciplinary perspectives, stakeholders involved, and the application of algorithmic calculations or deliberative processes." In accordance with this statement and the HTA Core Model, "[e]thical analysis aims to provide

a thorough understanding of norms and values that need to be taken into account during the HTA and in the decision-making process"[245]. To that end, we used the axiological approach in this HTA report. The axiological – or Socratic – approach is based on a series of questions and answers, with the intention to stimulate critical thinking and to draw out underlying presuppositions and is considered a valid methodological option in HTA.

The "Hofmann catalogue"[246,247] with 33 questions designed to identify the characteristics of a health technology, the involved stakeholders, and the relevant moral questions is a widely-used implementation of the axiological approach.[248–250] We are aware that the catalogue of 33 morally relevant questions presented by Hofmann is "not exhaustive […] moral questions […] have to be added, depending on the specific technology or its particular use".[246] Yet, we addressed selected questions from the catalogue to raise awareness for the underlying ethical concerns pertinent to the prescription of drugs in patients with mild and moderate dementia. We will not give answers in the sense of normative solutions. Please note that numbering of the questions outlined below follows that in Hofmann's paper. [246]

Q2: Does the implementation or use of the technology challenge patient autonomy?

Autonomy is one of the four principles of bioethics and is considered fundamental for ethical assessment of medical treatment.[251] Philosophical discourse, biomedical ethics, and care ethics increasingly define autonomy as a gradual concept. People can be more or less autonomous, depending not only on their cognitive capacities, but also on the extent to which they are granted self-determination by their context. Relational, cultural, or socioeconomic dependencies affect autonomy. Thus, different life situations allow a varying degree of autonomy, which is reflected in bioethical concepts of patient autonomy and care ethics. In a care perspective, patient autonomy is embedded in the relation between patient and the care giving person. As a result, autonomy has to be granted to the patient by the caregiver. Similarly, in biomedical ethics, differentiated approaches to patient autonomy have led to the definition of procedures of shared decision making.[252–256] Patient's agency might involve family members.

Regarding antidementia drugs, two aspects of patient autonomy must be taken into consideration: (1) the question whether these drugs have a positive **impact on patient autonomy**, and (2) the issue of how the **gradual decline of patient autonomy and judgment ability** as a characteristic of dementia affects the decision on taking antidementia drugs.

(1) **Impact on patient autonomy**

Autonomy consists of several capacities which enable self-determination. As Hofmann points out, medical treatment can alter the patient's self-determination by either reducing or extending auton-

omy.[246] With regard to antidementia drugs, the perspective of inhibiting and slowing down deterioration of cognitive capacities opens up a potential of extended autonomy and prolonged self-determination. While such an impact of antidementia drugs certainly seems desirable, careful consideration of correlating aspects is vital. If a patient in fact benefits from a delayed decrease in cognitive capacities, the patient still must cope with considerable uncertainty regarding their prognosis, as dementia is a highly variable progressing syndrome.[257] For what amount of time can the effect of the drug be expected to last to an extent which allows self-determination? While even an uncertain and limited delay of decrease of autonomy would seem valuable, a transitory state of partial autonomy might also be experienced as burdensome. Furthermore, this transitory state of autonomy might distort the awareness of inevitable changes in life settings ahead, such as moving to a nursing home. Even if the drug would allow patients to stay in their home vs. being institutionalized in a nursing home, this implies neither better quality of life per se in the long run nor autonomy. On the other hand, an early placement in a nursing home could also be of advantage as it would allow patients to become acquainted with the new environment while they still have command of more cognitive capabilities. Finally, autonomy consists not only of cognitive capacities, but also includes emotional, behavioral, and relational aspects. Although our analysis showed statistically significant better results for AChE inhibitors compared to placebo for functional and global outcomes, the clinical meaningfulness of the difference found is questionable, and we do not know if the differences persist over longer time horizons. In addition, there is very low certainty of evidence for neuropsychiatric outcomes and quality of life. Rather, symptoms within the category of behavioral disturbances such as aggressiveness or restlessness as well as alterations of mood, e.g. anxiety, are often seen in mild dementia and seem to persist if only treated with antidementia drugs (see also below question pertaining to endpoints).[258] As a result, the potential gain in autonomy in the cognitive sphere does not necessarily mean that patients benefit from good quality, self-determined life.

(2) **Gradual decline of patient autonomy and judgment ability**

In dementia, decision-making and informed consent are a general ethical challenge. Here, the question is, are patients with mild and moderate dementia cognitively capable of deciding whether they would want to take drugs with a statistically significant better outcome than placebo in some domains but potentially no effect in other relevant domains given an overall chance of not benefitting at all or solely from a clinically very small or even irrelevant difference? Especially among patients suffering from dementia anosognosia, the denial of their status as a disease is widespread and might lead to controversial situations. Also, if the drug is not continued in case of deterioration of the MMSE results, it might be the case that patients are not fully capable any more to understand the implications of that or take part in the decision whether the treatment should be stopped or

continued. In either case, a careful clarification of the patient's judgment ability is necessary. Complexity of the issues, as well as inconsistencies in expert clinical judgments on the issue of competence for mildly affected patients account for the difficulty, to assess patients' ability to give informed consent.[259] As the Swiss Academy of Medical Sciences (SAMS) states, judgment ability is always dependent on the issue at stake: 'The ability to make judgments must always be assessed *with reference to a specific decision*. It can still be present in the person with dementia, e.g. for simple interventions and everyday care measures, meal requests, etc., when it is already missing for more complex matters and those of major importance (e.g. concluding a care contract).'[260] (italics by authors) Concerning the decision of taking antidementia drugs, on one hand one could argue that the option is only for patients with mild to moderate symptoms and thus good cognitive capacities with only little cognitive impairment. On the other hand, the issue at stake is of rather complex nature. This is due not only to the uncertainties of effect of the drugs in some relevant domains (i.e. neuropsychiatric, quality of life) but should also be considered in terms of the question whether the effects are clinically relevant. Thus, the patient must understand a complex situation. In addition, judgment ability consists of a multifaceted set of capabilities. SAMS lists four mental capabilities composing judgment ability, which encompass emotional, motivational, volitional, and communicative capabilities: '(1) the ability to comprehend the decision-making situation at least in outline and to derive possible consequences; (2) the ability to ascribe personal and appropriate importance to the decision-making situation; (3) the ability to make one's own authentic decision; (4) the ability to communicate, justify and consistently defend this decision.'[260] Especially regarding the capability (3) of authenticity, an additional aspect must be considered. Since, lack of insight into the illness (anosognosia) is often part of dementia[260], patients may fail to recognize themselves and their state in a sense coherent with the actual situation.

Furthermore, the prospect of these patients is to become increasingly dependent on support of others, with potentially great social and economic impact not only on themselves, but also on others in their close context, such as relatives. This has two potential implications. First, patients' autonomy may be restricted, and judgment biased as they may be inclined to focus on preferences of those whom they are or will be increasingly dependent upon. Secondly, due to the loss of judgment capacity at a certain stage of the disease, proxy decision is inevitable. As decision-makers family members would be likely to be in a conflict of interests as they have to decide for their relative while at the same time, they are directly affected themselves by the possible effect of the antidementia drug. However, autonomy as a gradual and relational concept underpins the value of involving family members. In any case, shared decision making is a promising approach in the case of mild to moderate symptoms.

Q7: Does the technology challenge social values and arrangements?

The technology might challenge our values of autonomy and dependence. Dementia and the associated emotional and mental alterations in the patients narrow down their ability to judge and to live autonomously. Antidementia drugs themselves do not very much change the natural course of dementia. And patients face deterioration of their social and personal abilities. Thus, the disease has radical impact on social arrangements and the prospect of the positive effects the drug may have by inhibiting the decline of cognitive abilities might seem promising. “Initially, when symptoms are modest (the invisible phase), the situation is dominated by uncertainty and anxiety of both the patient and family members. Later, in moderate to severe dementia when the diagnosis is obvious, the more visible tragedy is dominated by organizing care, supervision, surveillance and coping with behavioural disturbances. In addition to the social consequences for the families, dementia care utilizes substantial resources from the healthcare system, social services, and the family, and hence has considerable cost implications for the individual and society.”[258] (see also section3.2.2) In consequence, social arrangements, such as institutional or home care might be affected by a drug that prolongs independence of a demented person. Availability of an effective treatment might appear as an appealing way of enabling someone to live at home. The effect on relatives, however, is ambiguous, since living together with the demented person might both mean prolonged proximity and to be burdened by an increasingly demanding responsibility. Wimo et al. report very high burden for caregiving family members at an early stage of the disease, compared to high burden with moderate to severe symptoms. The burden consists of aspects such as limitations on lifestyle, conflicts with job duties, loss of privacy, limitation in social activities.[258] If antidementia drugs potentially prolong the phase of mild to moderate symptoms, that would accordingly imply for caregiving family members a prolonged time of very high burden.

With the high emphasis on autonomy in our Western societies we might need to think about the meaning of independence and the relevance of autonomy. While in other cultures dependency is considered much more a “natural” phenomenon, in Western societies, the loss of autonomy and independence is regarded a drastic change in someone’s life, associated also with a loss of social status, more like an on-off-phenomenon. Thus, availability of effective treatment with the potential of preventing dependence or prolonging autonomous life might seem very desirable. However, the challenge of deciding at what point the patient and family members are better off with institutionalized care is rather complex given the uncertainty of the deterioration and the widespread position that social value is ascribed to self-determined life and the low status attached to being dependent on institutional care. The question whether antidementia drugs might facilitate the decision-making processes regarding social arrangements of care, does not seem to have a univocal answer. Advantages may be prolonged judgment capacity of the patient and prolonged time at home. Disadvantages are that the drugs seem to prolong

the early and very burdensome phase of the disease and that the gain in self-determination is at cost of this burden both for the patient and their surroundings. Considering what was stated above on autonomy as gradual and relational, the challenge is to grant patient autonomy, while making the restrictions in capacity and the dependencies of the patients part of the decision. As Dove et al. suggest, one should "leave the ultimate decision to the person most affected but encourage and facilitate the consideration of this person's care and responsibility for connected others".[252]

Q16: Can the technology harm the patient?

Typically, one would refer to adverse drug effects with respect to harm. For PICO 1, serious adverse events were statistically significantly higher at the one year follow-up and the difference in adverse events was also statistically significant at 24 weeks. All the other safety outcomes for all three PICOs did not show any statistically significant difference. However, the drug may harm in other ways. If the drug, for instance, prolongs the phase of cognitive capability only for some weeks or months this might not only be positive for the patients and their caregivers. They might be more concerned about the deterioration of their status and might not gain any quality of life of such a slowing down in the natural course of dementia. And as Post et al. 1998 mention, anxieties may return, and what is even more aggravating[261]: "First, for the individual who has already suffered cognitive decline but who has adjusted to the loss, does the introduction of an antidementia drug always enhance quality of life? Thus, temporary improvements of some months duration may or may not enhance quality of life for patients or caregivers."

Given that patients suffering from dementia are often multimorbid, drug interactions cannot be ruled out. Though we have no data about harm on the basis of drug interactions, we would like to mention that the risk of interactions in patients with multi-drug regimes should be weighed against the chance of the effect that may fail to materialize or be only of little advantage.

Q17: What patient group is the beneficiary of the technology?

Patients with mild and moderate symptoms of dementia are the target group of the drugs scrutinized in this HTA. Although our analysis showed statistically significant better results for AChE inhibitors compared to placebo for cognitive, functional and global outcomes, the difference observed is questionable in terms of clinical relevance to the patients, and we do not know if the differences persist over longer time horizons. This also raises the question if some patients benefit more from antidementia drugs than others. However, this question could not be answered as part of this HTA.

Q18: Are there third-party agents involved?

Family members are directly affected by the state of dementia patients and thus might be affected by their relatives' intake of antidementia drugs, as they are caregivers especially in early stages of the disease. 'Primary stressors include cognitive status of the patient, problematic behavior and decreased activities of daily living capacities, while secondary stressors impact on other areas of the caregiver's life and may result in family tensions, job conflicts or limitations on social life.'[258]

As briefly touched upon above, the view that home care is better than nursing home care is often in the mindset of many elderly people with a relative suffering from dementia. Family members of the patients might feel obliged to take care of the patients. Thus, family members of the patient might have an interest in the drug being prescribed to their family members. They might be inclined to think that the drug by inhibiting deterioration of the symptoms lessens the burden of home care. However, Wimo et al. point out that in an early stage of the disease, relatives are very highly burdened (see also above, Q7) by the occurrence of secondary symptoms, such as depression, apathetic inactivity, and psychotic symptoms, as well as behavioral disturbances occurring in patients such as aggressiveness, restlessness, wandering and vocal disruptive behavior.[258] While very low certainty of evidence exists regarding the effect of antidementia drugs on these symptoms it is often these secondary symptoms even in mild dementia; for instance, anxiety, depressive symptoms, or aggression, which are the reason for institutionalization.[258,262]

The actual effect of antidementia drugs on the situation of family members is obviously ambivalent. On one hand, the drugs might, if effective, prolong the period of time during which the patient can stay at home, allowing prolonged proximity. On the other hand, family members are heavily burdened by the caregiving situation at this early stage of the disease. These effects on family members should be taken into account when initiating a drug therapy and they have to be carefully weighed against the interests of the patients. Subsequently, due to the complexity of the situation and limited effects of antidementia drugs, reimbursement without comprehensive information and training for the relatives seems from a clinical point of view not advisable and in an ethical perspective not legitimate.

Q19: What are the interests of the users of the technology?

Nurses and physicians also belong to the wider circle of caregivers to (elderly) persons with dementia. They might have their own interests. It is, for instance, quite cumbersome to perform MMSE with patients with dementia and who, moreover, might not be as cooperative as healthy persons of the same age. Therefore, physicians might be reluctant to prescribe the drug to the effect that they can avoid these situations. By word of mouth, we also took note that some physicians avoid applying the test to a patient

for what they feel as a humiliating procedure since the patients are obviously put on the spot while taking the test.

The additional effort on behalf of the physicians should not be a valid argument. Nevertheless, it may influence the decision pro or contra the initiation of a drug therapy for persons with mild and moderate dementia especially in association with the relatively confined effect of the drug on the overall outcome for people with dementia.

Q20: What are the interests of the producers of technology (industry, universities)?

It is obvious that an industry has an interest in the distribution of the drugs while it might be more feasible to test combined strategies of non-pharmacological interventions for the patients and educational programs for their caring relatives in randomised controlled trials. Unfortunately, the data basis is small on the effect of non-pharmacological interventions. This in itself is an ethical problem as the effect of valid alternatives needs to be explored before persons are offered drug therapy. “Our findings suggest that simultaneously and sequentially combined interventions are efficacious for promoting cognitive alongside physical health in older adults, and therefore should be preferred over implementation of single-domain training.”[263] Though we have no direct comparison of pharmacological vs. non-pharmacological interventions of various kinds and combinations this needs to be further assessed.

Q24: Are there morally relevant issues related to the choice of endpoints in the assessment?

Even though dementia is defined as *a syndrome in which there is deterioration in cognitive function beyond what might be expected from the usual consequences of biological ageing”[264], consciousness is not affected, while it “is commonly accompanied, and occasionally preceded, by changes in mood, emotional control, behavio[u]r, or motivation.” Concerns about overall quality of life improvement are reported due to the fact that antidementia drugs might have a positive effect on cognitive symptoms, while other symptoms, such as anxiety, persist.[262] Thus, for patients and their environment the more relevant endpoints might encompass neuropsychiatric outcomes and quality of life.

Wimo et al. state: “Improvement in cognitive function *per se* may improve social capacity and the family situation. However, from a clinical viewpoint, other pharmacological interventions such as the effect on mood, psychotic symptoms and behavior disturbances are also of great interest.”[258]

Hence, the choice of endpoints entails morally relevant issues as the sole focus on intellectual outcomes may falsely limit the perspective on treatment options in the course of dementia. Hughes et al. 2000 point out: “Clearly one has a duty to do good to patients in the widest possible sense not just improve their scores on cognitive tests although that in itself can be counted as a good but also improve things more globally.”[262] Lacking data on patient-relevant endpoints such as being cared for at home, lessening of the burden for families and other caregivers, etc. poses a moral problem. NICE confirms in its report[9]: “The Committee noted that quality of life was not assessed in the majority of randomised controlled trials and that there was no evidence from randomised controlled trials that demonstrated any impact. The Committee considered evidence from patient experts that benefits to people with Alzheimer's disease and their carers were not necessarily those picked up by instruments measuring cognition, function, behaviour or global outcomes. In their experience, relevant benefits included maintaining mood, being

able to cope and interact with others, and functional activities that might not be scored on currently used scales, such as being able to pick up the phone or switch on the television. In particular, maintaining aspects of personal identity, such as a naturally methodical person being able to put things in order, was considered important. The Committee concluded that although there was no evidence available on health-related quality of life from a systematic review of randomised controlled clinical trials, there was some anecdotal evidence from clinical practice of benefits to patients and carers from using AChE inhibitors." Further into the report one reads: "The Committee acknowledged that time to institutionalisation was not generally included as an endpoint in randomised controlled trials and that published data were therefore limited."

In conclusion, it seems that patient-relevant outcomes like quality of life are not really included in the studies. Hence, it is debatable whether the drugs are overall of beneficence.

Another related question is about the comparator: Why should best supportive care be the only comparator? There should be an interest in assessing the drugs not only against best supportive care but against care with other interventions against dementia (cognitive training, physiotherapy, etc.).

Q33: What are the moral consequences of the HTA?

The moral consequences depend on the decisions taken based on our results. If the decision will be taken against general reimbursement of antidementia drugs, patients and their relatives are faced with the potentially daunting information that there is no pharmacological option for treatment. If there is a decision to initiate therapy in all and to stop it after reassessment this would require a reconsideration of the question which is the most feasible means for reassessment. As the findings of this report indicate some positive cognitive effects, yet unclear global outcomes in terms of their clinical relevance a more extensive means of assessment than the MMSE test should be considered as basis for a reappraisal of the initial therapeutic decision.

Given that it is unclear whether the effects are clinically relevant and also that there are questionable long-term effects one might well argue that the drug could be paid in form of private prescriptions. In national healthcare systems that strictly ensure that services do not depend on ability to pay private prescriptions may be not permitted, e.g., this was an argument in the debate around the prescription of statins to subgroups with a very low risk suffering from coronary heart disease as sequelae of high cholesterol levels in the early 2000s in the UK. Though Switzerland does allow private prescription due to a different overall perspective on the healthcare system the question could be raised: What is the minimum effect of a drug in the course of a disease that it should be fully reimbursed? What can be delegated to the individual patient and their family? If it were proven that the drug had a strong positive

effect on quality of life and slowing down the time to institutionalization the decision would be clear. Probably, a value-of-information analysis should be taken into consideration to find out where additional data on the course of the disease can help to make effective and especially cost-effective reimbursement decisions: Especially data on the effect on quality of life and the time to institutionalization could be important factors in future decision-making.

Conclusion

The ethical challenges delineated in this report are, from our perspective, centred on issues of patient autonomy, social arrangements, and choice of endpoints. In conclusion, we see relevant ethical questions in the decision-making process: As patients' cognitive abilities are already reduced in mild to moderate dementia and will continue to decline, it is vital to discuss how the decision is made in order to respect patient autonomy and what the consequences are for the proxies in case they are involved in the decision-making process. In that context we questioned the concepts of autonomy as on-off-relation and the perceptions of where the best care can be provided: home vs. nursing home.

Another crucial ethical issue is the focus on cognitive and global outcomes in the trials that might leave out many much more relevant signs and symptoms, such as alterations of mood, anxiety, psychotic symptoms, and insomnia (BPSD symptoms). It is the sum of these symptoms that change life patterns and challenge quality of life in patients and their relatives. From an ethical point of view, it seems important to create awareness that the potential improvement strived for by treatment with antidementia drugs mainly applies to cognitive, functional and global outcomes with unclear clinical relevance and there is very low certainty of evidence regarding neuropsychiatric outcomes and quality of life. Of utmost relevance to the decision-maker should be the lack of data on health-related quality of life and the delay of need of being transferred to institutionalized care, and overall activities of daily life. Decisions should be based on such endpoints which are much more relevant for patients and their loved ones. Also, these decisions should be based on global assessment of the entire treatment package, including pharmaceutical treatment and support given for both cognitive and BPSD symptoms. "Combining drug treatments with supportive coping strategies for caregivers may be a good approach to improving the quality of life for both the demented elderly and the caregiver."[258]

9.2.3 Findings legal issues

For the legal domain, we follow the objectives laid out by the HTA Core Model[245]: "The objective of the Legal Aspects (LEG) domain is to assist the HTA doers in detecting rules and regulations which need to be taken into consideration when evaluating the implications and consequences of implementing a

health technology" (p. 371). In this concept, "the aim within LEG is not, and indeed cannot be, to give or even propose a binding legal solution to a given question. Instead, the aim is to guide the HTA doers in recognising the relevant legal questions they need to consider when evaluating the technology and providing advice for decisionmakers" (p. 373).

Here, we discuss on the legal aspects of antidementia drugs. We developed several questions to guide our discussion, based on a checklist designed for the Swiss legal system.[265]

1. Patients' rights: Does the (non-)reimbursement of antidementia drugs affect fundamental and human rights issues of the patients?

Yes. A decision by the competent authorities must consider various fundamental and human rights guarantees. Of particular importance here are guarantees for the protection of people with disabilities and elderly persons. It should be noted that persons with age-related dementia are doubly vulnerable, on the one hand because of their age and on the other hand because of their chronic illness (disability). In addition, guarantees such as human dignity (Art. 7 of the Federal Constitution), equality of rights and the prohibition of discrimination (Art. 8 of the Federal Constitution), the constitutional protection of personality rights (Art. 10 para. 2 and Art. 13 of the Federal Constitution) as well as the right to assistance when in need (Art. 12 of the Federal Constitution) may be affected (not an exhaustive list).

The UN Convention on the Rights of Persons with Disabilities (CRPD) has strengthened awareness of the *self-determination of persons with disabilities*. It is a central concern of our legal system to enable people with disabilities to participate in social life autonomously and with equal rights (BGer, 2C_26/2019, 22.12.2021, E. 10.3.3). Disabilities also include chronic diseases such as AD or PD (Art. 1 sect. 2 CRPD). According to Art. 12 CRPD, all persons with disabilities have the right to find recognition everywhere as persons before the law. Art. 3 lit. a CRPD states the respect for inherent dignity, individual autonomy including the freedom to make one's own choices, and independence of persons with disabilities in a fundamental way. Art. 12 and Art. 3(a) of the CRPD thus oblige people with dementia (who may be incapable of judgment) to recognise that they are still able to make their own decisions and have their own preferences in certain areas (see 2). The freedom of choice of the person concerned must therefore be respected as far as possible. Furthermore, disabled persons have a right to independent living and to be included in the community (Art. 19 CRPD), which includes the choice of place of residence (Art. 19 lit. a CRPD).

In short, persons suffering from dementia must be protected from abuse, remain integrated in society and they are entitled to have their wishes and interests respected.

2. Therapeutic relationship: Who decides whether to use antidementia drugs?

In principle, the *person concerned* decides himself/herself – after appropriate information (informed consent) – whether to take antidementia drugs, if he/she is able to make this decision. This so-called "capacity of judgement" is legally presumed (Art. 16 of the Swiss Civil Code) and includes the ability to decide whether to take antidementia drugs. The capacity of judgement must always be assessed with reference to a specific decision: The more complex a decision, the higher the demands on mental abilities (see also Q7 in section 9.2.2).

The course of a dementia disease can lead to a state of weakness that excludes the capacity of judgement. The Federal Supreme Court has affirmed this for advanced dementia of the Alzheimer's type, for example (BGer, 5A_572/2017, 7.11.2017). However, dementia must not be inferred schematically as an incapacity of judgement; an individual case assessment is required. The decisive factor is whether the person concerned can recognize the significance and scope of a legally significant behaviour (taking medication) and of directing his or her will in accordance with this insight. If the person lacks the capacity of judgement, it must be checked whether a patient decree exists. In a patient decree, a person who is capable of judgement specifies which medical measures (e.g., taking medication) he or she agrees or does not agree to if he or she is no longer capable of judgement (Art. 370 SCC). If there is no patient decree, the attending doctor shall plan the required treatment in consultation with the person entitled to act as representative in relation to medical procedures (Art. 377 SCC). The Swiss Civil Code establishes a legal order of persons authorized to represent the patient (Art. 378 SCC). In urgent cases, the doctor may carry out medical procedures according to the presumed wishes and interests of the person lacking capacity of judgement (Art. 379 SCC).

The representatives must be guided by the presumed wishes and interests of the person lacking capacity of judgement (Art. 378 para. 3 SCC). If possible, the person lacking capacity of judgement shall also be involved in making the decision (Art. 377 para. 3 SCC; Art. 6 para. 3 of the Convention on Human Rights and Biomedicine [Oviedo Convention]; Art. 12 sect. 3 CRPD; BGE 127 I 6). The representative must therefore not be guided by his or her own wishes and interests but must be guided by the wishes of interests of the person lacking capacity of judgement. If the decision of the representative contradicts the presumed wishes or interests of the person concerned, the adult protection authority (KESB) must be involved.

See also Q7 in section 9.2.2.

3. Health insurance: From a legal perspective, should antidementia drugs be reimbursed even if the clinical benefit is unclear or low?

Antidementia drugs must meet the criteria of efficacy, appropriateness and cost-effectiveness (Art. 32 KVG). In the case of pharmaceuticals and medicinal products (SL), the conditions for inclusion (Art. 65 KVV) and the limitations (Art. 73 KVV) are regulated in more detail at the level of ordinances. The FOPH can generally attach conditions and requirements to inclusion in the SL (e.g. based on MMSE values). Without a specific legal basis, it would be inadmissible according to case law to include a drug whose efficacy is not sufficiently proven in the SL (EVG, K 156/01, 30.10.2003, E. 3.3.1).

If a drug is not included on the SL, reimbursement for the cost of medicinal products in individual cases is only possible under certain conditions (Art. 71a ff KVV). It should also be noted that the "hardship provision" (Härtefallklausel) under Art. 71a ss. KVV applies if a significant treatment benefit can be demonstrated in the individual case (Art. 71a sect. 1(b) KVV). This can cause difficulties as our analysis showed statistically significant results with questionable clinical relevance (see Q17 in section 9.2.2). Furthermore, according to case law, a large therapeutic benefit requires a favourable cost-benefit ratio, in the sense that the higher the costs, the more likely a significant therapeutic benefit must be expected (BGE 143 V 130). It would also have to be ensured that the insured persons' effective and legally equal access to treatment options is guaranteed.

In general, according to case law, a benefit is to be denied if there is a gross disproportion between expense and healing success (BGE 145 V 116; BGE 137 V 295). An established methodology for quantifying the “gross disproportion” (e.g. the assessment of cost-effectiveness based on QALYs) has not yet been developed or adopted by case law (BGE 145 V 116). From a legal point of view, the competent authorities shall consider fundamental rights and constitutional principles when construing social security benefit provisions (Art. 35 Abs. 2 BV; BGE 126 V 334). Therefore, the interests and personal circumstances of the insured persons protected by fundamental rights cannot be ignored (e.g. the risk of a significant loss of quality of life, family circumstances; Hardy Landolt, My Home is my Castle – ich will zu Hause gepflegt werden!, in: Jahrbuch zum Sozialversicherungsrecht 2019, Zürich/St. Gallen 2019, S. 173 ff., 181). If a drug can contribute to maintaining a person's ability to make judgments or to form and express wills, this should be considered when assessing cost-effectiveness. In the absence of clear criteria for evaluating the cost-effectiveness, it is important that the competent authorities include a human rights-based approach in the assessment of a reimbursement decision and provide for a corresponding weighing of interests.

Limitations (Art. 73 KVV) can be an outflow of the requirement of proportionality, which in turn must be objectively justified and must not have a discriminatory effect. In general, limitations are "milder means" (mildere Mittel) compared to a refusal to cost reimbursement. From a legal point of view, limitations are

permissible if they appear to be suitable and necessary to ensure the efficacy, appropriateness and cost-effectiveness of a therapy in the individual case, and in particular to promote the cost-effective use of the drug (Bernhard Rütsche/Andreas Wildi, Limitierung von Arzneimitteln im Krankenversicherungsrecht: Wo wird die Grenze zur Rationierung überschritten?, recht 2016, S. 199 ff., 21). Furthermore, the design of the limitation (e.g. MMSE test) must be reasonable for the insured person and must be proportionate with regard to the treating physician's freedom of therapy. In this respect, the competent authorities have a margin of discretion (for the limits see Rütsche/Wildi, a.a.O., passim).

For the ethical discussion, see Q33 in section 9.2.2. In 2020, the National Ethics Committee issued an opinion on "Drug prices. Considerations on the equitable management of expensive new medicines", which contains an in-depth ethical and legal discussion.

9.2.4 Findings social issues

All twelve studies we identified regarding social issues investigated patients who currently do not have good access to antidementia drugs. Six studies were from the US[266–271], three studies from UK[272–274], one from Denmark[275], one from Sweden[276] and one study was a systematic review[277]. The studies from the US mainly focused on the analysis of different ethnic groups. However, results were inconclusive. Two studies from the UK showed that patients from the least-deprived areas had higher rates of antidementia drug prescription.[272,274] In another study, people who owned their home were shown to have higher prescription rates.[273] A registry-based study from Denmark showed that patients with an immigrant background have worse access to antidementia drugs.[275] Three studies[270,271,276] concluded that women were more likely to receive antidementia drugs than men while one study[274] came to an opposite result. Finally, younger patients were more likely to receive antidementia drugs.[273,274]

Further social issues are the high burden on caregivers and how the treatment choices are explained to patients (including communication of expectations to patients and their caregivers and shared decision making). However, both aspects were already discussed in section 9.2.2.

9.2.5 Findings organisational issues

We identified 19 studies that investigated organisational issues related to the HTA topic. Seven studies were from the US[278–284], five studies from Germany[285–289], three studies from UK[290–292] and one study each from Colombia[293], Denmark[294], Spain[295] and Sweden[296]. The impact of a national dementia strategy was investigated in three studies from the UK.[290–292] However, results regarding the prescription of antidementia drugs were inconclusive. Two studies from the US showed that improvements in drug coverage can decrease antidementia drug disparities.[281,282] Two studies from Germany showed that

monetary incentives can improve the care of geriatric patients.[285,286] Three other studies analysed innovative care models: One study investigated a telephone clinic for evaluating continued effectiveness of antidementia treatment[278], one study investigated a collaborative dementia care model that targets both patients and their informal caregivers[279] and one study investigated a routine cognitive screening to increase the prescription of antidementia drugs[280]. Co-medications and related problems were investigated in two other studies.[293,296] Furthermore, variations in antidementia treatment were shown between different regions[294,295], patients living in rural areas versus patients living in urban areas[289], nursing home residents versus community-dwelling patients[283,287], and patients treated in outpatient psychiatric settings versus those treated by general practitioners[288].

Beside the organisational issues identified in the literature, there is a more Swiss specific aspect that needs to be mentioned: In the SL, the dementia severity is regulated by the MMSE. As already mentioned in section 9.2.2, it can be quite cumbersome to perform MMSE with dementia patients and some physicians perceive it even as a humiliating procedure. In addition, there are other assessments that are nowadays used more often in daily clinical practice such as the Montreal Cognitive Assessment (MoCA).

10 Discussion

Efficacy and safety

For PICO 1, 24 RCTs were included in the analysis. 15 trials investigated donepezil, 6 trials rivastigmine and 3 trials galantamine. We found statistically significant better results for AChE inhibitors compared to placebo in patients with mild to moderate dementia due to AD in regard to cognition, when patient results for the 24 and 26 weeks follow-up is combined. When cognition was measured with the ADAS-cog the MD was -2.15 (95%CI: -2.56 to -1.73) with the certainty of evidence rated as high according to GRADE. When cognition was measured with the MMSE the MD was 0.85 (95%CI: 0.49 to 1.22) with low certainty of evidence. Results for the one year follow-up were still in favour of the AChE inhibitors but not statistically significant. Furthermore, statistically significant better results were found for function when measured with the ADCS-ADL (MD 1.65 (95%CI: 0.48 to 2.83), low certainty of evidence) and global outcomes when measured with the CIBIC-plus (MD -0.37 (95%CI: -0.48 to -0.29), moderate certainty of evidence) and the CDR-SB (MD -0.45 (95%CI: -0.66 to -0.23), low certainty of evidence) when combining 24 and 26 weeks follow-up data. No longer follow-up data was available for these instruments. In addition, favourable but statistically not significant results were found for neuropsychiatric symptoms up to 24 weeks of follow-up (measured with the NPI-12, MD -2.84 (95%CI: -8.28 to 2.60), very low certainty of evidence). Regarding mortality (RR 1.14 (95%CI: 0.60-2.18), moderate certainty of evidence) and serious adverse events (RR 1.03 (95%CI: 0.87 to 1.21), low certainty of evidence) no statistically significant differences were observed up to 26 weeks of follow-up. These findings continued up to one year of follow-up for mortality, however, serious adverse events were statistically significantly higher for AChE inhibitors at the one year follow-up (RR 1.59 (95%CI: 1.10 to 2.31)). The difference in adverse events was also statistically significant at 24 weeks (RR 1.15 (95%CI: 1.09-1.21).

For PICO 2, only two RCTs were identified. We found statistically significant better results for memantine compared to placebo in patients with moderate to severe dementia due to AD in regard to function (measured with the ADCS-ADL, MD 1.41 (95%CI: 0.04 to 2.78), moderate certainty of evidence) and global outcomes (measured with CIBIC-plus, MD -0.3 (95%CI: -0.47 to -0.13), moderate certainty of evidence) up to 28 weeks of follow-up. In addition, favourable but statistically not significant results were found for cognition measured with the SIB (MD 3.26 (95%CI: -2.23 to 8.75), very low certainty of evidence) up to 28 weeks follow-up. Regarding mortality (RR 0.85 (95%CI: 0.22-3.32), very low certainty of evidence) and serious adverse events (RR 0.79 (95%CI: 0.54-1.15), low certainty of evidence), no statistically significant differences were observed up to 28 weeks of follow-up. No longer follow-up data than 28 weeks was available for PICO 2.

For PICO 3, only one RCT was identified. This trial showed statistically significant better results for rivastigmine compared to placebo in patients with mild to moderate dementia due to PD in regard to cognition measured with ADAS-cog (MD 0.50 (95%CI: 0.24 to 0.76)) and MMSE (MD -1.00 (95%CI: -1.67 to -0.34)), function measured with ADCS-ADL (MD -2.50 (95%CI: -4.63 to -0.37)), neuropsychiatric symptoms measured with NPI-10 (MD of 2.00 (95%CI: 0.18 to 3.82)) and global outcomes measured with ADCS-CGIC (MD 2.80 (95%CI: 1.37 to 4.23)) up to 24 weeks of follow-up. However, risk of bias was rated high for these outcomes due to missing outcome data according to the RoB 2 tool. Regarding mortality and serious adverse events, no statistically significant differences were observed.

Although many of the results observed in our analysis are statistically significant, it remains a question if they are also clinically relevant. Minimal Clinically Important Difference is a concept that addresses this aspect. MCID is defined as «The smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management»[297]. The definition of MCIDs for the treatment of patients with dementia seems to be challenging.[298,299] However, for some outcomes relevant for our analysis MCID cut-offs have been published: For ADAS-cog the MCID ranges between 2.6 and 4[300–303], for MMSE between 1 and 3[300,302,304,305], for CDR-SB between 1 and 2[302,304] and a recent study by Stanley et al., 2021[306] concluded that even small changes in the CIBIC-plus can be clinically relevant. Considering the published cut-off values for MCID, we must come to the conclusion that the clinical relevance of our statistically significant differences is questionable as none of the outcomes was within the established MCID.

Several Cochrane reviews already addressed the effectiveness, efficacy and safety aspects of the treatments under investigation.[68,307–309,62,66,65,23,67] They consistently observed statistically significant benefits of donepezil, rivastigmine or galantamine versus placebo regarding cognitive function evaluated by MMSE or ADAS-cog in patients with mild, moderate or severe AD. In addition, most Cochrane reviews found statistically significant better results for AChE inhibitors regarding global function assessed by CIBIC-plus. Furthermore, memantine resulted more effective than placebo on cognitive and global functions as evaluated by McShane et al., 2019[23]. Rolinski et al., 2012[65] analyzed the effect of AChE inhibitors compared to placebo on patients with PD dementia and observed an improvement in MMSE score.

Numerous other systematic reviews including meta-analysis stated that AChE inhibitors and memantine improve cognitive and global symptoms. Knight et al., 2018[76] conducted amongst others a meta-analysis combining all drugs and doses irrespective of dementia subtype at 6 months. They observed that AChE inhibitors were more effective than placebo in terms of MMSE with a pooled effect estimate of 1.00 (95%CI: 0.83 to 1.16). This effect was moderated by dementia subtypes. AChE inhibitors showed a twice as high effect for patients with PD or lewy bodies dementia, with an estimate of 2.11 (95%CI: 0.61

to 3.61) than for patients with AD or vascular dementia, with an estimate of 0.91 (95%CI: 0.77 to 1.05). Also memantine was reported to be more efficacious than placebo for MMSE but the effect was smaller, with an estimate of 0.40 (95%CI: 0.05 to 0.75). Blanco-Silvente et al., 2017[78] stated similar results. They carried out a meta-analysis of AChE inhibitors for AD independent of treatment length, the mean was 25 weeks. They observed that AChE inhibitors were superior to placebo for reducing cognitive symptoms, assessed with MMSE or ADAS-cog, the standardized MD was 0.38 (95%CI: 0.28 to 0.47) and improving global symptoms, standardized MD for CIBIC-plus of 0.28 (95%CI: 0.22 to 0.34). Therefore, we can conclude that our results are consistent with previous findings from Cochrane reviews and other systematic reviews including meta-analysis.

Other systematic reviews did not conduct a meta-analysis for all drugs combined. Regarding cognitive functions (mainly assessed by ADAS-cog, SIB and MMSE) the pairwise meta-analysis of Dou et al., 2018[77] found that all AChE inhibitors except rivastigmine 5cm^2 patch were significantly superior to placebo in patients with mild to moderate AD, standardized MD for donepezil 5mg was -0.38 (95%CI: -0.50 to -0.26); donepezil 10mg -0.394 (95%CI: -0.56 to -0.23); galantamine 24mg -0.511 (95%CI: -0.60 to -0.43); galantamine 32mg -0.527 (95%CI: -0.67 to -0.40); rivastigmine 12mg -0.296 (95%CI: -0.41 to -0.18); rivastigmine patch 10cm² -0.240 (95%CI: -0.36 to -0.12). Whereas memantine 20mg resulted statistically more efficacious than placebo in patients with moderate to severe AD, with a standardized MD of 0.36 (95%CI: 0.05 to 0.67). In terms of global changes evaluated by CIBIC-plus and CGIC donepezil 5 and 10mg, rivastigmine 12mg and galantamine 24mg, were more effective than placebo with a standardized MD for donepezil 5mg of 2.12 (95%CI: 1.43 to 3.14); donepezil 10mg 2.00 (95%CI: 1.62 to 2.46); rivastigmine 12mg 1.832 (95%CI: 1.40 to 2.40); galantamine 24mg 1.43 (95%CI: 0.98 to 2.08). Tricco et al., 2018[75] reported similar findings. They carried out a network meta-analysis considering any severity of AD (54.5% of RCTs included mild to moderate AD) and found that donepezil was superior to placebo for MMSE, with a MD of 1.39 (95% credible interval (CrI): 0.53 to 2.24) and ADAS-cog MD -3.29 (95%CrI: -4.57 to -1.99), transdermal rivastigmine for MMSE MD 2.02 (95%CrI: 0.02 to 4.08) and galantamine for ADAS-cog MD -2.13 (95%CrI: -3.91 to -0.27). All three AChE inhibitors resulted more effective than placebo for global status, MD for donepezil was -0.32 (95%CrI: -0.46 to -0.19); oral rivastigmine -0.38 (95%CrI: -0.56 to -0.17); galantamine -3.79 (95%CrI: -6.98 to -0.59). Zhang 2020[310], on the other hand, computed a network meta-analysis (duration of follow-up of RCTs was between 12 and 104 weeks) and found no statistically significant differences between AChE inhibitors and placebo for MMSE in patients with mild to moderate AD with a standardized MD for donepezil 5mg of 0.26 (95%CrI: -0.39 to 0.91); donepezil 10mg 0.28 (95%CrI: -0.20 to 0.76); rivastigmine 12mg -0.14 (95%CrI: -0.74 to 0.40); rivastigmine patch 5cm^2 -0.03 (95%CrI: -1.13 to 1.05); rivastigmine patch 10cm^2 0.04 (95%CrI: -0.67 to 0.73); galantamine 24mg 0.17 (95%CrI: -0.98 to 1.33).

Although our analysis has several strengths (e.g., up to date literature search, pooling data across 24 and 26 weeks etc.), we would like to highlight two important limitations. As we choose pooling results for the most frequently used instruments, there is data that did not contribute to our meta-analysis. Furthermore, last observation carried forward was the method that was most often reported in the identified trials. We used results based on this method although it is known that it can lead to bias.

Health economic analysis

We conducted a systematic literature review and identified enough studies for PICO 1 and PICO 2 that allowed us to investigate the potential cost-utility and cost-effectiveness of AD treatments by transferring existing results to the Swiss setting. For PICO 3 we found only one study that was not considered transferable based on a-priori specified criteria. Due to insufficient evidence regarding the effectiveness, efficacy, and safety of rivastigmine treatment in PD patients we did not build a de novo model and did not conduct a health economic analysis for PICO 3.

The costs were assessment from the healthcare payer perspective. As a result, indirect costs due to work absenteeism of the caregivers were not considered. This might lead to an underestimation of the costs related to AD.

The cost-utility was assessed based on four studies for PICO 1 and seven studies for PICO 2. The studies for PICO 1 were performed in the UK, Spain, and Germany. The results varied mainly due to the time horizon. Particularly, donepezil does not seem to be cost-effective over a time-horizon of up to 1.5 years, due to relatively high incremental costs compared to the few QALYs gained. In contrast, over a time-horizon of 10 years, donepezil becomes dominant with savings ranging between CHF 11'216[139] and CHF 22'237[144] and QALYs gained ranging between 0.109[139] and 0.131[144]. Treatment with galantamine seems to be cost-effective with an ICER of CHF 5’340 per QALY gained over a time-horizon of 5 years. The studies for PICO 2 were performed in the UK, Netherlands, Sweden, US, and Canada. Memantine treatment is shown to be dominant in four out of the seven transferable studies. In the remaining three studies it is shown to be cost-effective (assuming a hypothetical willingness-to-pay threshold of CHF 100’000 per QALY gained) with the ICER ranging between CHF 4’673 and CHF 96’064 per QALY gained. Time horizon does not seem to have a big impact on these results. Rather, the assumption of no survival effect of memantine and the assumption of no discontinuation of treatment until entrance to institutional care are shown to have a large impact.[141]

The cost-effectiveness was assessed based on six studies for PICO 1 and nine studies for PICO 2. The clinical meaningfulness of these effects was not assessed by the included health economic evaluations. Nevertheless, the associated assumptions of these studies were assessed in section 8.2.2. Regarding

PICO 1, all effectiveness results were based on models and were in favor of treatment with an AChE inhibitor. In particular, the identified studies showed that treatment with an AChE inhibitor can lead to more life years gained, less time in full-time and institutional care, less total care and caregiving time, less time in a severe state and more time with better function in terms of activities of daily living. These effectiveness results cannot be compared with the efficacy results of this HTA, as these outcomes were not available in the RCTs identified in the efficacy part. Regarding PICO 2, memantine was more effective than the comparator with respect to most effectiveness indicators, except for the Bristol Activities of Daily Living Scale indicating greater functional impairment with treatment with memantine. Regarding the other effectiveness indicators, the identified studies showed that treatment with memantine can lead to better cognition, more time in a moderate severity state, in independence, or not in complete dependence and in community as well as less caregiving time and less time in full-time care/institutional care. However, not all these differences were statistically significant. Furthermore, the estimated treatment effect of memantine in terms of sMMSE in Knapp et al. 2017[158], was higher than the effect shown in the RCT by Reisberg et al. 2003[119] in the efficacy part of this HTA (0.9 vs 0.7). However, in both studies the effect was not statistically significant. The other effectiveness results of the health economic models cannot be compared with the outcomes in the efficacy part of this HTA.

The budget impact was assessed based on the observed drug consumption of AD patients every year for a period of five years since their treatment initiation and their treatment distribution according to CSS health insurance claims data. The distribution of the AD population to institutional care, pre-FTC and death was based on data extracted from CSS that was extrapolated to the Swiss population. We identified only one US study[138] showing this distribution per year over a period of ten years. Compared to this study the share of AD patients requiring FTC during the first year after treatment initiation in Switzerland is approximately four to seven times higher, while it is almost the same during the remaining years. Similarly, the share of AD patients that die during the first year after treatment initiation is twice to five times higher in Switzerland, while it is almost the same during the remaining four years. Our budget impact analysis shows that an elimination of treatment with one of the AChE inhibitors or memantine leads to additional costs ranging from CHF 1.01 million for galantamine to CHF 12.42 million for rivastigmine. Note that the difference in additional costs is mainly because a lower proportion of AD patients is estimated to be treated with galantamine. Although savings are generated due to to lower expenses for drugs, physician visits, and home care, the increase in time spent in institutional care produces additional costs that exceed these savings. As a result, a removal of one of the AChE inhibitors or memantine would lead to additional costs and not to savings. Considering that the number of detected/diagnosed AD cases may increase not only due to the aging of the Swiss population, but also to preventive programs (like the National Dementia Strategy), the economic impact of AD treatments in the next few years may be even higher.

This is the first health economic analysis for Switzerland comparing AChE inhibitors and memantine with no drug treatment. As any health economic analysis our study has several limitations: (1) One major limitation concerns the comparability of the input parameters used in the economic analyses with those analysed in the clinical assessment of this HTA. As already mentioned, most economic analyses were based on a combination of several sources (non-necessarily related to RCTs). How these sources were combined to define a treatment effect was generally unclear. For example, the modelled treatment effect in terms of mean MMSE or ADAS-cog was rarely reported, and in the few cases where it was reported, the impression is that the authors tended to use more optimistic assumptions compared to the results of our clinical assessment (i.e., the change in score in favour of the intervention was higher than in our meta-analyses). In several studies one of the main economic outcomes was institutionalization (or time spent in FTC). This variable was unfortunately not reported in the RCTs included in the efficacy assessment. Similarly, information on utility or quality of life in the RCTs included in the efficacy assessment were extremely scarce. The considerable heterogeneity across economic studies reporting information on institutionalization rates or utility suggest a high level of uncertainty. (2) Although we carefully extracted the direct medical costs from the transferable studies in order to only account for costs from the healthcare payer perspective, due to lack of information on concrete parameters in some studies we might have over- or underestimated the costs. We might underestimate some costs, because we have excluded costs for social services, which in some studies[147,153] include costs for visiting nurses, which would be reimbursed by the Swiss social health insurance. On the other hand, we have included studies that calculated the costs for nursing home, which next to the medical costs might also include non-medical costs (e.g., accommodation-related costs). These non-medical costs are not reimbursed by the Swiss social health insurance. (3) As already mentioned in the methods section, the process of adapting costs from international studies according to different resource utilisation, price of healthcare services, and changes in healthcare costs over time cannot be interpreted as achieving fully realistic costs/ICERs for Switzerland. The results of the costs adaptation intended to achieve only a certain approximation of costs/cost-effectiveness levels to be expected for Switzerland. To fully adjust the costs of international studies it would be necessary to consider underlying costs differences between countries (e.g., physician visit costs or hospitalisation costs) as well as differences over time (including drug price changes over time due to patent expiry). Despite this clear limitation, the fact that in the last few years most drug prices decreased with the introduction of generics, while the costs for institutionalization/home care tended to increase, may suggest that AD treatment may be even more cost-effective or dominant than previously estimated in international studies. (4) A further limitation concerns the estimation of the direct costs in the studies included for PICO 2 who only reported total costs from a societal/social perspective. This cost approximation was based on the mean ratio of costs (between the healthcare payer, societal, and social care perspective) calculated among the studies that reported detailed information on direct

and indirect costs. Considering that the ratios varied considerably across the studies providing detailed information (e.g., from 3% to 69% for healthcare vs. societal perspectives), it can be assumed that direct costs were under- or overestimated in several studies. (5) An additional potential limitation may be related to the risk of bias due to the conflicts of interest of the authors of health economic analyses. Among the 30 articles identified in the systematic review, in 12 cases the presence of a conflict of interest was clearly stated, while in 6 cases no conflict of interest was declared. The remaining 12 articles did not provide information on potential conflicts of interests. However, in seven of them one or more authors were affiliated with a pharmaceutical company. Although the presence of a conflict of interest may not automatically lead to biased reports, we cannot exclude this possibility. (6) The budget impact analysis is based on several assumptions. We tested the impact of the main assumptions in the sensitivity analysis and found that some of them influence the net budget impact remarkably. It should also be noted that the data we used from CSS health claims provide an overview of the drugs bought and not on the ones that were effectively consumed. Finally, we did not consider treatment “breaks” but rather calculated the current treatment situation based on the accumulated number of grams per person per year.

Evidence gaps

We identified three areas where more evidence is needed. First, there is a lack of data on health-related quality of life, the delay of need of being transferred to institutionalized care, and overall activities of daily life. Second, we did not identify a trial that used the Montreal Cognitive Assessment (MoCA) which is used often in current daily clinical practice. Third, evidence on longer-term follow-up is very limited.

11 Conclusions

The review of the existing literature and the conducted meta-analysis of the main clinical outcomes showed statistically significant better results for AChE inhibitors compared to placebo in patients with mild to moderate dementia due to AD (PICO 1) in regard to cognition (high certainty of evidence), global outcomes (moderate certainty of evidence) and function (low certainty of evidence) when the data from 24 and 26 weeks follow-up are pooled together. Regarding safety outcomes, serious adverse events were statistically significantly higher for AChE inhibitors at the one year follow-up and the difference in adverse events was also statistically significant at 24 weeks. All the other safety outcomes at any follow-up time point investigated did not show any statistically significant difference. We found statistically significant better results for memantine compared to placebo in patients with moderate to severe dementia due to AD (PICO 2) in regard to function (moderate certainty of evidence) and global outcomes (moderate certainty of evidence) up to 28 weeks of follow-up. Regarding safety outcomes, no statistically significant differences were observed. For PICO 3, only one study was identified. This study showed statistically significant better results for rivastigmine compared to placebo in patients with mild to moderate dementia due to PD in regard to cognition, function, neuropsychiatric symptoms and global outcomes up to 24 weeks of follow-up. However, risk of bias was rated high for these outcomes due to missing outcome data. In regard to safety outcomes, no statistically significant differences were observed. Data on longer term follow-up was scarce. Our results are consistent with previous findings from Cochrane reviews and other systematic reviews including meta-analysis. Although we observed statistically significant differences for many outcomes investigated, we must conclude that the clinical relevance of our statistically significant differences is questionable based on published cut-off values for MCID.

Based on a systematic review of health economic evaluations we retrieved 30 studies, 17 of which were considered transferable and were numerically adapted to investigate the cost-effectiveness and cost-utility of treatments with an AChE inhibitor or memantine in Switzerland. Seven studies investigated PICO 1 (four for donepezil and three for galantamine), while ten studies focused on PICO 2 (i.e., on memantine). Only one study was identified for PICO 3 but was not considered transferable. Since the published evidence on rivastigmine treatment in PD patients was too limited we did not conduct any health economic analysis regarding PICO 3. The adapted cost-utility results showed that donepezil is not cost-effective in terms of costs per QALY gained over a time-horizon of up to 1.5 years at a hypothetical willingness-to-pay threshold of CHF 100’000, while it becomes dominant over a time-horizon of ten years. The one transferable study identified for galantamine showed that it can be cost-effective over a time-horizon of 5 years. Memantine treatment was shown to be dominant in four out of seven studies and cost-effective in the remaining three studies. However, these results should be interpreted

with caution as there is high uncertainty related to the input parameters and assumptions of the identified health economic evaluations. The main outcome in most of these studies influencing the cost-utility and cost-effectiveness results was the effect on institutionalization. As the direct treatment effect on institutionalization was not assessed in the RCTs, most economic analyses combined the treatment effects on cognitive function, global measures or functional capacity from RCTs with several other sources (non-necessarily related to RCTs) to model the mid- and longer-term treatment effect on institutionalization. However, these treatment effects referred to a time horizon of up to one year. Therefore, most identified health economic evaluations conservatively assumed that the duration of the treatment effect was one year, and then previous gains were maintained with continued treatment but no further slowing of the disease occurred. Additionally, the clinical treatment effects were not always reported in the health economic evaluations and when reported they were often more optimistic compared to the results of the efficacy part of this HTA. Finally, there was considerable heterogeneity across economic studies reporting information on institutionalization rates and utility values, which suggests a high level of uncertainty. Furthermore, we estimated the budget impact from removing donepezil, rivastigmine, galantamine or memantine from the treatment of AD, based on information on institutionalization and mortality rates of treated patients drawn from the CSS health insurance company, the assumption of no treatment effect on mortality and the assumption of a 10% reduction in the probability of being institutionalized over a period of 5 years. Our budget impact analysis suggests that the removal of the ACHE inhibitors or memantine would lead to an increase of the total costs for healthcare payers; the additional costs in 2021 would for example range from CHF 1.01 million for galantamine to CHF 12.42 million for rivastigmine. This corresponds to savings due to lower expenses for drugs, physician visits, and home care, ranging between CHF 0.88 million for galantamine and CHF 8.73 million for rivastigmine and to additional costs due to higher rates of institutionalization ranging between CHF 1.89 million for galantamine and CHF 21.15 million for rivastigmine. The assumption concerning the treatment effect on institutionalization rates showed the highest effect on the net budget impact. In the extreme assumption that there is no treatment effect on institutionalization, stopping AD treatment with one of the AChE inhibitors or memantine would lead to savings that vary from CHE 0.80 million for galantamine to CHF 7.87 million for rivastigmine in 2021. In summary, although the economic part of this HTA shows positive results for the treatment of AD with AChE inhibitors or memantine compared to placebo, it should be kept in mind that these results are associated with high uncertainty.

The ethical challenges delineated in this report are centred on issues of patient autonomy, social arrangements, and choice of endpoints. As patients' cognitive abilities are already reduced in mild to moderate dementia and will continue to decline, it is vital to discuss how the decision is made in order to respect patient autonomy and what the consequences are for the proxies in case they are involved in the decision-making process. Shared decision making may be a promising approach in the case of mild

to moderate symptoms. Another crucial ethical issue is the focus on cognitive and global outcomes in the trials that might leave out many much more relevant signs and symptoms (such as alterations of mood, anxiety, psychotic symptoms, and insomnia). Of utmost relevance to the decision-maker should be the lack of data on health-related quality of life and the delay of need of being transferred to institutionalized care, and overall activities of daily life. From a legal perspective, a decision by the competent authorities must consider various fundamental and human rights guarantees. Furthermore, the capacity of judgment should be considered for the decision whether to use antidementia drugs or not. Social issues identified are patients who currently do not have good access to antidementia drugs, the high burden on caregivers and how the treatment choices are explained to patients. A Swiss specific organisational issue identified is the regulation of the dementia severity in the SL by the MMSE as the performance of the MMSE can be seen as cumbersome and even humiliating and as other tools like the Montreal Cognitive Assessment (MoCA) are used more often in current daily clinical practice.

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13 Appendices

13.1 Search strategies for efficacy, safety, effectiveness and health economic searches

13.1.1 Search strategy Medline (via EBSCOhost)

	Search string	**Hits**
Concept 1	**PICO 1 and PICO 2:** exp Alzheimer Disease/ OR (alzheimer* OR (diffuse ADJ2 "cortical sclero*")).ti,ab. **PICO 3:** exp Parkinson Disease/ OR (parkinson* OR "paralysis agitans").ti,ab.	172601 135081
	AND	
Concept 2	**PICO 1 and PICO 2:** exp Donepezil/ OR exp Rivastigmine/ OR exp Galantamine/ OR exp Memantine/ OR (donepezil OR aricept OR asenta OR "doneliquid geriasan" OR "e 2020" OR e2020 OR eranz OR memac OR memorit).ti,ab. OR (rivastigmine OR alzest OR "ena 713" OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR "sdz 212 713" OR "sdz 212-713" OR "sdz 212713" OR "sdz212 713" OR "sdz212-713" OR sdz212713).ti,ab. OR (galantamine OR acumor OR alenzo OR aneprosil OR bergal OR consion OR elmino OR galantex OR galanthamine OR galanthen OR galanyl OR galatamin OR galatamina OR galema OR galnora OR galsya OR gatalin OR gazylan OR girlamen OR jilkon OR lotprosin OR loxifren OR luventa OR lycoremin OR lycoremine OR margal OR masparen OR "memoton life" OR "memoton-life" OR micol OR natagal OR nivalin OR razadyne OR reminyl OR spegal OR vertusal OR zentan OR zoroflog).ti,ab. OR (memantine OR akatinol OR alzantin OR axura OR "d 145" OR d145 OR ebix OR ebixa OR ebixza OR marixino OR maruxa OR memary OR "mn 08" OR mn08 OR namenda OR nemdatine OR "nsc 102290" OR nsc102290 OR "sun y7017" OR suny7017).ti,ab. **PICO 3:** exp Rivastigmine/ OR (Rivastigmine OR alzest OR 'ena 713' OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR "sdz 212 713" OR "sdz 212-713" OR "sdz 212713" OR "sdz212 713" OR "sdz212-713" OR sdz212713).ti,ab.	10858 2053
	AND	
Concept 3a	(randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab.OR randomised.ab. OR placebo.ab. OR drug therapy.fs. OR randomly.ab. OR trial.ab. OR groups.ab.) NOT (exp animals/ not humans.sh.)	4493436
	AND	
Concept 3b	exp Cost-Benefit Analysis/ OR "Costs and Cost Analysis"/ OR Health Care Costs/ OR exp Economics, Pharmaceutical/ OR (cost* OR "cost benefit analys*" OR economic* OR price OR prices OR pricing OR expenditure* OR pharmacoeconomic* OR "benefit-cost*").ti,ab.	1019856
	AND	

Concept 4	limit X to (english or german or french or italian)	RCTs: 3423; HE: 338

13.1.2 Search strategy Embase (via embase.com)

	Search string	**Hits**
Concept 1	**PICO 1 and PICO 2:** 'Alzheimer disease'/exp OR (alzheimer* OR (diffuse NEAR/2 'cortical sclero*')):ti,ab **PICO 3:** 'Parkinson disease'/exp OR (parkinson* OR 'paralysis agitans'):ti,ab	260284 219739
	AND	
Concept 2	**PICO 1 and PICO 2:** 'donepezil'/exp OR 'rivastigmine'/exp OR 'galantamine'/exp OR 'memantine'/exp OR (donepezil OR aricept OR asenta OR 'doneliquid geriasan' OR 'e 2020' OR e2020 OR eranz OR memac OR memorit):ti,ab OR (rivastigmine OR alzest OR 'ena 713' OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR 'sdz 212 713' OR 'sdz 212-713' OR 'sdz 212713' OR 'sdz212 713' OR 'sdz212-713' OR sdz212713):ti,ab OR (galantamine OR acumor OR alenzo OR aneprosil OR bergal OR consion OR elmino OR galantex OR galanthamine OR galanthen OR galanyl OR galatamin OR galatamina OR galema OR galnora OR galsya OR gatalin OR gazylan OR girlamen OR jilkon OR lotprosin OR loxifren OR luventa OR lycoremin OR lycoremine OR margal OR masparen OR 'memoton life' OR 'memoton-life' OR micol OR natagal OR nivalin OR razadyne OR reminyl OR spegal OR vertusal OR zentan OR zoroflog):ti,ab OR (memantine OR akatinol OR alzantin OR axura OR 'd 145' OR d145 OR ebix OR ebixa OR ebixza OR marixino OR maruxa OR memary OR 'mn 08' OR mn08 OR namenda OR nemdatine OR 'nsc 102290' OR nsc102290 OR 'sun y7017' OR suny7017):ti,ab **PICO 3:** 'rivastigmine'/exp OR (Rivastigmine OR alzest OR 'ena 713' OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR 'sdz 212 713' OR 'sdz 212-713' OR 'sdz 212713' OR 'sdz212 713' OR 'sdz212-713' OR sdz212713):ti,ab	28493 8070
	AND	
Concept 3a	'randomized controlled trial'/de OR 'controlled clinical trial'/de OR random*:ti,ab or 'randomization'/de or 'intermethod comparison'/de OR placebo:ti,ab OR (compare or compared or comparison):ti OR ((evaluated or evaluate or evaluating or assessed or assess) AND (compare or compared or comparing or comparison)):ab OR (open NEAR/1 label):ti,ab OR ((double or single or doubly or singly) NEAR/1 (blind or blinded or blindly)):ti,ab OR 'double blind procedure'/de OR "parallel group*":ti,ab OR (crossover or "cross over"):ti,ab OR ((assign* or match or matched or allocation) NEAR/5 (alternate or group* or intervention* or patient* or subject* or participant$)):ti,ab OR (assigned or allocated):ti,ab OR (controlled NEAR/7 (study or design or trial)):ti,ab OR (volunteer or volunteers):ti,ab OR 'human experiment'/de OR trial:ti NOT ((((random* NEAR/1 sampl* NEAR/7 ('cross section*' OR questionnaire$ OR survey* OR database$)):ti,ab) NOT ('comparative study'/de OR	4943955

	'controlled study'/de OR 'randomized controlled':ti,ab OR 'randomised controlled':ti,ab OR 'randomly assigned':ti,ab) OR ('cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'randomized controlled':ti,ab OR 'randomised controlled':ti,ab OR "control group$":ti,ab)) OR ((case NEAR/1 control*) AND random*)) NOT ('randomized controlled':ti,ab OR 'randomised controlled':ti,ab) OR ('systematic review':ti NOT (trial:ti OR study:ti)) OR (nonrandom*:ti,ab NOT random*:ti,ab) OR 'random field*':ti,ab OR (('random cluster' NEAR/3 sampl*):ti,ab) OR (review:ab AND 'review':it NOT trial:ti) OR ('we searched':ab AND (review:ti OR 'review':it)) OR 'update review':ab OR ((databases NEAR/4 searched):ab) OR ((rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset$:ti) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de)))	
	AND	
Concept 3b	'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp OR 'cost utility analysis'/exp OR 'cost'/de OR 'health care cost'/de OR 'pharmacoeconomics'/exp OR (cost* OR 'cost benefit analys*' OR economic* OR price OR prices OR pricing OR expenditure* OR pharmacoeconomic* OR 'benefit-cost*'):ti,ab	1608627
	AND	
Concept 4	NOT [conference abstract]/lim AND ([english]/lim OR [german]/lim OR [french]/lim OR [italian]/lim)	RCTs: 2283, HE: 1363

13.1.3 Search strategy Cochrane (via EBSCOhost)

	Search strings	**Hits**
Concept 1	**PICO 1 and PICO 2:** (alzheimer* OR (diffuse NEAR/2 "cortical sclero*")):ti,ab,kw **PICO 3:** (parkinson* OR "paralysis agitans"):ti,ab,kw	11853 11505
	AND	
Concept 2	**PICO 1 and PICO 2:** (donepezil OR aricept OR asenta OR "doneliquid geriasan" OR "e 2020" OR e2020 OR eranz OR memac OR memorit):ti,ab,kw OR (rivastigmine OR alzest OR "ena 713" OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR "sdz 212 713" OR "sdz 212-713" OR "sdz 212713" OR "sdz212 713" OR "sdz212-713" OR sdz212713):ti,ab,kw OR (galantamine OR acumor OR alenzo OR aneprosil OR bergal OR consion OR elmino OR galantex OR galanthamine OR galanthen OR galanyl OR galatamin OR galatamina OR galema OR galnora OR galsya OR gatalin OR gazylan OR girlamen OR jilkon OR lotprosin OR loxifren OR luventa OR lycoremin OR lycoremine OR margal OR masparen OR "memoton life" OR "memoton-life" OR micol OR natagal OR nivalin OR razadyne OR reminyl OR spegal OR vertusal OR zentan OR zoroflog):ti,ab,kw OR (memantine OR akatinol OR alzantin OR axura OR "d 145" OR d145 OR ebix OR ebixa OR ebixza OR marixino OR maruxa OR memary OR "mn 08" OR mn08 OR	3905

	namenda OR nemdatine OR "nsc 102290" OR nsc102290 OR "sun y7017" OR suny7017):ti,ab,kw **PICO 3:** (Rivastigmine OR alzest OR 'ena 713' OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR "sdz 212 713" OR "sdz 212-713" OR "sdz 212713" OR "sdz212 713" OR "sdz212-713" OR sdz212713):ti,ab,kw	749
	AND	
Concept 3b	(cost* OR "cost benefit analys*" OR economic* OR price OR prices OR pricing OR expenditure* OR pharmacoeconomic* OR "benefit-cost*"):ti,ab,kw	94292

13.1.4 Search strategy EconLit

	Search string	**Hits**
Concept 1	**PICO 1 and PICO 2:** (alzheimer* OR (diffuse N2 cortical sclero*)) **PICO 3:** (parkinson* OR paralysis agitans)	123 87
	AND	
Concept 2	**PICO 1 and PICO 2:** (donepezil OR aricept OR asenta OR doneliquid geriasan OR e 2020 OR e2020 OR eranz OR memac OR memorit) OR (rivastigmine OR alzest OR ena 713 OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR sdz 212 713 OR sdz 212-713 OR sdz 212713 OR sdz212 713 OR sdz212-713 OR sdz212713) OR (galantamine OR acumor OR alenzo OR aneprosil OR bergal OR consion OR elmino OR galantex OR galanthamine OR galanthen OR galanyl OR galatamin OR galatamina OR galema OR galnora OR galsya OR gatalin OR gazylan OR girlamen OR jilkon OR lotprosin OR loxifren OR luventa OR lycoremin OR lycoremine OR margal OR masparen OR memoton life OR memoton-life OR micol OR natagal OR nivalin OR razadyne OR reminyl OR spegal OR vertusal OR zentan OR zoroflog) OR (memantine OR akatinol OR alzantin OR axura OR d 145 OR d145 OR ebix OR ebixa OR ebixza OR marixino OR maruxa OR memary OR mn 08 OR mn08 OR namenda OR nemdatine OR nsc 102290 OR nsc102290 OR sun y7017 OR suny7017) **PICO 3:** (Rivastigmine OR alzest OR ena 713 OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR sdz 212 713 OR sdz 212-713 OR sdz 212713 OR sdz212 713 OR sdz212-713 OR sdz212713)	123 3

13.1.5 Search strategy international HTA database (INAHTA)

Search strategy: (alzheimer)[Title] AND (donepezil OR galantamine OR rivastigmine OR memantine) [Title]
Hits: 16
Search strategy: (parkinson)[Title] AND (rivastigmine) [Title]
Hits: 0

13.1.6 Search strategy NHS Economic Evaluation Database (NHSEED)

Search strategy: (alzheimer):TI AND (donepezil OR galantamine OR rivastigmine OR memantine):TI
Hits: 45
Search strategy: (parkinson):TI AND (rivastigmine):TI
Hits: 1

13.1.7 Search strategy EUnetHTA Planned and Ongoing Projects (POP) database

Search term: "dementia"
Dementia (non-Alzheimer) - new pharmaceutical treatments [ID380]
Status: suspended
Effectiveness and cost-effectiveness of cognitive training for patients with dementia
Status: ongoing; Agency: AETSA (Andalusian HTA Agency)
Search term: "alzheimer*"
Dementia (non-Alzheimer) - new pharmaceutical treatments [ID380]
Status: suspended
Search term: "parkinson*"
Magnetic resonance (MRI)-guided high-intensity focused ultrasound
Status: planned
Radiosurgery for epilepsy, Parkinson, tremor, trigeminal and glossopharyngeal neuralgia
Status: ongoing
RVG 126934 (Lecigon®) for the treatment of advanced Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available oral combinations of Parkinson medicinal products have not given satisfactory results
Status: ongoing
Search term: "memantine"
No hits
Search term: "donepezil"
No hits
Search term: "rivastigmine"
No hits
Search term: "galantamine"
No hits

13.2 Risk of bias assessment

Table 31 Risk of bias for PICO 1, ADAS-Cog

Study ID	D1	D2	D3	D4	D5	Overall			
Andersen 2012	-	+	-	+	+	-		+	Low risk
Corey-Bloom 1998	!	+	!	+	!	!		!	Some concerns
Winblad 2007	+	+	+	+	!	!		-	High risk
Rosler 1999	+	+	+	+	!	!			
Burns 1999	+	+	-	+	!	-		D1	Randomisation process
Maher-Edwards 2011	+	+	!	+	-	-		D2	Deviations from the intended interventions
Maher-Edwards 2015	+	+	!	+	-	-		D3	Missing outcome data
Gold 2010	!	+	!	+	+	!		D4	Measurement of the outcome
Brodaty 2005	+	+	-	+	-	-		D5	Selection of the reported result
Feldman 2007	+	+	+	+	!	!			
Gault 2016	-	+	!	+	-	-			
Wilcock 2000	+	+	+	+	!	!			
Rogers 1998	+	+	+	+	!	!			
Raskind 2000	+	+	+	+	!	!			
Krishnan 2003	+	+	!	+	-	-			
Nakamura 2011	+	+	-	+	+	-			
Homma 2000	+	+	+	+	!	!			
Seltzer 2004	!	+	+	+	!	!			

Table 32 Risk of bias for PICO 1, MMSE

Study ID	D1	D2	D3	D4	D5	Overall			
Winblad 2001	+	+	+	+	!	!		+	Low risk
Winblad 2007	+	+	+	+	!	!		!	Some concerns
Seltzer 2004	!	+	+	+	!	!		-	High risk
Rosler 1999	+	+	+	+	!	!			
Rogers 1998	+	+	+	+	!	!		D1	Randomisation process
Nakamura 2011	+	+	-	+	+	-		D2	Deviations from the intended interventions
Mazza 2006	!	+	-	+	!	-		D3	Missing outcome data
Andersen 2012	-	+	+	+	+	-		D4	Measurement of the outcome
Corey-Bloom 1998	!	+	!	+	!	!		D5	Selection of the reported result
Feldman 2007	+	+	+	+	!	!			
Gault 2016	-	+	!	+	-	-			
Maher-Edwards 2015	+	+	!	+	-	-			
Tariot 2001	+	+	+	+	-	-			
Mohs 2001	!	+	+	+	!	!			
Gauthier 2002	!	+	-	+	!	-			

Table 33 Risk of bias for PICO 1, CIBIC-plus

Risk of bias for PICO 1, CIBIC-plus												
Study ID	**D1**	**D2**	**D3**	**D4**	**D5**	**Overall**						
Wilcock 2000	+	+	-	+	!	-		+	Low risk			
Rosler 1999	+	+	+	+	!	!		!	Some concerns			
Rogers 1998	+	+	+	+	!	!		-	High risk			
Raskind 2000	+	+	+	+	!	!						
Nakamura 2011	+	+	-	+	+	-		D1	Randomisation process			
Burns 1999	+	+	-	+	!	-		D2	Deviations from the intended interventions			
Maher-Edwards 2015	+	+	!	+	-	-		D3	Missing outcome data			
Feldman 2007	+	+	+	+	!	!		D4	Measurement of the outcome			
Gault 2016	-	+	!	+	-	-		D5	Selection of the reported result			
Gauthier 2002	!	+	-	+	!	-						
Maher-Edwards 2011	+	+	!	+	-	-						
Gold 2010	!	+	!	+	+	!						
Brodaty 2005	+	+	-	+	-	-						
Corey-Bloom 1998	!	+	!	+	!	!						

Table 34 Risk of bias for PICO 1, other efficacy outcomes

Study ID	Outcome	D1	D2	D3	D4	D5	Overall			
Winblad 2007	ADCS-ADL	+	+	+	+	!	!		+	Low risk
Brodaty 2005	ADCS-ADL	+	+	-	+	!	-		!	Some concerns
Gault 2016	ADCS-ADL	-	+	!	+	-	-		-	High risk
Maher-Edwards 2015	ADCS-ADL	+	+	!	+	-	-			
Winblad 2007	ADCS-CGIC	+	+	+	+	!	!		D1	Randomisation process
Rogers 1998	CDR-SB	+	+	+	+	!	!		D2	Deviations from the intended interventions
Burns 1999	CDR-SB	+	+	-	+	!	-		D3	Missing outcome data
Tariot 2001	CDR-SB	+	+	+	+	-	-		D4	Measurement of the outcome
Homma 2000	CDR-SB	+	-	+	+	-	-		D5	Selection of the reported result
Gauthier 2002	DAD	!	+	-	+	!	-			
Maher-Edwards 2011	DAD	+	+	!	+	-	-			
Wilcock 2000	DAD	+	+	+	+	!	!			
Nakamura 2011	DAD	+	+	-	+	!	-			
Winblad 2001	GDS	+	+	+	+	!	!			
Rosler 1999	GDS	+	+	+	+	!	!			
Corey-Bloom 1998	GDS	!	+	!	+	!	!			
Feldman 2007	GDS	+	+	+	+	!	!			
Homma 2000	J-CGIC	+	+	+	+	!	!			
Winblad 2001	NPI	+	+	+	+	!	!			
Winblad 2007	NPI	+	+	+	+	!	!			
Brodaty 2005	NPI	+	+	-	+	!	-			
Maher-Edwards 2011	NPI	+	+	!	+	-	-			
Tariot 2001	NPI	+	+	+	+	-	-			
Gault 2016	NPI	-	+	!	+	-	-			
Gault 2016	NPI	-	+	!	+	-	-			
Gauthier 2002	NPI	!	+	-	+	!	-			
Rogers 1998	QoL	+	+	+	+	!	!			
Ballard 2005	SIB	!	+	-	+	!	-			
Gauthier 2002	SIB	!	+	-	+	!	-			

Table 35 Risk of bias for PICO 1 safety outcomes

Study ID	Outcor	D1	D2	D3	D4	D5	Overall			
Winblad 2001	AE	+	+	+	+	!	!		+	Low risk
Winblad 2007	AE	+	+	+	+	!	!		!	Some concerns
Wilcock 2000	AE	+	+	+	+	!	!		-	High risk
Seltzer 2004	AE	+	+	+	+	!	!			
Rosler 1999	AE	+	+	+	+	!	!		D1	Randomisation process
Raskind 2000	AE	+	+	+	+	!	!		D2	Deviations from the intended interventions
Nakamura 2011	AE	+	+	+	+	+	+		D3	Missing outcome data
Mazza 2006	AE	!	+	+	+	!	!		D4	Measurement of the outcome
Feldman 2007	AE	+	+	+	+	!	!		D5	Selection of the reported result
Maher-Edwards 2015	AE	+	+	+	+	!	!			
Tariot 2001	AE	+	+	+	+	!	!			
Mohs 2001	AE	+	+	+	+	!	!			
Homma 2000	AE	+	+	+	+	!	!			
Krishnan 2003	AE	+	!	+	+	!	!			
Andersen 2012	AE	-	!	+	+	!	-			
Brodaty 2005	AE	+	+	+	+	!	!			
Gauthier 2002	AE	!	+	+	+	!	!			
Maher-Edwards 2011	AE	+	+	+	+	+	+			
Gold 2010	AE	!	+	+	+	+	!			
Gault 2016	AE	-	+	+	+	+	-			
Winblad 2001	SAE	+	+	+	+	!	!			
Winblad 2007	SAE	+	+	+	+	!	!			
Seltzer 2004	SAE	+	+	+	+	!	!			
Rosler 1999	SAE	+	+	+	+	!	!			
Rogers 1998	SAE	+	+	+	+	!	!			
Raskind 2000	SAE	+	+	+	+	!	!			
Nakamura 2011	SAE	+	+	+	+	+	+			
Tariot 2001	SAE	+	+	+	+	!	!			
Mohs 2001	SAE	+	+	+	+	!	!			
Gauthier 2002	SAE	!	+	+	+	!	!			
Burns 1999	SAE	+	+	+	+	!	!			
Feldman 2007	SAE	+	+	+	+	!	!			
Maher-Edwards 2011	SAE	+	+	+	+	+	+			
Gold 2010	SAE	!	+	+	+	+	!			
Gault 2016	SAE	-	+	+	+	+	-			
Winblad 2001	Death	+	+	+	+	!	!			
Winblad 2007	Death	+	+	+	+	!	!			
Rosler 1999	Death	+	+	+	+	!	!			
Rogers 1998	Death	+	+	+	+	!	!			
Raskind 2000	Death	+	+	+	+	!	!			
Nakamura 2011	Death	+	+	+	+	+	+			
Maher-Edwards 2015	Death	+	+	+	+	+	+			
Tariot 2001	Death	+	+	+	+	!	!			
Ballard 2005	Death	-	+	+	+	!	-			
Brodaty 2005	Death	+	+	+	+	!	!			
Burns 1999	Death	+	+	+	+	!	!			
Corey-Bloom 1998	Death	!	!	+	+	!	!			
Gault 2016	Death	-	+	+	+	+	-			
Maher-Edwards 2011	Death	+	+	+	+	+	+			
Mohs 2001	Death	+	+	+	+	!	!			
Gold 2010	Death	!	+	+	+	+	!			

Table 36 Risk of bias for PICO 2

Study	Outcome	D1	D2	D3	D4	D5	Overall			
van Dyck 2007	ADCS-ADL	!	+	+	+	!	!		+	Low risk
Reisberg 2003	ADCS-ADLsev	+	+	+	+	!	!		!	Some concerns
van Dyck 2007	CIBIC plus	!	+	+	+	!	!		-	High risk
Reisberg 2003	CIBIC plus	+	+	+	+	!	!			
Reisberg 2003	GDS	+	+	+	+	!	!		D1	Randomisation process
Reisberg 2003	MMSE	+	+	+	+	!	!		D2	Deviations from the intended interventions
van Dyck 2007	NPI	!	+	+	+	!	!		D3	Missing outcome data
Reisberg 2003	NPI	+	+	+	+	!	!		D4	Measurement of the outcome
van Dyck 2007	SIB	!	+	+	+	!	!		D5	Selection of the reported result
Reisberg 2003	SIB	+	+	+	+	!	!			
van Dyck 2007	AE	!	+	+	+	!	!			
Reisberg 2003	AE	+	+	+	+	!	!			
van Dyck 2007	SAE	!	+	+	+	!	!			
Reisberg 2003	SAE	+	+	+	+	!	!			
van Dyck 2007	Death	!	+	+	+	!	!			
Reisberg 2003	Death	+	+	+	+	!	!			

Table 37 Risk of bias for PICO 3

Study	Outcome	D1	D2	D3	D4	D5	Overall			
Emre 2004	ADCS-CGIC	+	+	-	+	!	-		+	Low risk
Emre 2004	ADAS-cog	+	+	-	+	!	-		!	Some concerns
Emre 2004	NPI	+	+	-	+	!	-		-	High risk
Emre 2004	ADCS-ADL	+	+	-	+	!	-			
Emre 2004	MMSE	+	+	-	+	!	-		D1	Randomisation process
Emre 2004	AE	+	+	+	+	!	!		D2	Deviations from the intended interventions
Emre 2004	SAE	+	+	+	+	!	!		D3	Missing outcome data
Emre 2004	Death	+	+	+	+	!	!		D4	Measurement of the outcome
									D5	Selection of the reported result

13.3 Additional information regarding the findings for efficacy and safety

Figure 39 Forest-plot of ADAS-cog 24 weeks (PICO 1)

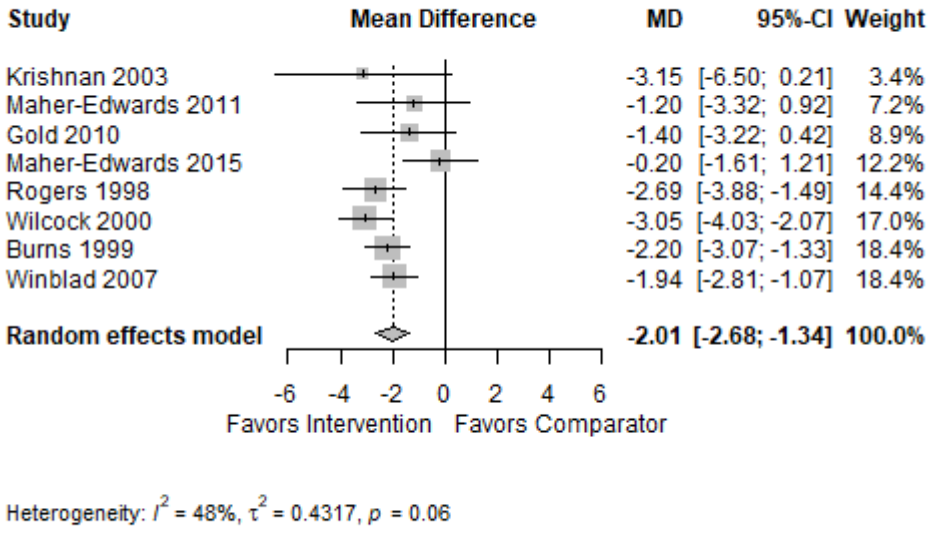


Figure 38 Forest-plot of ADAS-cog 26 weeks (PICO 1)

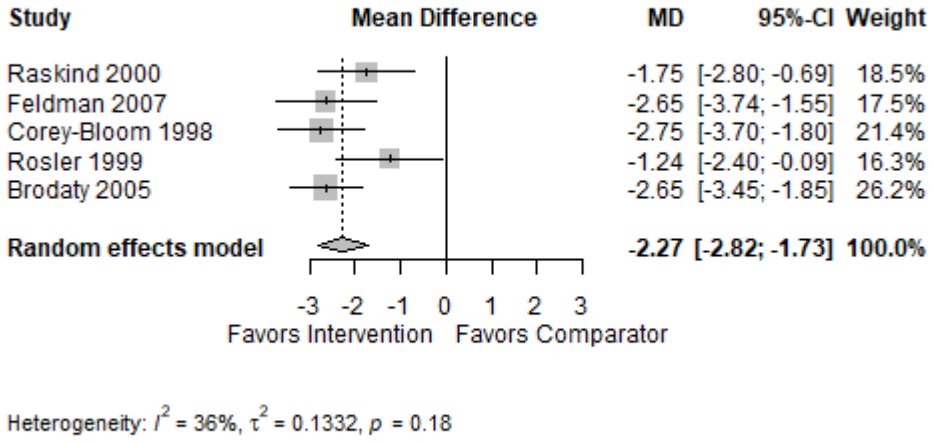
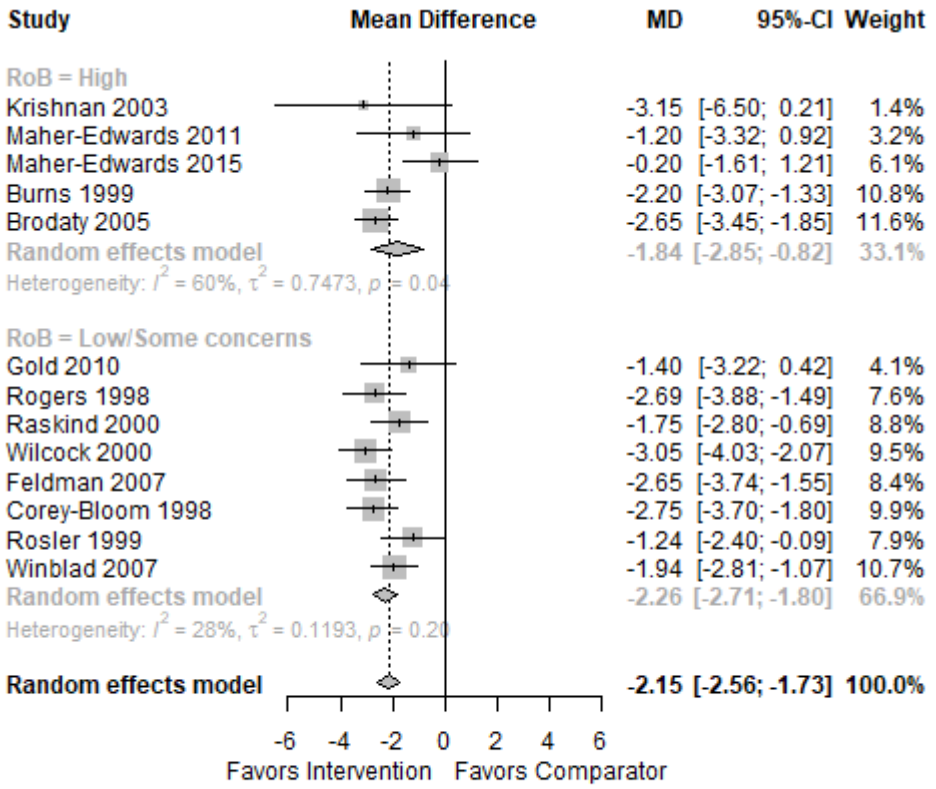
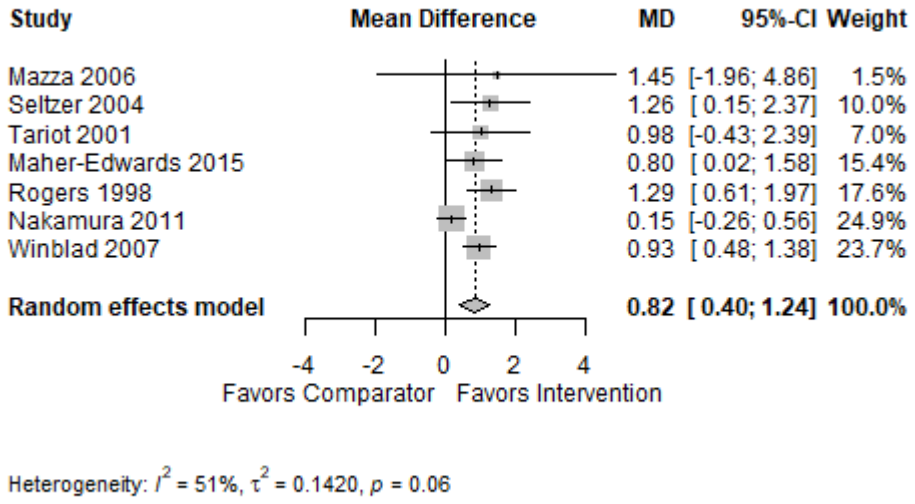


Figure 40 Forest-plot of ADAS-cog 24 weeks and 26 weeks RoB subgroup analysis (PICO 1)



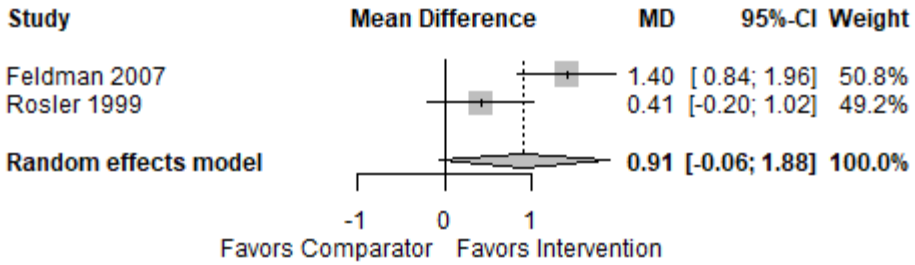
Heterogeneity: I^2 = 40%, τ^2 = 0.2197, p = 0.07
Test for subgroup differences: χ^2_1 = 0.55, df = 1 (p = 0.46)

Figure 42 Forest-plot of MMSE 24 weeks (PICO 1)



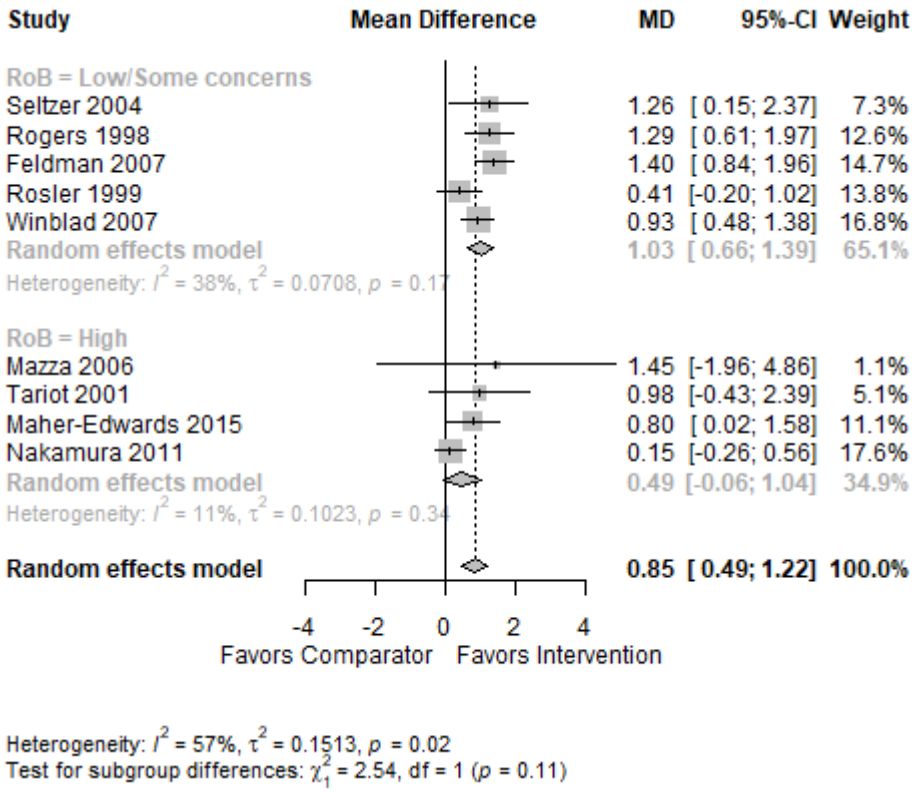
Heterogeneity: I^2 = 51%, τ^2 = 0.1420, p = 0.06

Figure 41 Forest-plot of MMSE 26 weeks (PICO 1)



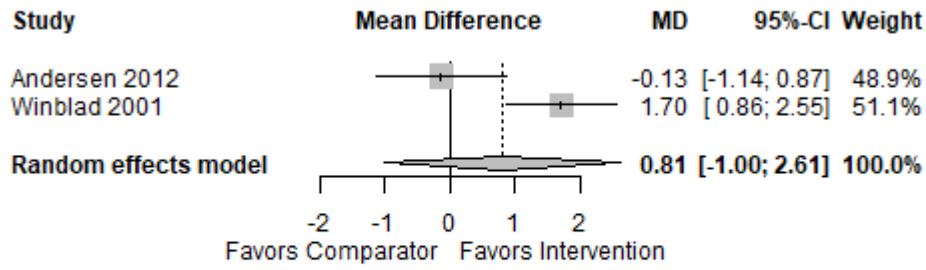
Heterogeneity: I^2 = 82%, τ^2 = 0.3987, p = 0.02

Figure 44 Forest-plot of MMSE 24 weeks and 26 weeks RoB subgroup analysis (PICO 1)



Heterogeneity: I^2 = 57%, τ^2 = 0.1513, p = 0.02
Test for subgroup differences: χ^2_1 = 2.54, df = 1 (p = 0.11)

Figure 43 Forest-plot of MMSE 52 weeks (PICO 1)



Heterogeneity: I^2 = 87%, τ^2 = 1.4654, p < 0.01

Figure 45 Forest-plot of ADCS-ADL 24 weeks (PICO 1)

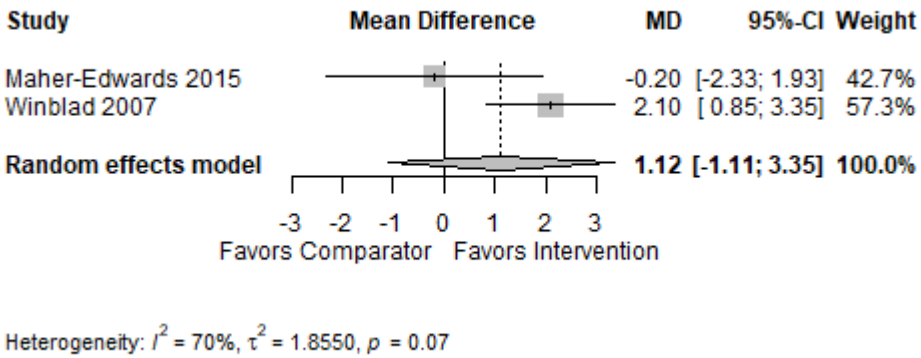


Figure 46 Forest-plot of CIBIC-plus 24 weeks (PICO 1)

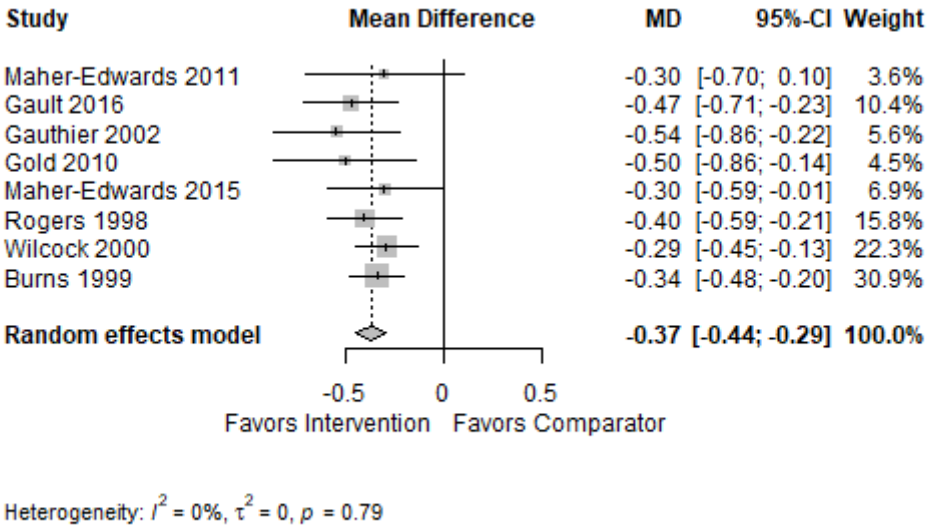


Figure 48 Forest-plot of CIBIC-plus 26 weeks (PICO 1)

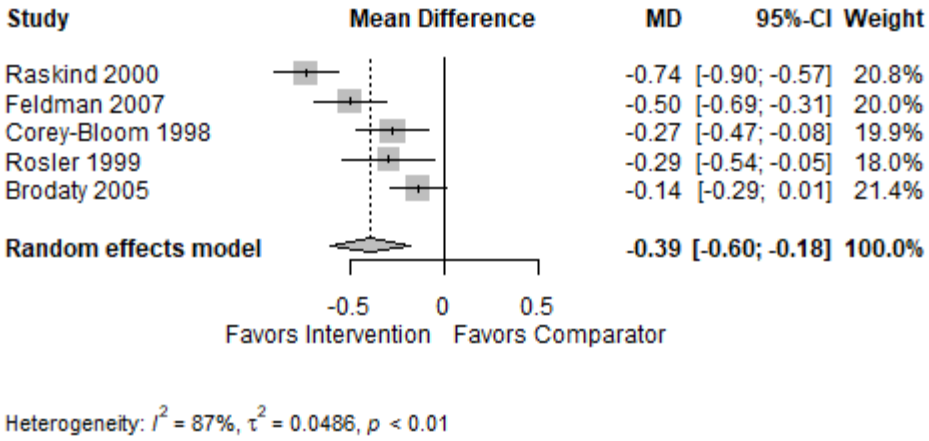


Figure 47 Forest-plot of CIBIC-plus 24 weeks and 26 weeks RoB subgroup analysis (PICO 1)

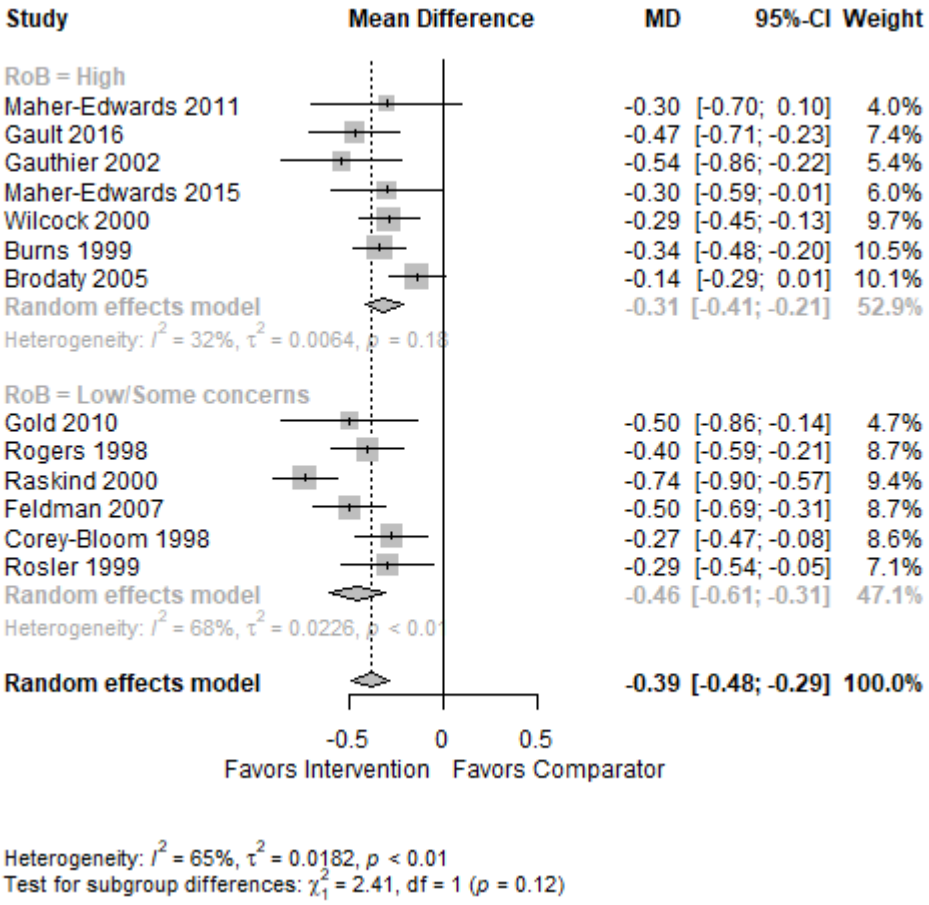
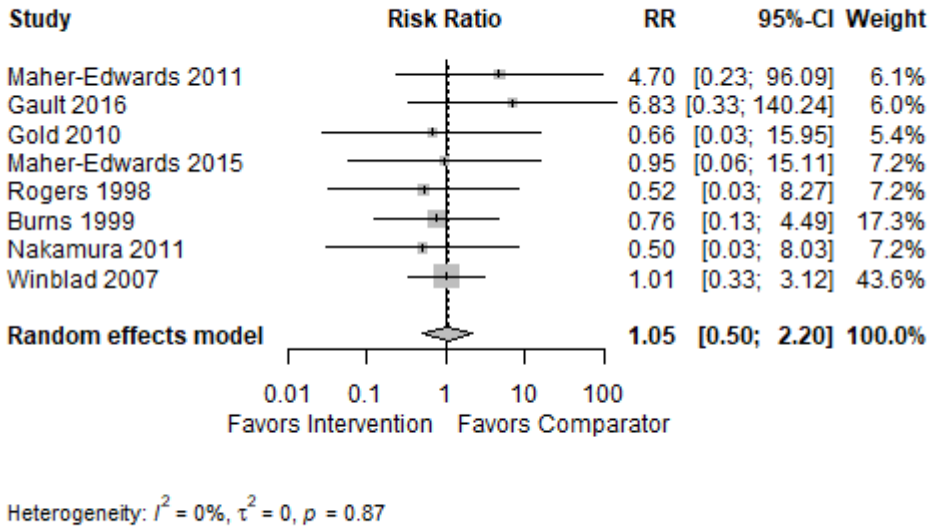
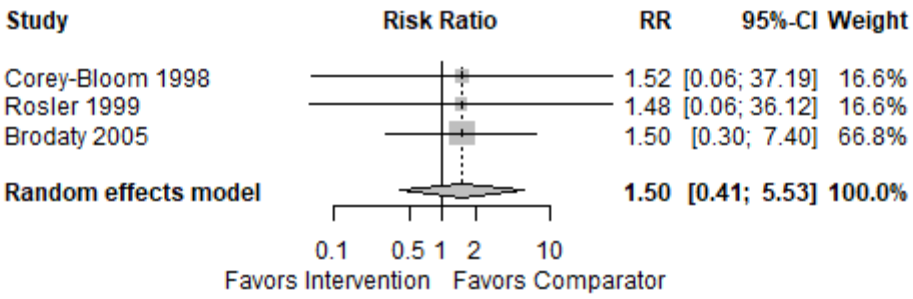


Figure 49 Forest-plot of mortality 24 weeks (PICO 1)



Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.87

Figure 50 Forest-plot of mortality 26 weeks (PICO 1)



Heterogeneity: I^2 = 0%, τ^2 = 0, p = 1.00

Figure 51 Forest-plot of mortality 52 weeks and 54 weeks (PICO 1)

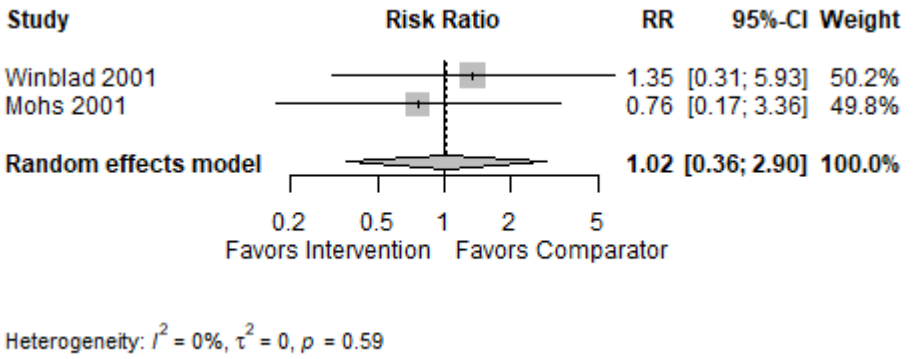


Figure 52 Forest-plot of serious adverse events 24 weeks (PICO 1)

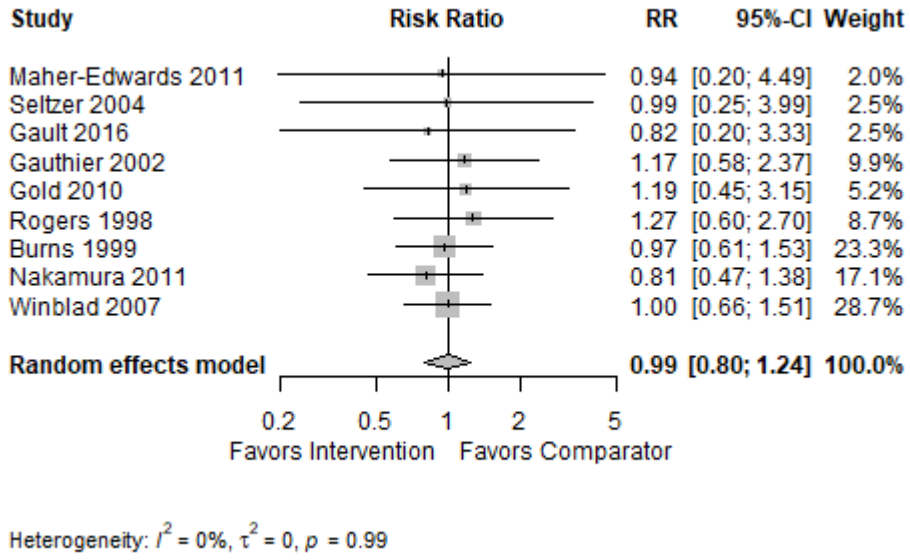


Figure 53 Forest-plot of serious adverse events 26 weeks (PICO 1)

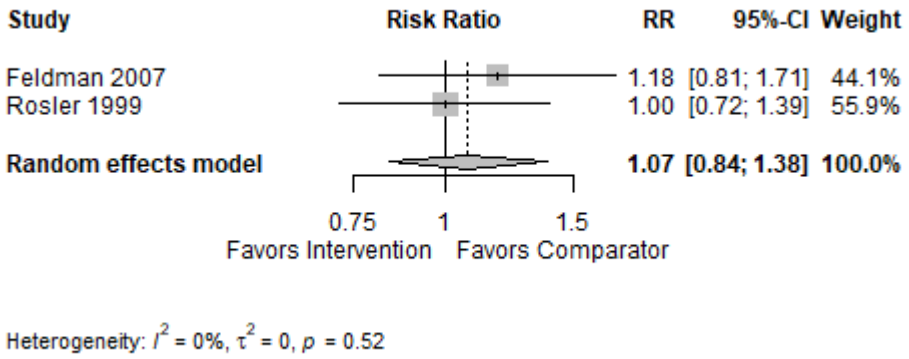


Figure 54 Forest-plot of serious adverse events 52 weeks and 54 weeks (PICO 1)

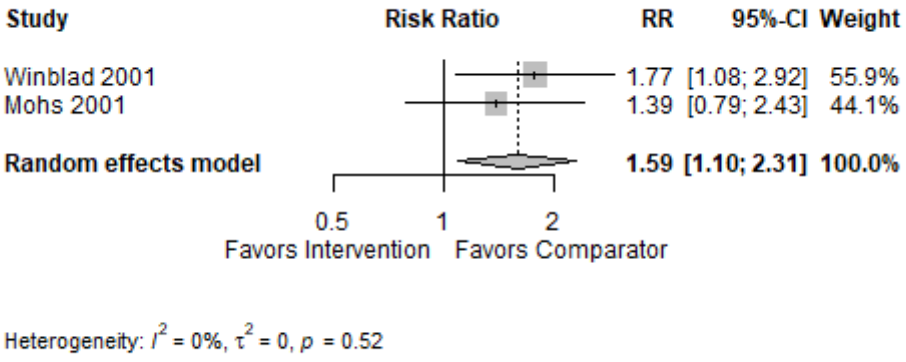
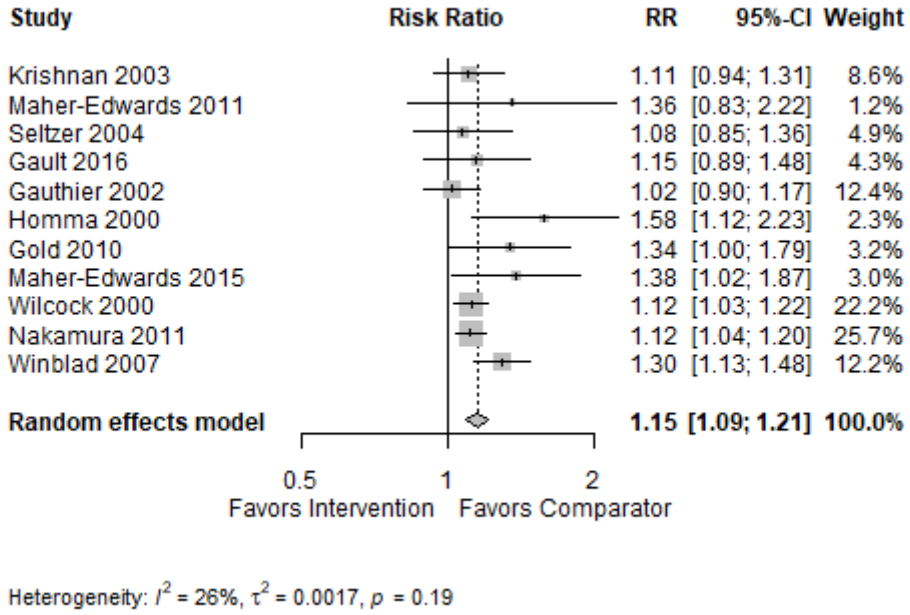
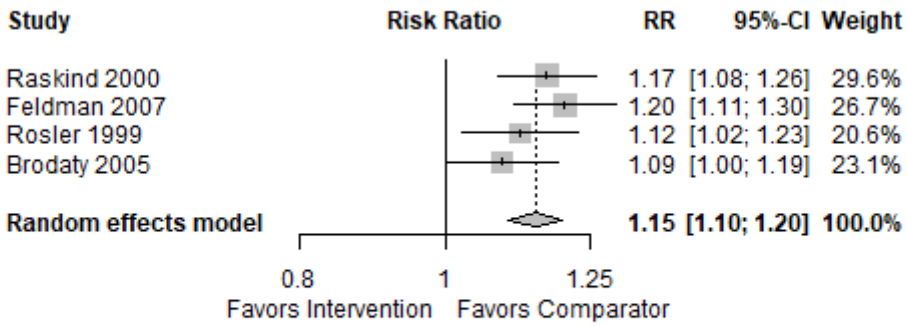


Figure 55 Forest-plot of adverse events 24 weeks (PICO 1)



Heterogeneity: I^2 = 26%, τ^2 = 0.0017, p = 0.19

Figure 56 Forest-plot of adverse events 26 weeks (PICO 1)



Heterogeneity: I^2 = 4%, τ^2 < 0.0001, p = 0.37

Figure 57 Forest-plot of adverse events 52 weeks (PICO 1)

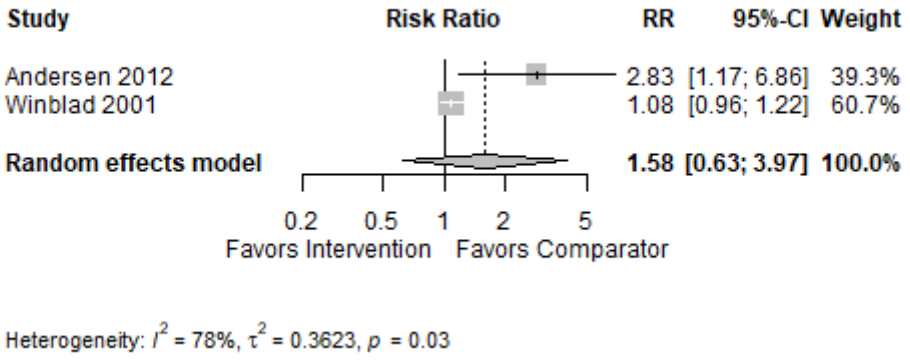


Figure 58 Forest-plot of discontinuation due to adverse events 24 weeks (PICO 1)

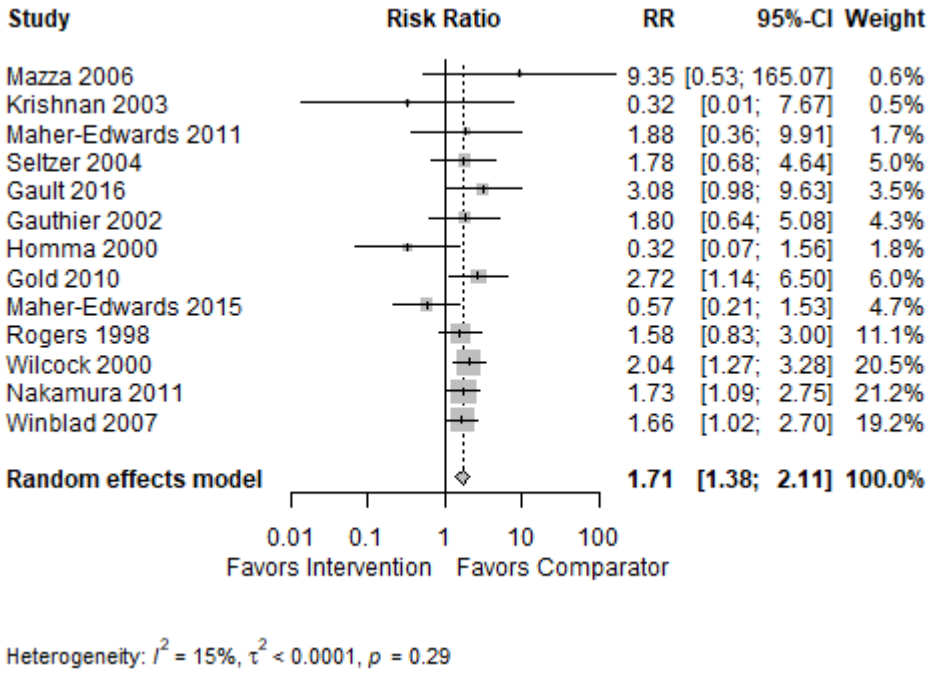


Figure 59 Forest-plot of discontinuation due to adverse events 26 weeks (PICO 1)

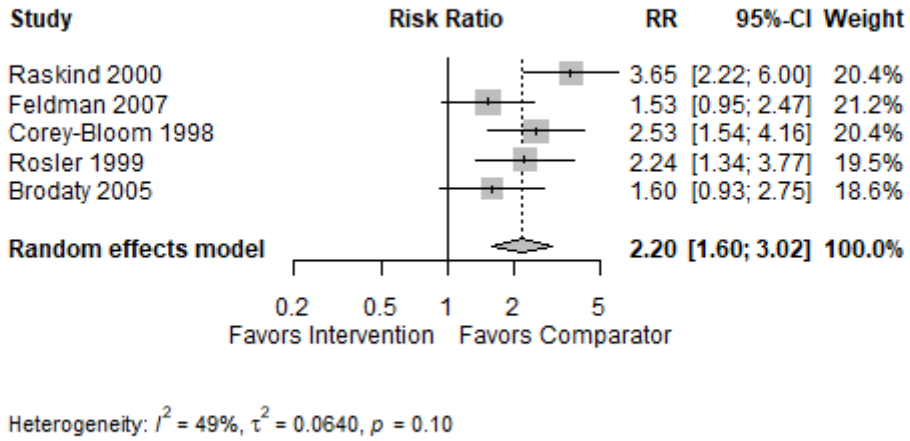


Figure 60 Forest-plot of discontinuation due to adverse events 52 weeks (PICO 1)

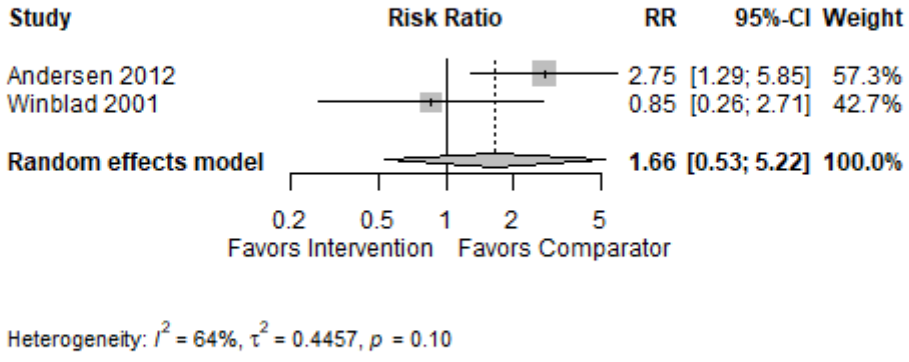


Figure 61 Forest-plot of discontinuation due to any reason 24 weeks (PICO 1)

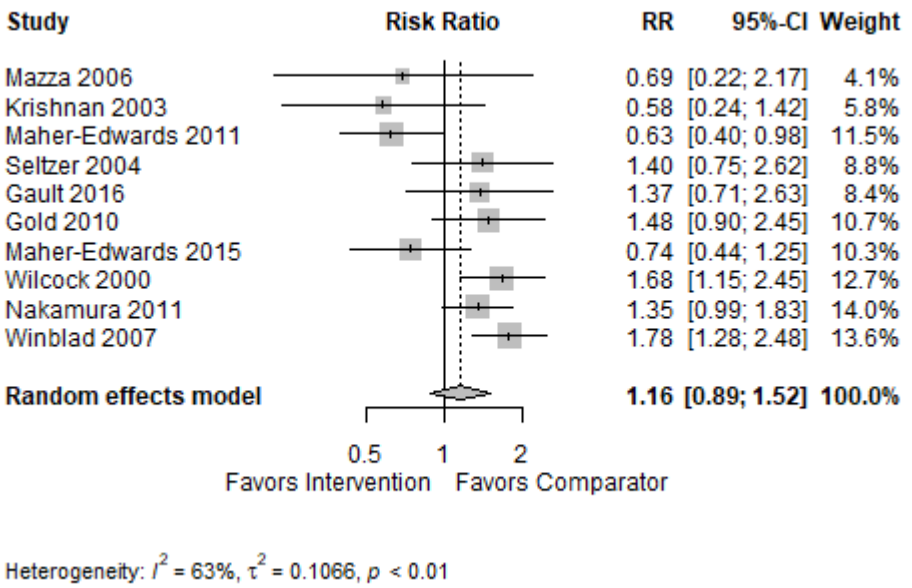


Figure 62 Forest-plot of discontinuation due to any reason 26 weeks (PICO 1)

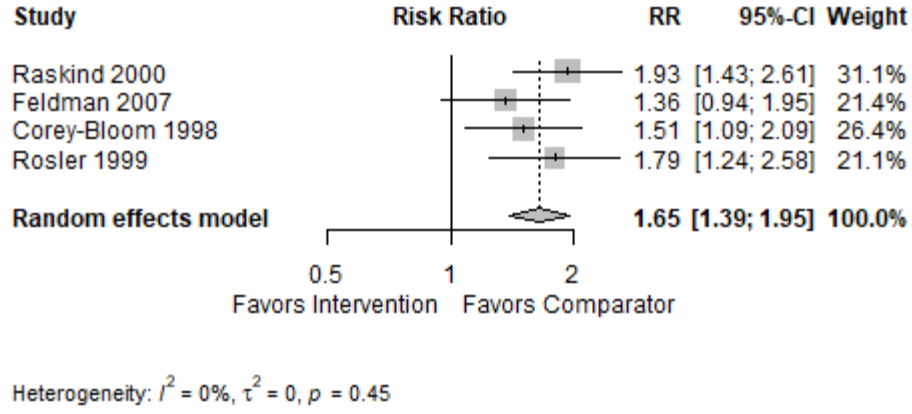
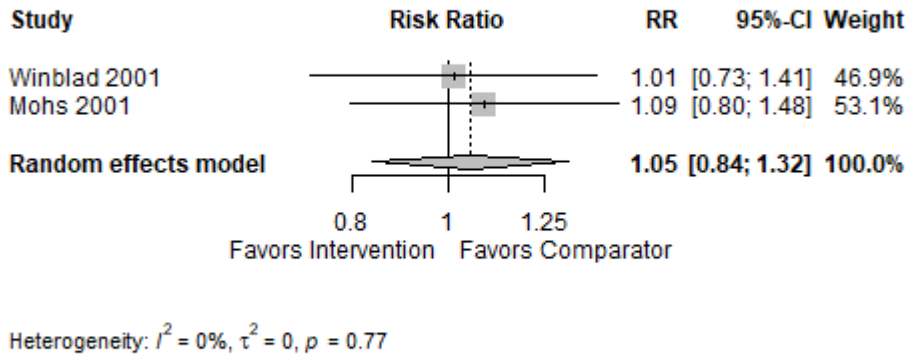


Figure 63 Forest-plot of discontinuation due to any reason 52 weeks and 54 weeks (PICO 1)



Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.77

13.4 Adaptation tables to adjust international cost-effectiveness results for Switzerland

Correction for different resource utilisation

Current expenditure on health, per capita, US$ purchasing power parities.

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Canada	2'278	2'451	2'623	2'758	2'912	3'121	3'292	3'485	3'707	3'849	3'950	4'155	4'226	4'333	4'425	4'533	4'631	5'040	5'138	5'331	5'370
Finland	1'610	1'876	1'981	2'201	2'277	2'478	2'573	2'751	3'003	3'244	3'287	3'429	3'598	3'786	3'933	3'956	3'992	4'104	4'215	4'379	4'559
Germany	2'698	2'894	3'008	3'240	3'329	3'391	3'430	3'564	3'749	3'955	4'166	4'425	4'567	4'745	4'951	5'151	5'296	5'671	5'960	6'291	6'518
Netherlands	2'372	2'646	2'882	3'297	3'308	3'494	3'583	3'827	4'075	4'378	4'442	4'477	4'567	4'782	4'924	4'935	4'927	5'096	5'254	5'538	5'739
Spain	1'370	1'523	1'635	1'803	2'015	2'123	2'212	2'392	2'483	2'672	2'748	2'738	2'734	2'729	2'764	2'858	3'019	3'149	3'321	3'444	3'600
Sweden	1'959	2'195	2'399	2'637	2'675	2'773	2'811	3'008	3'224	3'415	3'457	3'433	4'460	4'680	4'732	4'866	5'004	5'128	5'219	5'457	5'552
Switzerland	3'104	3'325	3'553	3'887	3'914	4'107	4'106	4'231	4'595	4'905	5'068	5'092	5'260	5'565	5'924	6'159	6'466	6'808	6'866	6'978	7'138
United Kingdom	1'672	1'893	2'109	2'353	2'473	2'734	2'736	2'932	3'071	3'204	3'271	3'390	3'452	3'587	3'691	3'780	3'832	3'989	4'096	4'289	4'500
USA	4'262	4'536	4'888	5'316	5'726	6'088	6'443	6'814	7'167	7'387	7'646	7'880	8'081	8'348	8'533	8'950	9'399	9'777	10'106	10'528	10'948

Ratio Switzerland/Country - Current expenditure on health, per capita.

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Canada	1.362	1.357	1.355	1.409	1.344	1.316	1.247	1.214	1.240	1.274	1.283	1.225	1.245	1.284	1.339	1.359	1.396	1.351	1.336	1.309	1.329
Finland	1.928	1.772	1.793	1.766	1.719	1.657	1.596	1.538	1.530	1.512	1.542	1.485	1.462	1.470	1.506	1.557	1.620	1.659	1.629	1.594	1.566
Germany	1.150	1.149	1.181	1.200	1.176	1.211	1.197	1.187	1.226	1.240	1.217	1.151	1.152	1.173	1.196	1.196	1.221	1.201	1.152	1.109	1.095
Netherlands	1.308	1.256	1.233	1.179	1.183	1.175	1.146	1.106	1.128	1.120	1.141	1.137	1.152	1.164	1.203	1.248	1.312	1.336	1.307	1.260	1.244
Spain	2.265	2.183	2.173	2.155	1.943	1.935	1.856	1.769	1.851	1.836	1.844	1.859	1.924	2.040	2.143	2.155	2.141	2.162	2.068	2.026	1.983
Sweden	1.584	1.515	1.481	1.474	1.463	1.481	1.461	1.407	1.425	1.436	1.466	1.483	1.179	1.189	1.252	1.266	1.292	1.328	1.316	1.279	1.286
Switzerland	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
United Kingdom	1.857	1.756	1.685	1.652	1.583	1.502	1.501	1.443	1.496	1.531	1.549	1.502	1.523	1.551	1.605	1.629	1.687	1.707	1.676	1.627	1.586
USA	0.728	0.733	0.727	0.731	0.684	0.675	0.637	0.621	0.641	0.664	0.663	0.646	0.651	0.667	0.694	0.688	0.688	0.696	0.679	0.663	0.652

Correction for different prices of healthcare services

Purchasing Power Parities for GDP, National currency per US$

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Canada	1.190	1.230	1.220	1.230	1.230	1.230	1.210	1.210	1.210	1.230	1.200	1.220	1.240	1.240	1.220	1.230	1.250	1.210	1.210	1.220	1.260
Finland	0.992	0.984	1.000	0.998	1.000	0.973	0.979	0.953	0.935	0.912	0.897	0.900	0.898	0.908	0.905	0.907	0.908	0.881	0.864	0.855	0.862
Germany	0.954	0.943	0.930	0.913	0.896	0.875	0.873	0.848	0.837	0.820	0.811	0.805	0.789	0.787	0.775	0.769	0.778	0.753	0.745	0.736	0.750
Netherlands	0.906	0.891	0.905	0.901	0.926	0.908	0.897	0.872	0.860	0.848	0.848	0.854	0.836	0.824	0.798	0.809	0.810	0.795	0.782	0.778	0.794
Spain	0.739	0.740	0.748	0.742	0.759	0.766	0.770	0.736	0.732	0.726	0.719	0.727	0.714	0.695	0.675	0.662	0.665	0.643	0.631	0.633	0.632
Sweden	9.310	9.160	9.400	9.410	9.490	9.290	9.480	9.110	8.870	8.780	8.920	9.020	8.840	8.650	8.600	8.730	8.850	8.820	8.850	8.880	8.990
Switzerland	1.800	1.790	1.770	1.710	1.720	1.690	1.690	1.600	1.530	1.490	1.470	1.470	1.400	1.350	1.310	1.280	1.240	1.200	1.190	1.180	1.180
United Kingdom	0.726	0.705	0.695	0.690	0.696	0.688	0.708	0.696	0.709	0.702	0.710	0.702	0.706	0.702	0.695	0.698	0.693	0.689	0.685	0.688	0.687
USA	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Ratio Switzerland/Country - Purchasing Power Parities for GDP.

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Canada	1.513	1.455	1.451	1.390	1.398	1.374	1.397	1.322	1.264	1.211	1.225	1.205	1.129	1.089	1.074	1.041	0.992	0.992	0.983	0.967	0.937
Finland	1.815	1.819	1.770	1.713	1.720	1.737	1.726	1.679	1.636	1.634	1.639	1.633	1.559	1.487	1.448	1.411	1.366	1.362	1.377	1.380	1.369
Germany	1.887	1.898	1.903	1.873	1.920	1.931	1.936	1.887	1.828	1.817	1.813	1.826	1.774	1.715	1.690	1.664	1.594	1.594	1.597	1.603	1.573
Netherlands	1.987	2.009	1.956	1.898	1.857	1.861	1.884	1.835	1.779	1.757	1.733	1.721	1.675	1.638	1.642	1.582	1.531	1.509	1.522	1.517	1.486
Spain	2.436	2.419	2.366	2.305	2.266	2.206	2.195	2.174	2.090	2.052	2.045	2.022	1.961	1.942	1.941	1.934	1.865	1.866	1.886	1.864	1.867
Sweden	0.193	0.195	0.188	0.182	0.181	0.182	0.178	0.176	0.172	0.170	0.165	0.163	0.158	0.156	0.152	0.147	0.140	0.136	0.134	0.133	0.131
Switzerland	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
United Kingdom	2.479	2.539	2.547	2.478	2.471	2.456	2.387	2.299	2.158	2.123	2.070	2.094	1.983	1.923	1.885	1.834	1.789	1.742	1.737	1.715	1.718
USA	1.800	1.790	1.770	1.710	1.720	1.690	1.690	1.600	1.530	1.490	1.470	1.470	1.400	1.350	1.310	1.280	1.240	1.200	1.190	1.180	1.180

Correction for healthcare costs changes over time

Healthcare cost growth rate in Switzerland, %

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Switzerland	3.13%	4.21%	6.23%	4.10%	3.78%	3.91%	2.00%	1.26%	4.57%	5.57%	4.43%	2.30%	2.68%	3.53%	3.92%	3.34%	4.14%	4.13%	2.82%	0.75%	2.78%

Overall healthcare cost increase depending on reference year.

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Switzerland	1.9955	1.9147	1.8025	1.7316	1.6685	1.6057	1.5743	1.5547	1.4867	1.4083	1.3485	1.3182	1.2838	1.24	1.1932	1.1546	1.1087	1.0648	1.0355	1.0278	1

Example: To adjust the costs for 2019, all costs reported for the year 2005 should be multiplied with 1.5747 (i.e., the costs in 2019 are 57.47% higher than in 2005)

13.5 CHEERS 2022 checklist

Title and abstract		
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.
Introduction		
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.
Methods		
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).
Setting and location	6	Provide relevant contextual information that may influence findings.
Comparators	7	Describe the interventions or strategies being compared and why chosen.
Perspective	8	State the perspective(s) adopted by the study and why chosen.
Time horizon	9	State the time horizon for the study and why appropriate.
Discount rate	10	Report the discount rate(s) and reason chosen.
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.
Measurement and valuation of resources and costs	14	Describe how costs were valued.
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.

Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.
Results		
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study
Discussion		
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.
Other		
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.

13.6 CHEERS 2022 evaluation of the identified literature

Authors, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q23	Q24	Q25	Q26	Q27	Q28
Getsios et al. 2010	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	0	0.5	1	1	0	1	0.5	1
López-Bastida et al. 2009	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0.5	0	0	1	1	0	0.5	1	1	0	1	1	0
Teipel et al. 2007	1	1	1	0	**0**	1	0.5	1	1	1	1	1	0.5	1	1	0.5	0.5	0	0	0.5	0	0.5	1	1	0	1	1	1
Happich et al. 2005	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0.5	1	0	1	1	0	1	1	1	0	1	0	1
Hartz et al. 2012	1	1	1	0	0.5	1	1	1	1	1	1	1	1	1	1	0.5	1	0	1	1	0	1	1	1	0	1	1	1
Baladi et al. 2000	0.5	1	1	0	**0**	**0**	0.5	1	1	1	1	0	0	1	1	0	0	0	0	0	0	0	**0**	0	0	1	1	0
Courtney et al. 2004	0	1	1	0	1	1	1	1	1	0	1	1	1	1	**0**	0	0	1	1	0	1	1	1	1	0	1	1	1
da Silva et al. 2019	0.5	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0.5	0	0	1	0.5	0	1	1	1	0	1	1	1
Fagnani et al. 2004	0.5	1	1	0	0.5	1	1	1	1	1	1	1	1	1	**0**	0.5	0	0	0	0.5	0	0.5	1	0.5	0	0.5	1	0
Fuh et al. 2008	1	1	1	0	1	1	0.5	1	1	1	1	1	1	1	**0**	0.5	0	0	0	1	0	1	1	1	0	1	1	0
Garfield et al. 2002	1	1	1	0	0.5	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	0	0.5	**0**	1	0	0.5	1	1
Guo et al. 2010	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	0	1	1	1	1	1	1	1
Hauber et al. 2000	0	1	1	0	0.5	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	0	0	0.5	**0**	0	0	1	1	1
Kongpak-wattana et al. 2020	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	0	1	1	1	0	1	1	1
Marin et al. 2003	1	1	1	0	**0**	**0**	1	1	1	0	1	1	1	1	1	0.5	1	1	0	1	1	0.5	**0**	0.5	0	1	1	1
Migliac-cio-Walle et al. 2003	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0.5	1	0	0	1	0	1	1	1	0	1	1	0
Suh et al. 2008	1	0.5	1	0	1	1	1	1	1	1	1	1	1	0	0.5	0	1	0	0	1	0	0.5	**0**	1	0	1	1	0

Wimo et al. 2003 (donezepil)	1	0.5	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	0.5	1	1	0	1	1	0
Wimo et al. 2003 (memantine)	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	0	0	0	0	1	0	1	1	1	0	1	0	1
Willan et al. 2006	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	0	0	0	0	0	0	1	**0**	0	0	1	1	1
Yunusa et al. 2021	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	0.5	1
Knapp et al. 2017	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	0.5	0	0.5	1	0.5	0	1	1	1
Bond et al. 2012	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	0	1	1	1	1	1	1	1
Hoogveldt et al. 2011	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0.5	0	0	0	1	0	0.5	1	1	0	1	0	1
Gagnon et al. 2007	1	1	1	0	0.5	1	1	1	1	1	1	1	1	1	1	0.5	0	0	0	1	0	0.5	1	1	0	1	1	0
Antonanzas et al. 2006	1	1	1	0	0.5	1	1	1	1	1	1	1	1	1	1	0.5	0	0	0	1	0	1	1	1	0	1	0	0
Loveman et al. 2006	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0.5	0	0	0	0	0	0	**0**	0	1	1	1	0
Jönsson 2005	1	1	1	0	0.5	1	1	1	1	1	1	1	1	1	1	0.5	1	0	1	0	0	1	1	1	0	1	1	0
Francois et al. 2004	1	1	1	0	0.5	1	1	1	1	1	1	1	1	1	1	0.5	1	0	1	1	0	1	1	1	0	0.5	1	1
Jones et al. 2004	1	1	1	0	0.5	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	0	1	1	1	0	1	1	0

13.7 Additional remark on conflict of interest

Comment: following table briefly illustrate whether a conflict of interest was declared or not (CHEERS 2022 Q28) as well as if a conflict was present or not (presence of a conflict of interest). In 12 studies the presence of a conflict of interest was declared, while in 6 studies the absence of a conflict of interest was stated. A total of 12 studies did not provide information concerning potential conflicts of interest. In 7 of them one or more author were affiliated to a pharmaceutical industry.

Authors, year	Q28 (Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.)	Presence of a conflict of interest
Getsios et al. 2010	1	1
López-Bastida et al. 2009	0	NR
Teipel et al. 2007	1	0
Happich et al. 2005	1	0
Hartz et al. 2012	1	1
Baladi et al. 2000	0	NR (but first Author works for industry)
Courtney et al. 2004	1	1
da Silva et al. 2019	1	1
Fagnani et al. 2004	0	NR
Fuh et al. 2008	0	NR
Garfield et al. 2002	1	0
Guo et al. 2010	1	1
Hauber et al. 2000	1	1
Kongpakwattana et al. 2020	1	NR
Marin et al. 2003	1	1
Migliaccio-Walle et al. 2003	0	NR (but 1 author work for industry...)
Suh et al. 2008	0	NR (but 1 author work for industry...)
Wimo et al. 2003 (donezepil)	0	NR (but several authors work for industry)

Wimo et al. 2003 (meman-tine)	1	1
Willan et al. 2006	1	1
Yunusa et al. 2021	1	0
Knapp et al. 2017	1	1
Bond et al. 2012	1	0
Hoogveldt et al. 2011	1	1
Gagnon et al. 2007	0	NR (but several authors work for industry...)
Antonanzas et al. 2006	0	NR (but several authors work for industry...)
Loveman et al. 2006	0	0
Jönsson 2005	0	NR
Francois et al. 2004	1	1
Jones et al. 2004	0	NR (but 1 author work for industry...)

Abbreviations: NR = not reported

13.8 Costs originally reported in the identified health economic studies

Costs originally reported in the identified health economic studies (healthcare perspective).

Authors, year	Country	Intervention	Comparator	PICO	Cost year	Currency	Time horizon	Mean intervention costs	Mean control costs	Incremental costs
Getsios et al. 2010	UK	donepezil	Placebo	1	2007	GBP	10	88,875	91,212	-2,337
López-Bastida et al. 2009	ES	donepezil	Placebo	1	2006	EUR	0.5	1,136	542	594
López-Bastida et al. 2009	ES	donepezil	Placebo	1	2006	EUR	1	2,302	1,136	1,166
López-Bastida et al. 2009	ES	donepezil	Placebo	1	2006	EUR	1.5	3,429	2,302	1,127
López-Bastida et al. 2009	ES	donepezil	Placebo	1	2006	EUR	2	4,543	3,429	1,114
López-Bastida et al. 2009	ES	donepezil	Placebo	1	2006	EUR	2.5	5,664	4,543	1,121
Happich et al. 2005	DE	galantamine	Placebo	1	2004	EUR	5	24,600	24,349	251
Hartz et al. 2012	DE	donepezil	Placebo	1	2008	EUR	10	119,856	126,863	-7,007
Guo et al. 2010	DE	galantamine	Placebo	1	2009	EUR	10	40,116	43,459	-3,343
Migliaccio-Walle et al. 2003 [a]	US	galantamine	Placebo	1	2000	USD	10	64,260	66,669	-2,409
Migliaccio-Walle et al. 2003 [b]	US	galantamine	Placebo	1	2000	USD	10	63,068	66,669	-3,601
Wimo et al. 2003	Mixed (SE)	donepezil	Placebo	1	1999	SEK	1	20,235	7,554	12,681
Wimo et al. 2003	US	memantine	Placebo	2	1999	USD	0.5	2,844	865	1,978
Yunusa et al. 2021	US	memantine	NPT	2	2020	USD	20	16,102	12,713	3,389
Knapp et al. 2017	UK	memantine	Placebo	2	2013	GBP	1	6,599	5,755	844
Bond et al. 2012	UK	memantine	NPT	2	2009	GBP	20	55,979	55,690	289
Hoogveldt et al. 2011	NL	memantine	SC	2	2006	EUR	5	36,381	37,647	-1,266
Gagnon et al. 2007	CA	memantine	NPT	2	2005	CAD	2	24,847	25,268	-422
Antonanzas et al. 2006	ES	memantine	NPT	2	2005	EUR	2	7,949	8,169	-220
Jönsson 2005	SE	memantine	NPT	2	2004	SEK	5	656,021	727,683	-71,662

Francois et al. 2004	FI	memantine	NPT	2	2001	EUR	5	28,876	29,433	-557
Jones et al. 2004	UK	memantine	NPT	2	2003	GBP	2	43,139	44,538	-1,399
Willian et al. 2006	CA	rivastigmine	Placebo	3	2004	CAD	0.5	NA	NA	719.76
Willian et al. 2006	UK	rivastigmine	Placebo	3	2004	GBP	0.5	NA	NA	451.17

[a] *Galantamine dosage 16 mg/day,* [b] *Galantamine dosage 24 mg/day.*

13.9 Strategy targeted search ELSO

Concept 1 - Antidementia drug	(("Dementia"[Mesh] AND “drug therapy”[Title/Abstract]) OR (“antidementia drug”[Title/Abstract] OR antidementia*[Title/Abstract] OR “dementia drug”[Title/Abstract]))
Concept 2 - Ethical, social, legal items	("Ethical Analysis"[Mesh] OR "Legislation, Drug"[Mesh] OR "Social Change"[Mesh] OR (ethics[Title/Abstract] OR legal[Title/Abstract] OR law[Title/Abstract] OR social[Title/Abstract]))
Concept 3 - Organizational items	("Organization and Administration"[Mesh] OR "Policy"[Mesh] OR "Insurance, Health"[Mesh] OR "Insurance Coverage"[Mesh] OR "Drug Approval"[Mesh] OR "Health Services Accessibility"[Mesh] OR (organization[Title/Abstract] OR policy[Title/Abstract] OR approval[Title/Abstract] OR coverage[Title/Abstract] OR regulation[Title/Abstract] OR regulatory[Title/Abstract] OR reimburse*[Title/Abstract] OR access[Title/Abstract] OR disinvestment[Title/Abstract] OR “drug dispensing”[Title/Abstract]))