Long-term treatment response, predictors and biochemical markers in Alzheimer's disease.

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Abstract

Alzheimer's disease (AD) is clinically characterised by an insidious onset with progressive symptoms of memory impairment, dysphasia, dyspraxia, dygnosia and visuospatial difficulties. Degeneration of neurons in specific regions of the brain, formation of senile plaques and neurofibrillary changes are some of the neuropathological features of the disease. As a result of the degenerating process a deficiency in cholinergic function occurs in AD. This has been a target for therapy since the cholinesterase inhibitors (ChEIs) (tacrine, donepezil, rivastigmine, galantamine) were introduced as treatments for AD. Multiple short-term randomised clinical trials of ChEI treatment show beneficial effects on cognition, global functioning and activities of daily living in AD. Whether the effects of long-term ChEI treatment in a routine clinical setting are equally positive remains to be investigated. In the present study patients from naturalistic settings were investigated in long-term treatment studies (tacrine-study and The Swedish Alzheimer Treatment Study, SATS). Patients were repeatedly assessed with cognitive scales and global ratings over 3-5 years. A positive response to treatment was described in different response models. At 6 months 3/4 of the patients and at 3 years 1/3 were better or unchanged. Treatment for more than a year and positive response to tacrine treatment delayed nursing-home placement but did not influence survival. CSF T-tau and P-tau were possible markers for disease severity and P-tau for the abundance of symptoms in AD. A fast pre-treatment progression rate was a positive predictor for response to ChEI treatment even after adjusting for disease severity, another positive predictor of response. Baseline factors such as age, gender, CSF biomarkers and APOE genotype did not predict response to treatment. Dropout in these naturalistic settings was lower than expected. ChEI treatment changed the progression of the disease for more than 6 months and stabilised groups of patients for even longer.

Key words: Alzheimer's disease, cholinesterase inhibitor, treatment response, predictors, CSF-biomarkers, pre-treatment progression

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Contents

Abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale—cognitive subscale
ADL	Activities of Daily Living
Aß	Beta amyloid
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase inhibitor
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
Aß42	Beta-amyloid 1–42
Aß40	Beta-amyloid 1–40
BuChE	Butyrylcholinesterase
BuChEI	Butyrylcholinesterase inhibitor
CNS	Central nervous system
CIBIC	Clinician Interview-Based Impression of Change
ChE	Cholinesterase
ChEI	Cholinesterase inhibitor treatment
CSF	Cerebrospinal fluid
CT	Computerized tomography
CYP	Cytochrome P
DAD	Disability Assessment for Dementia
DSM-IV	Diagnostic and Statistical manual of Mental disorders, 4th edition
ELISA	Enzyme-Linked Immunosorbent Assay
FAD	Familiar Alzheimer's disease
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Disease 10th edition
M1, M2	Muscarinic receptors type 1 and 2
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
NGF	Nerv growth factor
NMDA	N-methyl-D-aspartate
NFT	Neurofibrillary tangles
NHP	Nursing-home placement

NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PDS	Progressive Deterioration Scale
PET	Positron emission tomography
PS-1	Presenilin 1
PS-2	Presenilin 2
PSMS	Physical Self-Maintenance Scale
RCTs	Randomised clinical trials
SATS	Swedish Alzheimer Treatment Study
T-tau	Total tau
P-tau	Phosphorylated tau
qEEG	Quantified elecroencephalography

Introduction

Background

In 1901, when Alois Alzheimer was a senior at the Municipal Mental Asylum in Frankfurt am Main, a 51-year-old woman was admitted to the clinic. She was disoriented, had speech difficulties and suffered from paranoia and hallucinations. When she died in 1906 Alzheimer performed an autopsy and used the new staining methods he and his co-worker Nissl had developed. He described organic changes in the brain such as cortical atrophy, senile plaques and neurofibrillary tangles (NFT) (Alzheimer 1907). Using The Bielschowsky silver method Alzheimer saw thick coiled masses of fibers, both in the cytoplasma of cells and freely in the brain. This led him to form the hypothesis that a chemical change had occurred in the neurofibrills causing cell death and leaving tangles as a marker of this cell death (Alzheimer 1911). Four similar cases were reported in the years to follow by Bonfiglio (1908), Sarteschi (1909) and Perusini (1909). Based on these five cases Emil Kraepelin described the novel disease Alzheimer's (AD) as a presenile disease "senium precox" in his textbook, Psychiatrie 1910. During the same time period Otto Fischer, a member in a group led by Arnold Pick in Prague, was doing extensive research on the senile plaques seen in senile dementia. He did not support the idea of a separate diagnosis of AD or that there was a difference in senile dementia and in Alzheimer dementia. It was, however Kraepelin's point of view that dominated for many years and the diagnosis of AD was equal to a presenile disease with a debut before the age of 65 (Beach 1987). For many years dementia occurring late in life, senile dementia, was considered to be caused by aging or arterosclerosis. This point of view changed in the 1960s. Alzheimer pathology was identified also in senile dementia and the distinctive focal features (parietal lobe symptoms) of apraxia, agnosia and aphasia were also described in senile forms of AD (Lauter and Meyer 1968). Today the diagnosis of Alzheimer's disease is used both for early onset AD (onset before 65 years) and late onset AD (onset after 65 years). In recent years however the role of vascular changes and vascular risk factors in AD is once again a point of interest (Ott et al. 1999; Luchsinger et al. 2005).

Epidemiology

Approximately 28 million people suffer from dementia worldwide (Wimo et al. 2006). AD is the most common neurodegenerative dementia accounting for 50%–70% of dementia cases (Ott et al. 1995; Fratiglioni et al. 2000a). Both the prevalence and the incidence of AD increase exponentially up to the age of 90 (Jorm et al. 1987;

Jorm and Jolle 1998; Fratiglioni et al. 1999) and the incidence probably continues to increase even in the very old (Fratiglioni et al. 2000a). No gender differences were found in the incidence of AD (Jorm and Jolle 1998) but women have been described to have a higher incidence in the older ages (Fratiglioni et al. 2000a). The prevalence of late onset AD between the ages of 65–70 is 0.6 %. The prevalence doubles every 5 years and after 90 years of age at least 22% are affected (Lobo et al. 2000). The total prevalence of AD above 65 years of age is about 4.4% (Lobo et al. 2000). Early onset AD (onset before 65) is very rare and in a population aged 55–106 approximately 2 % of the total AD cases had an early onset (Ott et al. 1995). With increasing age in the population of the world AD is a major health problem.

Genetics

Observations that patients with trisomy 21 (Down's syndrome) invariably develop AD and that in some families (Selkoe and Podlisny 2002) AD appears to be inherited in a manner consistent with an autosomal dominant trait, led to the search for AD-genes.

Autosomal dominantly inherited AD

A linkage between chromosome 21 and familiar AD (FAD) was described in 1987 (St George-Hyslop et al. 1987) and the first mutation in the gene coding for the amyloid precursor protein (APP) in chromosome 21 was later identified in a family with autopsy verified AD (Goate et al. 1991).

Since then several different APP mutations localised in Chromosome 21 have been identified. The APP mutations code for regions where the APP protein is split by α-, β-, or γ-secretase and these mutations are the cause of enhanced levels of Aβ peptides (Selkoe 1997).

Two other genes, presenilin-1 (PS-1) on chromosome 14 (Sherrington et al. 1995) and presenilin-2 (PS-2) on chromosome 1 (Levy-Lahad et al. 1995), have also been identified in FAD. Both genes code for large transmembraneous proteins and these mutations lead to higher levels of Aß peptides (Lemere et al. 1996; Selkoe 1997).

In the autosomal dominant inherited AD approximately 50% have PS-1 mutations, and 15% have APP mutations. PS-2 mutations, however, are very rare (Campion et al. 1999). Still in 30–40% of autosomal dominant inherited AD no mutations can be identified (Campion et al. 1999). Most autosomal dominant inherited AD cases have an early onset, but some cases have an onset later in life. There is a risk that the possibility of an autosomal dominant disease in late onset AD is not acknowledged (Selkoe 2001).

APOE genotype

Apolipoprotein E (Apo E) is a protein that assists cells in the uptake of lipoproteins. In the brain it is synthesised by astrocytes. In brain injuries, when neurons are damaged, the protein ApoE is produced to take care of the excess cholesterol and lipids coming from dead neurons (Weisgraber and Mahley 1996; Mahley et al. 2006). There is a polymorphism in the *APOE* gene. Three different alleles exist: ε2, ε3, and ε4. The *APOE* ε4 allele is associated with increased risk of late onset AD of both familiar and sporadic forms (Strittmatter et al. 1993; Saunders et al. 1993). The *APOE* ε4 allele is also associated with an earlier onset of AD in both sporadic and familiar cases (Corder et al. 1993). Compared to individuals with the most common *APOE* genotype, ε3/ ε3, individuals with one ε4 allele are approximately three times more likely to develop AD, and those with two ε4 alleles are 8–10 times more likely to develop AD (Farrer et al. 1997; Bertram and Tanzi 2001; Selkoe and Podlisny 2002). The *APOE* ε2 allele on the other hand lowers the risk for AD and increases the age of onset (Corder et al. 1993). Having two ε4 alleles does not invariantly cause AD, and AD without the e4 allele occurs (Selkoe and Podlisny 2002). Thus *APOE* ε4 is a susceptibility gene (risk factor) for AD (Saunders et al. 1993). The mechanism by which the *APOE* ε4 allele increases the risk of AD is not fully understood, however a decrease in the beta amyloid (Aβ) peptide clearance (Selkoe and Podlisny 2002) or an effect on lipid homeostasis effecting APP processing have been proposed (Poirier 2000).

APOE genotype testing can be provided by companies via the internet (Couzin 2008). The testing of healthy people is, however, not recommended by health authorities (Ags Ethics Committee 2001) as the results could be difficult for the individual to interpret and cope with (Gooding et al. 2006). Issues such as this as well as genetic testing as a requirement for health insurance coverage are challenges that will have to be addressed in the future.

Other risk genes

The APOE ε4 allele has been calculated to account for the majority of the genetic risk in sporadic AD. Thus the contribution of other genes is probably minor. Many other putative genes have however, been discussed among them genes located on chromosome 11, 12 and 9. Verifications of the first positive reports in larger populations are needed (Waring and Rosenberg 2008).

Risk factors

The most consistent risk factors for sporadic AD include family history, *APOE* ε4 allele and high age (Fratiglioni et al. 2000a; Lindsay et al. 2002). Hypertension and

high cholesterol levels in midlife have been proposed as independent risk factors for development of AD later in life (Kivipelto et al. 2002). Moreover, life style components such as a fuctioning social network (Fratiglioni et al. 2000b), higher education levels and mental and physical activity (Yoshitake et al. 1995) could protect against dementia (Fratiglioni et al. 2004). Whether head trauma, female gender, alcohol use or smoking are risk factors for AD remains ambiguous (Wang et al. 1999; Launer et al. 1999; Lindsay et al. 2002; Jellinger 2004).

Hypotheses of AD

Along with the sequencing of the β-amyloid peptide in plaques (Masters et al. 1985a) and the revelation of the APP gene on chromosome 21 (St George-Hyslop et al. 1987) the amyloid cascade hypothesis was introduced (Hardy and Allsop 1991; Selkoe 1991, Hardy and Higgins 1992). This hypothesis postulated that β-amyloid accumulation was the primary event starting the degenerative process in AD eventually leading to production of tangles and cell death. The amyloid cascade hypothesis has been modified since its introduction. The senile plaques are now regarded more as reservoirs of toxic Aβ rather than being toxic in themselves (Hardy and Selkoe 2002) whereas the Aβ42 fragment has been identified as the toxic component (Hardy 2006). The Aβ42 fragment is formed by the splicing of the protein APP by the enzymes β- and γ-secretase (Figure 1).

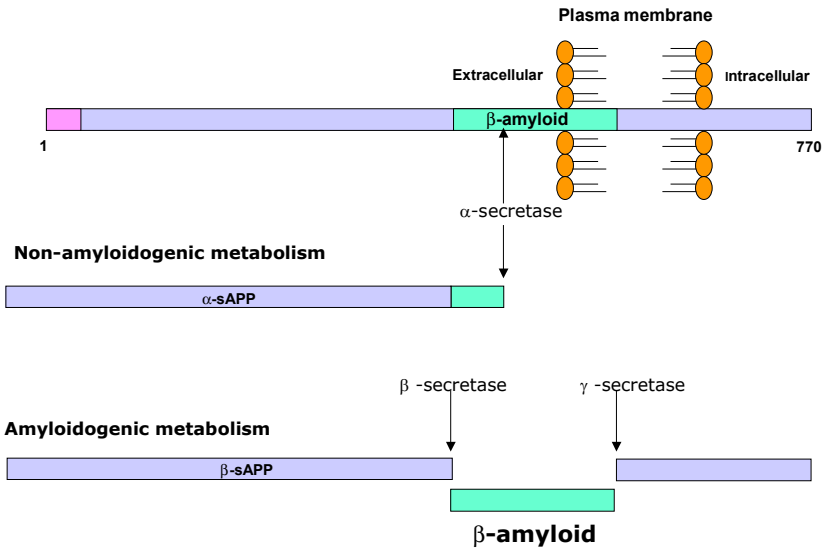

Figure 1. APP and Aβ metabolism. *Drawing by Kaj Blennow*

Another theory, the tau hypothesis (tauism), states that the primary critical step toward AD pathology is the abnormal hyper-phosphorylation of tau (Grundke-Iqbal et al. 1986). Tau is a protein, located in the axons of neurons stabilizing the microtubules (Matus 1994) involved in the axonal transport within the neuron. In AD the tau protein is abnormally phosphorylated (Grundke-Iqbal et al. 1986; Goedert et al. 1994), resulting in an unstable cytoskeleton, deranged axonal transport and eventually cell death.

There are different observations that support the amyloid cascade hypothesis. For example, mismetabolism of APP is a critical feature in the known hereditary forms of AD and transgenic mice with mutant human tau and APP develop more tangles compared to mice overexpressing tau alone (Lewis et al.2001).

The most frequently voiced objection against the amyloid cascade hypothesis is that the number of plaques does not correlate with the level of cognitive impairment in AD but the extent of spread of neurofibrillary tangles does (Braak and Braak 1991; Giannakopoulos et al. 2003). Some studies have suggested a correlation between neuritic plaques and cognitive impairment (Cummings et al. 1996) but these findings have been criticised (Silverman et al. 1996).

Both amyloid deposition and tau phosphorylation are presumably crucial in AD pathogenesis but further investigation is needed to understand the link between the two (Lovestone 1996; Mudher and Lovestone 2002). Alternative AD hypotheses have been proposed including cholesterol and inflammatory pathways (Höglund and Blennow 2007) but they are beyond the scope of this thesis.

Clinical features

In AD the pathological processes probably start years or even decades before the first clinical symptoms appear (Price and Morris 1999). In the first phase (preclinical phase) there are no evident symptoms. This is followed by a phase of mild cognitive impairment (MCI) (prodromal phase)(Hodges 1998) were affective and/or cognitive symptoms appear. The term MCI is however not equivalent with pre AD since the MCI entity is a condition with a heterogeneous aetiology (Petersen et al. 1999; Petersen 2004). In recent years researchers have struggled to find methods to accurately diagnose Alzheimer's disease as early as in the prodromal phase (Winblad et al. 2004; Hansson et al. 2006). This work will be essential when new disease modifying AD drugs become available (Winblad et al. 2004). The earliest cognitive symptom in the prodromal phase of AD is memory impairment (episodic memory) (Petersen et al. 1994). When the disease progresses from amnestic MCI towards diagnosable AD other symptoms appear.

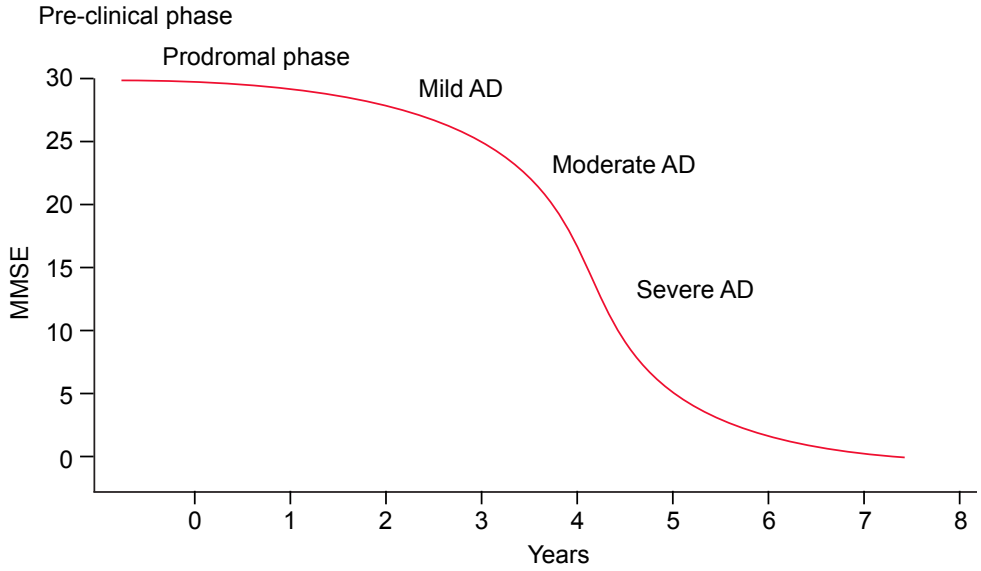

Figure 2. Clinical course of Alzheimer's disease.

A three-stage model of AD symptoms in a mild, moderate and a severe stage has been used. In the first stage the memory impairment is followed by one or more other areas of impairment such as difficulty with orientation, speech (dysphasia), practical abilities (dyspraxia), and recognising objects and faces (dysgnosia) as well as visuospatial difficulties (Cummings and Benson 1986). In addition social and functional impairment and reduced executive functioning appear. The transition from the MCI phase to manifest AD is however gradual and the clinicians have to use their experience and judgment to diagnose AD rather than rely on a cut off score on a scale (Petersen 2004). The progression of AD is typically slow especially in the early stages but a heterogeneity of both progression rates (Agüero-Torres et al. 1998) and clinical manifestations exist. The patient's personality is well preserved and at this stage the patient is often aware of the difficulties and reacts to them. Lack of insight can on the other hand be a prominent feature in some cases.

In the moderate stage of AD the symptoms become more pronounced and gradually lead to a lack of independence. By the end of this phase the patient must often move to a nursing home.

In the severe stage of the illness the patient becomes more passive and need help with all tasks of ADL including dressing, eating and going to the bathroom. Muscle rigidity can set in, epileptic seizures can occur and eventually the patient dies as a consequence of the disease.

AD is often associated with psychiatric symptoms such as lack of vigour, anxiety, depression, hypochondria and paranoid reactions (Burns et al. 1990a; Burns et al. 1990b; Lyketsos et al. 2002). Depression is most prominent in the early phase (Burns et al. 1990a) but psychotic symptoms often occur in the more severe stages (Ropacki and Jeste 2005). Different medical strategies can be used to treat these symptoms. The behavioural and psychiatric symptoms (BPSD) often result in the use of psychotropic medication (Selbaek et al. 2007) and sometimes even the use of constraints (Kirkevold et al. 2004). This can increase the risk for adverse events and falls in nursing home populations.

Progression rate

There is a large variability in the progression rate in the AD population (Agüero-Torres et al. 1998; Holmes and Lovestone 2003). Why this is so is not fully understood.

Factors that have previously been suggested to be of importance in enhanced progression rates include extrapyramidal signs (Stern et al. 1994), early age at onset (Jacobs et al. 1994), aphasia (Bracco et al. 1994), *APOE* ε4 allele (Craft et al. 1998), and tau pathology (Wahlund and Blennow 2003). Conflicting results stating that progression is independent of extrapyramidal signs (Burns et al. 1991) age at onset (Bracco et al. 1994), and aphasia (Burns et al. 1997) and *APOE* ε4 allele (Frisoni et al. 1995) have however also been reported.

Mortality

Alzheimer disease is associated with increased risk of death, compared to age-matched non-demented individuals (Agüero-Torres et al. 1999). In older studies AD patients' survival was reported to be 6–8 years from onset till death (Barclay et al. 1985; Walsh et al. 1990). Predictors for shorter survival include impaired ADL status and co-morbidity (Bowen et al. 1996; Agüero-Torres et al. 1998; Heyman et al. 1996). Disease severity could predict survival in studies with a duration of 5 years or longer (Agüero-Torres et al. 1998). Other factors outlined as increasing the risk of death in AD, though not totally consistent in different trials, include increasing age (Heyman et al. 1996; Bowen et al. 1996), fast progression rates (Wilson et al. 2006; Carcaillon et al. 2007), male gender (Heyman et al. 1996; Bowen et al. 1996) and severe level of cognitive impairment (Bowen et al. 1996). In some studies early age of onset was independent of survival (Bracco et al. 1994) yet in others it was not (Ueki et al. 2001). The presence of the ApoEε4 allele has been associated with earlier death

in AD (Dal Forno et al. 2002) but other studies have shown conflicting results (Bonsignore and Heun 2003). One study did not show any association between increased mortality rate and a fast progression rate (Bonsignore and Heun 2003).

Diagnostic criteria

The clinical diagnosis of AD is currently based on the identification of dementia and specific clinical symptoms suggesting AD. In clinical practice the patient goes through a clinical investigation, including medical history, physical and neurological examination, cognitive testing, laboratory tests and a structural brain imaging (computerized tomography (CT) or magnetic resonance imaging (MRI)). This procedure aims to rule out other causes of dementia and symptoms are checked against clinical criteria manuals. Three criteria-based systems are used at present: the International Classification of Disease-10, ICD-10 (WHO 1992), the Diagnostic and Statistical Manual of Mental Disorders, 4th ed, DSM-IV (American Psychiatric Association 1994) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and related Disorders Association, NINCDS-ADRDA (McKhann et al. 1984).

ICD-10

The diagnosis of AD in clinical practice in Sweden is based on the International Classification of Disease-10, ICD-10 (WHO 1992). Symptoms such as deterioration of memory and thinking to a degree sufficient to impair the function in daily living (ADL) must be present. Memory impairment includes registration, storage and retrieval of new information. An insidious onset, slow deterioration and absence of other diseases are required. In this classification system the symptoms must have been present for at least 6 months and the age of onset, either before or after 65, is defined.

DSM-IV

Dementia is defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, DSM-IV, (American Psychiatric Association 1994), DSM-IV, text revision, (American Psychiatric Association 2000) as a disturbance in more than one area of higher cortical function i.e. objective evidence of memory impairment and at least one additional area of dysfunction (aphasia, apraxia, agnosia, disturbance in executive functioning). The cognitive disturbances represent a significant change from a previous higher level of functioning and interfere with occupational or social functioning. According to the DSM-IV AD involves a gradual onset and a progressive worsening of symptoms. The consciousness may not be clouded and other causes of dementia must be ruled out, for example cerebrovascular disease, Parkinson's disease, Huntington's disease, systemic diseases and drug induced conditions.

NINCDS-ADRDA

In AD research the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and related Disorders Association, NINCDS-ADRDA, are used (McKhann et al. 1984). In this manual the criteria for AD is divided into definite, possible or probable AD. A *definite* diagnosis of AD can only be obtained by neuropathological investigations of AD and clinical criteria prior to death of probable AD. For *probable AD* deficits in two or more areas of cognitive functions (orientation, memory, aphasia, apraxia, attention, agnosia, problem solving, social ability) are required. In the NINCDS-ADRDA criteria there is no requirement for a functional disability but progressive deterioration of symptoms, no disturbance of consciousness, onset between 40–90 and absence of other systemic or brain disease must be established. Supportive features and unlikely features are also listed.

The diagnosis of *possible AD* may be made on the basis of variation of clinical onset or in the presence of systematic or other disorders not considered to be the cause of dementia. Also in this case, if no other identifiable cause of dementia is identified but a gradual progressive severe cognitive deficiency is present the diagnosis of probable AD can be considered.

The diagnosis of dementia based on the clinical criteria of NINCDS-ADRDA has been evaluated in post mortem investigations giving a diagnostic accuracy of 65–96% (Tierney et al. 1988; Galasko et al. 1994; Kosunen et al. 1996). However, practical, economical and ethical difficulties often stand in the way of obtaining post-mortem confirmations in the clinical practice.

New criteria

It has recently been suggested that new methods such as the identification of cerebrospinal fluid (CSF) biomarkers, magnetic resonance imaging (MR) volumetric measures and positron emission tomography (PET) scans be incorporated in the diagnostic research criteria (Dubois et al. 2007). It is important to increase the accuracy of the diagnosis to be able to make the diagnosis of AD at an earlier stage as new treatments are becoming available. Validation of new criteria is, however necessary (Foster 2007).

Neuropathology

Macroscopic features of AD include atrophy of the cortex, predominately in the limbic structures (amygdala, hippocampus), and temporal and parietal regions. Frontal regions can be affected late in the disease but the sensory motor cortex is often spared. In severe AD brain mass is reduced and ventricles and sulci are widened as a result of atrophy.

The senile plaques were described for the first time as early as 1892 (Blocq and Marinesco 1892) while the neurofibrillary tangles (NFT) were described in 1907 by Alzheimer (Alzheimer 1907). The underlying neuropathological changes in AD include degeneration of neurons and synapses in defined regions of the brain and formation of senile plaques and neurofibrillary changes (Galasko et al. 1995; Jellinger 2008). The senile plaques consist of a protein core in which the main protein is beta-amyloid 1–42 (Aβ42) (Masters et al. 1985b; Braak and Braak 1991). Neurofibrillary changes in AD include NFT, neuropil threads and dystrophic neuritis (Braak et al. 2006). The distribution and abundance of the NFT in specific brain regions, (i.e. in the hippocampus and entorhinal cortex) increase with the progression of the disease (Braak and Braak 1991; Braak et al. 2006). Vascular changes such as cerebral amyloid angiopathy can also be seen in AD (Jellinger 2002). As a consequence of the lesions in various regions of the brain a reduced function of several neurotransmittor systems occur. Reduction of cholinergic neurons from the nucleus basalis of Meynert projecting to the hippocampus and cortex has a key role in the loss of memory, learning and attention (Whitehouse et al. 1982). Cell loss in locus ceruleus of noradrenegic neurons and loss of serotonergic cells in nucleus raphe (Zarow et al. 2003) can be linked to depressive symptoms in AD (Zweig et al. 1988). Dopaminergic cell loss in the substantia nigra may produce bradyphrenia and bradykinesia in AD (Burns et al. 2005).

The neuropathological diagnosis of AD is based on different diagnostic classification systems. One classification, the CERAD classification, is based on the senile plaque load (Mirra et al. 1991), in a classification by Braak et al based on the occurrence of NFT (Braak et al. 2006). The National Institute of Aging and Reagan criteria are based on both (The National Institute on Aging and The Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. 1997).

Biochemical markers

A clinically useful diagnostic marker should have a sensitivity exceeding 80 % and a specificity above 80 % according to the statement of the Consensus group for biomarkers (The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and The National Institute on Aging Working Group. 1998). Biochemical markers that reflect pathogenic processes in AD such as degeneration of neurons, Aß peptide accumulation in plaques and hyperphosporylation of tau would be valuable.

Cerebrospinal fluid biomarkers

The cerebrospinal fluid (CSF) surrounds the brain and thus biochemical changes in the brain could be detectible in the CSF.

In Sweden the CSF levels of β-amyloid 1–42 (Aβ42), total tau (T-tau) and phosphorylated tau (P-tau) are currently measured in routine clinical settings (Andreasen N. et al. 2001). In a typical AD case the level of CSF Aβ42 is lower, while T-tau and P-tau are higher than in healthy controls (see review (Blennow and Hampel 2003)). The sensitivity of the three CSF biomarkers in different studies was 90 % or above and the specificity was 86 % for Aβ42, 81 % for T-tau and 80 % for P-tau (Blennow and Hampel 2003). Thus the CSF biomarkers live up to the demands of a reliable biomarker (The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and The National Institute on Aging Working Group. 1998). In normal aging, depression, other psychiatric diseases and many other neurological diseases the levels of CSF-biomarkers are often normal.

ß-Amyloid (Aß)

ß Amyloid is found in the core of plaques (Braak and Braak 1991). The amyloid precursor protein (APP) is cleaved by different secretases (α-, β-, γ-) into shorter fragments. Different peptide fragments are produced, most frequently Aβ40 and Aβ42. The Aβ42 fragment has the highest tendency to aggregate and form oligomers and fibrils and ultimately form plaques. Why the cerebrospinal fluid (CSF) level of Aβ42 is reduced in AD is not fully understood (Miller et al. 1993; Jarrett et al. 1993; Motter et al. 1995; Andreasen and Blennow 2002). One theory is that Aβ42 gets stuck in brain plaques and this is supported by the fact that CSF levels of Aβ42 correlate with amyloid neuropathology (Strozyk et al. 2003). Low levels of CSF Aβ42 can however, also be found in diseases without plaques such as Creutzfeldt-Jacobs Disease (Otto et al. 2000).

Tau

Elevated CSF levels of ***total tau (T-tau)*** have been suggested to reflect the intensity of the neuronal damage and axonal degeneration in different conditions (Blennow and Hampel 2003). In Creutzfeldt-Jacobs Disease high levels of CSF T-tau are detected reflecting the high intensity of neural degeneration in this disease. In ischemic stroke transient elevation of CSF T-tau correlates with the size of infarction (Hesse et al. 2001). CSF T- tau is also elevated after blows to the head in boxing (Zetterberg et al. 2006). Moderately elevated levels of CSF T-tau is seen in AD (Arriagada et al. 1992) and have shown to positively correlate with neuropathological NFT load in this condition (Tapiola et al. 1997). Normal levels of CSF T-tau are found in depression, Parkinsons disease, progressive supranuclear palsy and alcohol dementia.

NFTs are paired helical filaments mostly consisting of pathologically phosphorylated tau. Elevated CSF levels of ***phosporylated tau (P-tau)*** in AD have been suggested not to reflect cerebral cell loss but to represent hyperphosphorylation of tau and

formation of NFT (Arriagada et al. 1992; Arai et al. 1995; Blennow et al. 1995; Tapiola et al. 1997; Andreasen 2003).

The fact that normal levels of P-tau are found in patients after acute stroke (Hesse et al. 2001), in vascular dementia and in Lewy body dementia (Sjögren et al. 2001; Parnetti et al. 2001) supports the theory that elevated P-tau may be AD specific.

Severity of dementia symptoms has in some studies correlated to higher CSF T-tau levels (Tato et al. 1995; Kanai et al. 1998) but not in others (Galasko et al. 1997; Andreasen et al. 1998). The individual levels of the CSF biomarkers have been shown to be stable over time (Andreasen et al. 1999b; Andreasen et al. 1999a; Zetterberg et al. 2007). Low levels of CSF Aβ42 and high levels of CSF T-tau and P-tau are found already years before AD symptoms appear in cases of mild cognitive impairment (MCI) that later convert to AD (Andreasen et al. 1999c; Buerger et al. 2002; Blennow and Hampel 2003; Hansson et al. 2006). It has been proposed that this might reflect the fact that the activity of the degenerative process remains stable during the different phases of dementia (Andreasen et al. 1998; Andreasen et al. 1999a). There is a large variability in the levels of the CSF T-tau within the AD population (Andreasen et al. 1999b). Similarly a large variability in the clinical expression (progression rate) has been described in AD. However the possibility of a connection between high levels of CSF T-tau and progression rates remains uncertain (Andreasen et al. 1999b; Wahlund and Blennow 2003).

Cholinergic treatment

Background

In the 1970s cognitive functioning and cholinergic mechanisms in AD were explored. Treatment with central acting anticholinergic drugs in healthy individuals was found to decrease their cognitive performance as opposed to cholinergic enhancers which improved the cognition in elderly individuals (Drachman 1977). Reports of reduced choline tranferase activity in the cerebral cortex of AD patients (Bowen et al. 1976) were followed by investigations localising loss of cholinergic neurons projecting from the brainstem and basal forebrain (Rossor et al. 1982; Whitehouse et al. 1982). The cholinergic deficit in AD was found to correlate with both cognitive and histological features (Perry et al. 1978) as well as behavioural disturbances (Whitehouse 1998). Thus, the cholinergic lesions in AD were not spread generally throughout the brain but rather selectively concentrated to specific regions of the brain.

Furthermore levels of the major receptors modulating cholinergic transmission in the central nervous system (CNS) were investigated. Loss of cholinergic nicotine receptors in the cortex (temporal areas) and hippocampus as well as reduction of muscarinic receptors (M2 but not the M1 receptor) were described in AD patients (Whitehouse 1998). The presynaptic M2 receptors regulate acetylcholine (ACh) release and the postsynaptic M1 receptors transduce signals to the postsynaptic neuron (Mash et al. 1985). Nicotine receptors are predominantly localized presynaptically and facilitate the release of acetylcholine in the CNS (Araujo et al. 1988). Acetylcholinesterase (AChE), the enzyme responsible for the degradation of acetylcholine into acetyl and choline, was found to be slightly reduced in postmortem AD patients (Perry et al. 1977) but butyrylcholinesterase (BuChE) activity was increased (Perry et al. 1978). All these findings formed the background of the early trials of cholinergic treatment for AD and the so called *"cholinergic hypothesis"* (Bartus et al. 1982). Different approaches for treatments were designed to facilitate the activity of the surviving cholinergic system (Lane et al. 2006). Precursor loading (choline, lecithin) (Heyman et al. 1987), and cholinergic agonists (muscarin) (Jones et al. 1992; Fisher et al. 1996), (nicotine)(Jones et al. 1992), were tried but the cholinesterase inhibitors (ChEIs) were the first compounds to show clinical efficacy with tolerable side-effects leading to the development of tacrine, the first drug approved for treating AD. Now for the first time patients suffering from AD could be offered treatment. This was a major milestone in the care of AD patients.

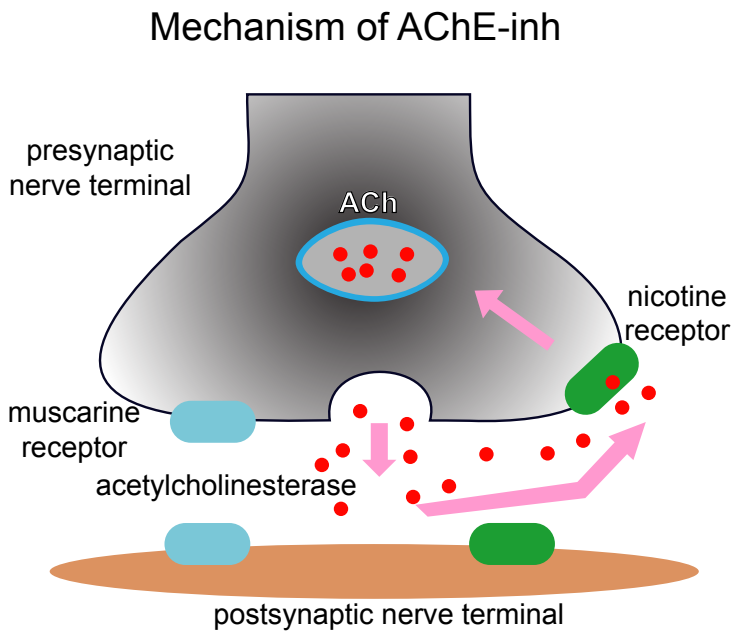

Figure 3. Cholinergic synaptic transmission. Mechanism of ChEI treatment.

Cholinesterase inhibitors

Tacrine was one of the "the first generation ChEI" and was followed by multiple compounds with ChEI effect. Some of the new drugs developed were never approved. Metrifonate, a long-acting irreversible ChEI, was withdrawn due to 20 cases of neuromuscular dysfunction and respiratory failure (López-Arrieta and Schneider 2006). Eptastigmine, a long-lasting reversible ChEI, was withdrawn because of hematologic (granulocytopenia) effects (Braida and Sala 2001). Tacrine is no longer recommended as a treatment in AD (Qizilbash et al. 2007) since "the second generation" ChEIs have favourable properties with longer half-life and no hepatic side effects. At present three ChEIs are used in clinical practice in Sweden: donepezil (Aricept®), rivastigmine (Exelon®) and galantamine (Reminyl®).

Tacrine

Tacrine, tetrahydro-aminoacridine, was the first cholinesterase inhibitor (ChEI) to be approved for AD treatment in clinical praxis in 1993. In Sweden it was licensed in 1995, as Cognex, for treating mild to moderate AD. Tacrine is a reversible inhibitor

of both AChE and BuChE. Tacrine is also active on receptor level (Nordberg et al. 1992) and in addition tacrine induces prolongation of action potentials by blockade of potassium channels (Adem 1992). Tacrine is metabolised by the cytochrome P (CYP) 450 enzymes and can interact with similarly metabolised drugs such as cimetidine and theofylline (Nordberg and Svensson 1998). Cholinergic side effects such as nausea/vomiting, dyspepsia, diarrhoea, dizziness and sweating occur but these are dose dependent. Hepatic side effects were reported in approximately 50% of the patients in the larger tacrine treatment trials (Farlow et al. 1992; Davis et al. 1992; Watkins et al. 1994). This was thought to be an idiosyncratic reaction i.e. neither an allergy nor an adverse event occurring only in susceptible individuals at the first contact with the drug. The possibility of genetic susceptibility was discussed (Carr et al. 2007). Liver enzymes were elevated in a non-predictable fashion, which required liver function monitoring in the initial phase of treatment (12 weeks). However approximately 88 % of patients could recommence tacrine treatment after liver enzymes normalized and then tolerated long-term treatment (Watkins et al. 1994). Tacrine has a short elimination half-life (2–4 hours) and was taken 4 times daily. Because of the disadvantages of hepatic effects and multiple daily dosages, tacrine use declined when the second generation ChEIs (donepezil, rivastigmine, galantamine) were introduced. Tacrine is no longer available for prescription in Sweden.

Donepezil

Donepezil is a non-competitive, rapidly reversible inhibitor of AChEI and the first second generation ChEI to gain approval in Sweden in 1997. The serum half-life is long, approximately 70 hours. Donepezil treatment in higher doses is associated with more cholinergic side effects than placebo (Burns et al. 1999) but no significant hepatic side effects have been reported. Donepezil is metabolised by CYP 450 enzymes CYP 2D6 and CYP 3A4 which could lead to interactions with phenytoin, carbamazepine or dexamethasone (Nordberg and Svensson 1998).

Rivastigmine

Rivastigmine is a non-competitive, slow reversible inhibitor of both AChEI and BuChEI. Rivastigmine was approved for AD treatment in Sweden 1999. The half-life is short, 1.5 hours. Oral administration requires a two-dose regime but recently (2007) a patch (sticking plaster) administered once daily was approved in Sweden. Oral rivastigmine treatment is associated with higher cholinergic side effects than placebo but no hepatic side effects have been reported. Rivastigmine is only minimally metabolised by the CYP450 enzymes and therefore not susceptible to drug interactions (Grossberg et al. 2000).

Galantamine

Galantamine is a tertiary alkaloid that originates from botanic sources. It has dual mechanisms of action as competitive, rapidly reversible inhibitor of AChE and allosteric modulator of nicotin receptors (Samochocki et al. 2000). It was approved in Sweden in 2000. Half-life is 6 hours. Galantamine treatment is associated with higher cholinergic side effects than placebo but no hepatic side effects have been reported (Nordberg and Svensson 1998). Galantamine is metabolised by CYP 450 enzymes: CYP 2D6 and CYP 3A4 which could lead to interactions with phenytoin, carbamazepine or dexamethasone (Nordberg and Svensson 1998).

Symptomatic or protective effects

In a chronic and progressive neurodegenerative disease different drug effects can be modelled (Chan and Holford 2001). The response to a symptomatic drug will typically be a rapid initial response with no change of the linearity of further deterioration. Drugs can also be protective, i.e. slowing or stopping the long-term degenerative process, thus changing the slope of deterioration.

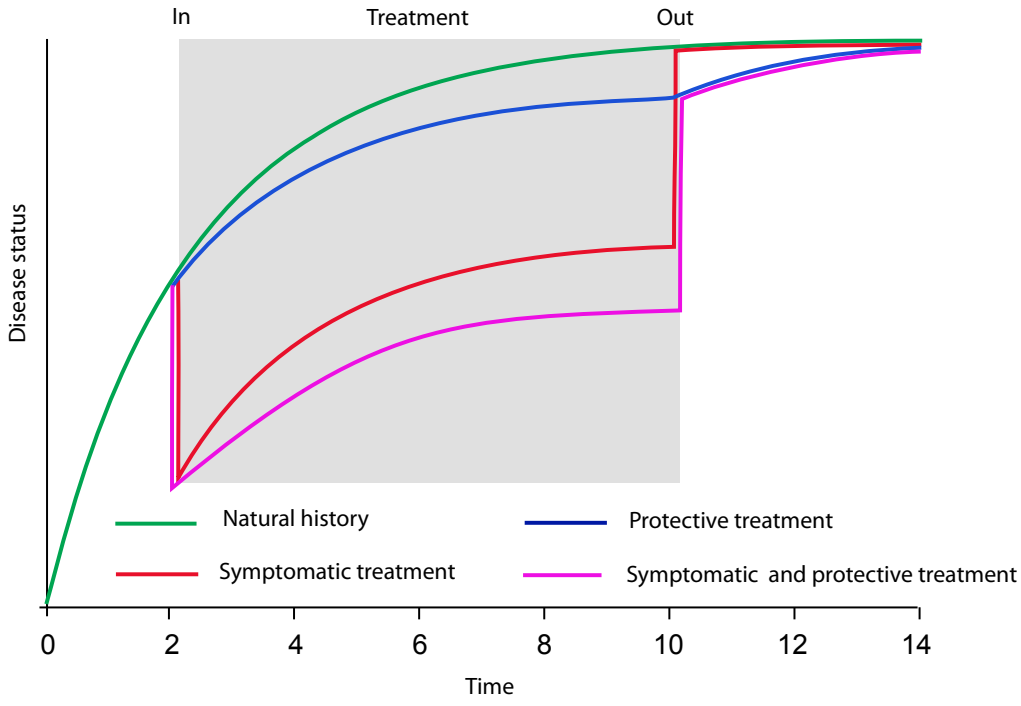

Figure 4. Models of treatment effects in Alzheimer's Disease. (After Chan and Holford 2001).

Theoretically one drug can have both symptomatic and protective effects. If a symptomatic drug is withdrawn the beneficial effects disappear swiftly. A protective drug changes the rate of progression and this can take years to be manifested. If treatment is stopped however, effects can remain for a period of time. A medical product can be considered disease modifying if the progression of the disease is modified as measured by cognitive, functional or global assessment tools and if these results are linked to an effect on the underlying disease process (Mani 2004). Analysing the slope of curves in ADAS-cog and IADL in long-term studies has been proposed (Broich 2007). The use of robust markers of progression such as brain imaging, CSF-biomarkers or PET will be needed to further evaluate protective treatment effects in long-term treatment studies (Nordberg 2004; Mori et al. 2006; Blennow et al. 2007).

ChEIs are mostly considered to have a symptomatic effect but additional neuroprotective effects of ChEIs have been proposed both in cellular models and in vivo (Geerts 2005; Hashimoto et al. 2005; Mori et al. 2006). Different mechanisms for the ChEIs potential protective effect have been proposed. ChEIs in general may counteract β amyloid toxicity, aggregation and APP release (Svensson and Giacobini 2000). Two studies showed a slowing of hippocampal atrophy in donepezil treated patients compared to controls (Krishnan et al. 2003; Hashimoto et al. 2005). Rivastigmine is an effective inhibitor of both AChE and BuChE and an additional inhibition of BuChE could be favourable in long-term treatment (O'Brien et al. 2003). Galantamine stimulates the postsynaptic nicotinic receptor α 7 nAChR and this could protect cells from β amyloid toxicity, glutamate toxicity (Takada-Takatori et al. 2006), and cholinergic neural stress (Geerts 2005).

Outcome measures

MMSE

The Mini-Mental State Examination (MMSE)(Folstein et al. 1975) was originally designed as a screening instrument to distinguish dementia from functional brain disorders in psychiatric patients. It is often included as a secondary outcome measure in placebo-controlled trials (Winblad et al. 2001) but widely used in clinical practice.

The MMSE scale ranges from 0–30, the lower the score the more cognitive deterioration. Orientation, memory, attention, language and visuo-constructive abilities are measured. Test- retest reliability is high (spearmen correlation coefficient = 0.899 –0.939) (Knopman et al. 1994).

In historic cohorts a natural annual decline of 2–4 points is expected (Salmon et al. 1990; Brooks et al. 1993; Agüero-Torres et al. 1998; Han et al. 2000). In a one-year placebo-controlled study the MMSE declined by 2.2 points in the placebo group

(Winblad et al. 2001). The decline is however non-linear and depends on disease stage (Galasko et al. 1995; Mendiondo et al. 2000). The MMSE decline is less in the early and late stages of the disease and faster in the moderate stages (Mendiondo et al. 2000).

ADAS-cog

The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) (Rosen et al. 1984) ADAS-cog is a scale from 70–0, the higher the score the more cognitively impaired patient. ADAS-cog is widely used in randomised clinical AD trials as a primary outcome measure. Since the test takes about 30–45 minutes to perform it is time-consuming and not practical for use in the routine clinical setting. It is an 11-item scale that measures orientation, verbal episodic memory, language and praxis. The test-retest reliability of ADAS-cog has been described as high (Spearman's correlation coefficient = 0.947–0.939) (Knopman et al. 1994).

In historic cohorts a natural annual increase (clinical decline) of 4–9 points is expected (Kramer-Ginsberg et al. 1988; Yesavage et al. 1988; Stern et al. 1994). In a controlled trial an annual increase in the placebo arm was 5 points (Feldman et al. 2005). The decline is nonlinear and depends on the disease stage (Stern et al. 1994). The ADAS-cog change is less in the early and late stages of the disease and faster in the moderate stages. A mathematical model of expected decline in untreated AD patients was derived by Stern et al. (Stern et al. 1994). The Stern model is a baseline dependent equation of expected ADAS-cog change over time in non-treated AD patients (Stern et al. 1994). This equation was based on a fairly small cohort of AD patients (n=111) where the individuals were repeatedly assessed (5 times, mean value) over a mean of 35 months. Grossberg and colleagues showed that in a treatment study with rivastigmine the decline in a placebo group corresponded to the calculations by the Stern equation (Grossberg et al. 2004) and the equation has been used to evaluate long-term treatment in multiple studies (Grossberg et al. 2004; Pirtilla et al. 2004; Small et al. 2005).

Global assessments of change

A clinical global impression was proposed as a mandated primary outcome measure by the Food and Drug Administration in the US already in 1990 (Leber 1990). The Clinician Interview-Based Impression of Change (CIBIC) was constructed to be used in clinical trials and it was used and validated in early tacrine trials (Knopman et al. 1994; Schneider et al. 1997). There are different variants of the test used with (Schneider et al. 1997) or without (Knapp et al. 1994) structured interviews and with (CIBIC plus) or with out caregiver input. In clinical trials clinicians focus on four areas of function: general, cognitive, behavioral and activities of daily living. An

assessment of stage is done at baseline in 7 steps grading the severity of disease. The assessments of change of global function from baseline are made at intervals using a 7-point scale that varies from 1 = very much improved to 7 = marked worsening, with 4 indicating no change since baseline. One of the difficulties with the CIBIC score is to define the steps of change, since it is left to the raters' clinical judgment. The test-retest reliability is lower (Spearman's correlation coefficient = 0.439 – 0.593) than for the cognitive tests (Knopman et al 1994). When the scale was reduced to a 3 point scale this improved the inter rater reliability (Quinn et al. 2002). As other assessments measuring changes CIBIC it is sensitive to disease severity. CIBIC ratings in untreated AD patients show greater worsening in moderately impaired AD patients than in the mildly or severely affected patients (Schneider et al. 1997). The CIBIC plus rating is widely used in clinical trials and ChEI treated patients show significant improvement of CIBIC compared to placebo in 6 months placebo controlled trials (Birks 2006).

Activities of daily living

The decline in functional autonomy is an important part of the diagnosis of AD (American Psychiatric Association 1994) (WHO 1992). Different activities of daily living (ADL) scales have been constructed to assess possible meaningful responses to treatments. In AD a gradual loss of functional abilities over time is expected. Basic ADL functions and more complex tasks (Instrumental ADL) can be applied in different stages of disease. In randomised clinical trials, RCTs, several different variants of ADL scales are used such as The Progressive deterioration scale, PDS, (DeJong et al. 1989), the Disability Assessment for Dementia scale, DAD, (Gélinas et al. 1999), Physical Self-Maintenance Scale, PSMS, (Lawton and Brody 1969) and The Instrumental Activities of Daily Living, IADL, (Lawton and Brody 1969).

The IADL scale used in the studies of this thesis (Lawton and Brody 1969) scores eight different items: phoning, shopping, food preparation, housekeeping, laundry, transportation, medication and money handling. Some of the items are gender and culture-based and this can cause difficulties if particular a task not applicable for a patient, for example a man that never prepared food. Longitudinal studies have shown declines in IADL of approximately 2 points a year in untreated patients but also described ceiling and floor effects and high variability (Green et al. 1993).

In our changing society the use of everyday technology such as handling mobile phones, remote controls, I-Pods, credit cards and computers is a part of everyday life. New dimensions have to be added to the Instrumental ADL scales to assess this (Broich 2007). Activities of daily living have been seen to improve with ChEI treatment compared to placebo in 6 months trials (Birks 2006).

Endpoints—clinical milestones

Delaying the *time until nursing home placement (NHP)* has been suggested as a long-term outcome measure in AD treatment studies (Winblad et al. 2000). The disadvantage of this endpoint is that prolonged follow up periods are necessary, and this is difficult in large patient populations. NHP is a valuable endpoint, since this event is the most "costly" step in AD-care both for society, from a socioeconomic point of view (Wimo et al. 2003), as well as on an emotional level. Other endpoint approaches can be time until *reaching a specified endpoint* in a cognitive or ADL scale (Winblad et al. 2000) or the *time until the event of death*.

Short-term studies

Short-term studies, 6 months or less

1. RCT-Randomised clinical trials, placebo-controlled
2. Open studies from naturalistic settings

How to define "short-term" is not totally clear. In the early trials of tacrine short-term often meant studies of 6 to 12 weeks (Davis et al. 1992; Farlow et al. 1992), and "long-term" was applied to studies of 30 weeks or more (Knapp et al. 1994). More recently 6 months of treatment has been defined as short-term (Winblad and Jelic 2004) and since at present it is thought to be unethical to have patients on placebo for more than 6 months, only short-term studies can be placebo-controlled.

1. RCT—Randomised clinical trials, placebo-controlled

Multiple double blind placebo controlled short-term studies have reported beneficial effects of ChEI treatment on cognition and general function (global assessments) (Farlow et al. 1992; Rogers et al. 1998; Burns et al. 1999; Rösler et al. 1999; Tariot et al. 2000; Birks 2006) activities of daily living (Rösler et al. 1999; Tariot et al. 2000; Feldman et al. 2003) and behaviour (Tariot et al. 2000). In these studies cognitive outcome remained above baseline and in all domains treatment was better than no treatment (Seltzer 2007). Severity in most studies in terms of MMSE scores have often been mild to moderate (MMSE score range 10–26) but similar positive results have also been seen in very mild early stage (Seltzer et al. 2004), moderate to severe (Farlow et al. 1992; Feldman et al. 2003) and in severe AD (Winblad et al. 2006a; Black et al. 2007).

The cognitive response "peek" induced by treatment often occurs after 6 – 12 weeks of treatment and thereafter often returns to baseline levels after 6 – 12 months (Rogers et al. 1998). This pattern gives the typical impression of a prompt symptomatic effect of ChEI treatment. Washout periods of 6 weeks have been said to be

sufficient to get the patient back to the level expected without treatment which would support a symptomatic drug effect (Rogers et al. 1998) and a fast cognitive relapse after discontinuation of ChEI has been described (Rainer et al. 2001). Patients in the placebo-arm of a 26 weeks RCT of rivastigmine however, never caught up with the patients on continuous rivastigmine treatment in the 26 week open extension which could suggest protective effects (Farlow et al. 2000). Longer studies would however be needed to detect possible protective effects of ChEIs (Chan and Holford 2001).

In the most recent Cochrane report 13 trials of ChEI treatment with 7298 patients included were evaluated (Birks 2006). The main result of this review was that after six months of treatment with ChEIs cognitive function improved an average of –2.7 points (95 % CI –3.0 – 2.3, p <0.00001), in the midrange of the 70 ADAS-cog scale. Benefits of treatment were also seen in global clinical states, ADL and behaviour.

Since only placebo controlled closed studies with high evidence strength (randomised controlled trials, RCTs) are evaluated in the Cochrane reports, with the exception of one 1 year donepezil study (Winblad et al. 2001), only studies with a 6 months duration were evaluated.

2. Open studies from naturalistic settings

See open studies from naturalistic settings long-term treatment.

Long-term studies

Long-term studies, longer than 6 months

1. RCT-Randomised clinical trials, placebo-controlled
2. Former RCTs with open extensions
3. Open studies from naturalistic settings
4. Head to head studies, randomised or open

1. RCT—Randomised clinical trials, placebo-controlled

According to the discussion above long-term studies could be defined as studies of more than 6 months of treatment. The longest placebo controlled studies of substantial size are two 1 year studies with donepezil (Winblad et al. 2001; Mohs et al. 2001). These studies showed significant effects of donepezil up to one year compared to placebo even if patients reached their pre-treatment level after 9–12 months of therapy (Johannsen 2004).

AD 2000 (Courtney et al. 2004) was a placebo controlled long-term, randomised study of donepezil. The goal for this study was to enroll 3000 patients in order to assess possible effects of ChEI treatment on NHP. Only 565 patients were recruited however and the dropout rate was extensive as the study progressed. This study did not fulfill the standards required by the Cochrane Institute (Birks 2006) and

was criticised on several points. Among these were the complex design (randomised twice), dubious inclusion criteria (no effect of drug was to be expected for patients entering), multiple washout periods (4–6 weeks repeated every year) and the large dropout rate (20 % remained after 2 years)(Black and Szalai 2004; Standridge 2004). The cognitive outcome results were however in line with previous ChEI studies.

2. Former RCTs with open extensions

In the absence of robust placebo-controlled data in the long-term we are confined to results of open label extensions of previously shorter placebo controlled trials. Different models of expected decline in cognitive tests have been used to try to evaluate the long-term treatment response in open studies.

1. Models of predicted decline built on projections of the outcome in the placebo phase (MMSE, ADAS-cog) assuming patients commence to deteriorate at the same rate. (Linear models)

2. Models of expected change in untreated historic cohorts (Rogers et al. 2000) (Raschetti et al. 2005).

3. Patients from the same study with minimal exposure of the substance are compared to the ones receiving continuous treatment for years (Doody et al. 2001; Lopez et al. 2002; Geldmacher et al. 2003).

4. Mathematical models of change based on cognitive test data from untreated AD patients (Stern et al. 1994; Mendiondo et al. 2000) used in multiple studies (Grossberg et al. 2004; Pirtilla et al. 2004; Small et al. 2005; Bullock and Dengiz 2005).

Even though the latest Cochrane report stated that “the results of open-label extension trials must be interpreted with caution” (Birks 2006), the statement that the benefits of long-term ChEI treatment probably can exist for several years (4–5 years) has been the opinion expressed in several review articles (Waldemar 2001; Winblad and Jelic 2004; Johannsen 2004; Bullock and Dengiz 2005; Seltzer 2007).

Multiple studies have claimed better cognitive outcomes in ChEI treated patients in the long-term as compared to the outcomes predicted by the methods explained above (Table 1).

Table 1. Long-term studies

	Reference	Drug	No. of subjects	Duration
1 year	Winblad et al 2001	donepezil	286	1 year, RCT
	Mohs et al 2001	donepezil	431	1 year, RCT
	Farlow et al 2000	rivastigmine	533	26 w RCT+26 w open label extension
	Raskin et al 2000	galantamine	353	26 w RCT+26 w open labeled extension
2 year	Doody et al 2001	donpezil	753	2.8 years, open label extension
	Grossberg et al 2004	rivastigmine	2010	2 years, open label extension
3 year	Winblad et al 2006	donepezil	286	3 years, open label extension
	Pirtillä et al 2004	galantamine	1039* (12 m. completers)	3 years, open label extension
	Raskin et al 2004	galantamine	194* (12 m. completers)	3 years, open label extension
4 year	Rockwood et al 2008	galantamine	240 (36 m. completers)	4 years , open label extension
	Rogers et al 2000	donepezil	133	4.9 years, open label extension
	Lyle et al 2008	donepezil	88	4 years , naturalistic cohort
5 year	Small et al 2005	rivastigmine	1998*	5 years, open label extension

* Only patients on continuous treatment

RCT= Randomised clinical trial

In addition, treatment with tacrine (Knopman et al. 1996) and donepezil (Geldmacher et al. 2003) have been reported to delay NHP, but other studies have reported different results (Courtney et al. 2004)

Results have been conflicting as to whether or not ChEI treatment actually postpones the time of death (Knopman et al. 1996; Ott and Lapane 2002) or not (Lopez et al. 2002).

All long-term studies experience the same problem of high dropout rates (Appendix Table C). There is an obvious risk that dropout can favour patients with little decline in the long-term phase (Birks 2006; Rockwood et al. 2008) thus exaggerating long-term treatment effects. Survivor bias in long-term studies is another risk. Patients that do not respond to treatment, or suffer from a more aggressive disease die during the study leaving the fitter patients for outcome measures.

3. Open studies from naturalistic settings

A major limitation when trying to generalise findings from clinical trials is that the participating AD patients in these are highly selected (Cummings 2003) and do not have the same range of co morbidity or medications as the general population (Albert et al. 1997). Both the trial participants and the trial circumstances are unlike those of a routine clinical setting (Cummings 2003). Longitudinal studies of the effects of ChEI treatment of AD patients from "real world " clinical practice are rare (Matthews et al. 2000; Lopez et al. 2002; Arsland et al. 2003; Bellelli et al. 2005; Raschetti et al. 2005; Chu et al. 2007) but important (Kelly et al. 1997; Waldemar 2001).

The reports from open studies in the "routine clinical setting" are often short-term (Relkin et al. 2003; Patterson et al. 2004; Froelich et al. 2004; Bellelli et al. 2005) and/or suffer from high dropout rates (see Appendix Table C). In one cohort study 59% of the included patients remained on treatment beyond 1 year and only 88 of potentially 2000 patients received treatment after 4 years (Lyle et al. 2008). One open study could confirm that also in the routine clinical setting ChEI treatment could delay NHP (Lopez et al. 2002). The findings from the studies from routine clinical settings have confirmed the results of the RCTs documenting good clinical improvement and long-term safety (Waldemar 2001).

4. Head to head studies, randomised or open

In the most recent Cochrane report the effects of the three available second generation ChEIs (donepezil, rivastigmine, galantamine) are considered equally efficacious for mild to moderate AD (Birks 2006). A few head to head studies have been done and some of these studies have been criticised (Bullock and Truyen 2005; Birks 2006) for being open label (Wilkinson et al. 2002; Wilcock et al. 2003; Jones et al. 2004) or too short (Wilkinson et al. 2002; Jones et al. 2004). Only one head to head study fulfilled the demands of the Cochrane report (Bullock et al. 2000).

Predictors of response

Possible predictors of response to ChEI treatment are reviewed by Lanctôt et al (Lanctôt et al. 2003). She concludes that disease progression rate (Farlow et al. 2001), quantified electroencephalography (qEEG) profiles after a test dose of drug (Alhainen et al. 1991; Knott et al. 2000; Almkvist et al. 2001), baseline blood flow profiles (Minthon et al. 1993; Hanyu et al. 2003; Connelly et al. 2005) and baseline magnetic resonance imaging (MRI) measures of substantia innominata (location of nc basalis of Meynert) (Tanaka et al. 2003; Hanyu et al. 2007) all showed association with response to ChEI treatment. Other factors outlined as possible positive predictors of treatment response to ChEI treatment in AD include severity of cognitive

impairment (Pakrasi et al. 2003; Van Der Putt et al. 2006) and high performance on alertness tests (Connelly et al. 2005). Conflicting results for the prediction of response by gender (Macgowan et al. 1998; Winblad et al. 2001; Rigaud et al. 2002), age (Schneider et al. 1991; Evans et al. 2000) and *APOE* ε4 allele have been described (Farlow et al. 1998; Almkvist et al. 2001; Winblad et al. 2001).

Researchers have also looked at factors that can be assessed during treatment to detect possibly treatment effects. Increased plasma Aβ42 after two weeks of rivastigmine treatment predicted treatment response at 6 months (Sobow et al. 2007). Red blood cell cholinesterase inhibitor activity was associated with positive treatment effects in donepezil treatment (Rogers and Friedhoff 1996). Responders to tacrine showed increase in CSF homovanillic acid (Alhainen et al. 1993) but the levels of the CSF biomarkers did not change over six months of ChEI treatment (Blennow et al. 2007).

Different approaches to define a good treatment response have been used. Methods applied include changes in cognitive tests such as MMSE (Alhainen et al. 1991; Farlow et al. 1998; Knott et al. 2000), ADAS-cog (Pomara et al. 1991; Schneider et al. 1991; Farlow et al. 1998; Aerssens et al. 2001; Rigaud et al. 2002) but also in global assessments, and ADL or combination of the assessments. A complication in evaluating response is that in studies outcomes were evaluated at different time points from hours to 12 months (Lanctôt et al. 2003). The US Food and Drug Administration has defined a change in ADAS-cog by 4 points as clinically important however does not define within which time span. The European Medicines Evaluation Agency proposed to use Cognition, ADL and global response to define short-term responders. The response should be assessed at 6 months as improved, based on a defined cognitive endpoint and at least not worsened in either ADL or global assessment (Broich 2007). A consensus with standardised methods for evaluating treatment response in AD trials is warranted (Broich 2007).

Non-cholinergic treatments

Multiple non-cholinergic treatment approaches have been tried but apart from the ChEIs only one drug ***Ebixa*** ® is at present licensed for AD treatment in Sweden.

Activation of glutamate receptors is believed to induce neurotoxic effects leading to cell death in the cortex and the hippocampus in neurological disorders. N-methyl-D-aspartate (NMDA) is one of many glutamate receptors. The NMDA receptor is activated by glutamate and overstimulation of this receptor produces synaptic noise probably through excess influx of calcium in cells, an event which is thought to be neurotoxic. ***Memantine (Ebixa ®)*** is a NMDA antagonist but has also been seen to inhibit hyperphosphorylation of tau in rat brain (Li et al. 2004) and was licensed in Sweden for treating moderate to severe AD in 2002.

Several other treatments have been tried such as ***disease modifying agents*** *propentofylline* (Rother et al. 1998)*, selegelin* (Sano et al. 1997), ***antioxidantias*** *vitamine E* (Sano et al. 1997), *ginko biloba* (Birks and Grimley Evans 2007), ***anti-inflammatory agents*** (Aisen et al. 2003) (Szekely et al. 2004), ***estrogen*** (Mulnard et al. 2000) and ***statines*** (Höglund and Blennow 2007) with effects not convincing enough to render approvals. Epidemiological studies however still suggest protective effects with lower occurrence of AD in cohorts with intake of antioxidantias (Engelhart et al. 2002), anti-inflammatory agents (Szekely et al. 2004) and estrogen (Paganini-Hill and Henderson 1996).

Administration of ***nerv growth factor (NGF***) to possibly counteract neuron cell death in AD has been tried in small samples of patients with some positive effects (Eriksdotter Jönhagen et al. 1998; Tuszynski et al. 2005)

Anti-amyloid ***vaccination*** trials in mouse models were promising and rationalized by the belief that the β-amyloid peptide has toxic effects on the brain in AD (Schenk et al. 1999). Phase II trials with active vaccines to humans were stopped early when 18 of 298 patients developed a meningo encephalitis syndrome (Orgogozo et al. 2003). Trials of immunisation are currently ongoing e.g. in Malmö and Stockholm.

Putative mechanisms for future approaches in AD treatment include counteracting the hyperphosphorylation of tau and the pathologic splicing of APP (α-secretase agonists) (β-, γ-secretase inhibitors) (Imbimbo 2008) the clotting of β-amyloid peptides (A β degrading enzymes) (Spencer et al. 2007) and stem cell research (Sugaya et al. 2007).

Aims of the Thesis

The overall aim of this thesis was to evaluate response to ChEI treatment in Alzheimer's disease in the routine clinical setting and to identify possible predictors of treatment response. Response models built on change in cognitive and global scales as well as on important endpoints such as time until nursing-home placement (NHP) and mortality were used. Predictors of treatment response such as clinical factors, *APOE* ε4 carrier and cerebrospinal fluid (CSF) biomarkers were investigated.

Study I

To describe the long-term (five years) effects of tacrine treatment on cognition, NHP and mortality rate in AD patients in the routine clinical setting. To investigate clinical predictors of treatment response and analyse dropout.

Study II

To study whether the CSF biomarkers could support the AD diagnosis, whether the severity of the cognitive symptoms was influenced by the levels of the different CSF biomarkers and whether the levels of CSF biomarkers were related to time until nursing home placement, survival or *APOE* ε4 carrier.

Study III

To investigate the cognitive, global and functional outcome in 435 patients receiving the ChEI donepezil in the Swedish Alzheimer Treatment Study (SATS) for three years.

Study IV

To investigate potential predictors for ChEI treatment response including baseline factors, pre-treatment progression rate and the levels of the CSF biomarkers Aβ42, T-tau and P-tau. To evaluate whether treatment with ChEI changed the cognitive progression**.**

Material and Methods

Patients

The patients in the studies of this thesis were investigated prior to inclusion in the studies with a thorough clinical investigation including medical history, physical and neurological examination, cognitive testing, laboratory tests and a cerebral computerized tomography (CT) in order to rule out other causes of dementia. All patients were longitudinally assessed with MMSE and ADAS-cog.

Table 2. Number of patients included in Study I – IV

Study	No. of patients included	Inclusion criteria	Centers (treatment)
I	50	AD, probable	Malmö (tacrine)
II	21 24	AD, (included in study **I**) with CSF Controls with CSF	Malmö (tacrine) Mölndahl
III	435	AD, probable, possible	SATS, multicenter (donepezil)
IV	191	AD, probable, possible, with pre-treatment progression rate with CSF (n=169)	SATS, Malmö (donepezil, rivastigmine, galantamine)

Patients in study I and II

Patients were consecutively recruited from the out-clinic in Malmö at the Neuropsychiatric Clinic with start 1995. Patients were self-referred or were referred by general practitioners, geriatricians, internists or psychiatrists. The inclusion criteria for the study were broad. Patients with AD that gave their consent to participate, were living at home at inclusion, and could be tested with MMSE at baseline were considered eligible. Exclusion criteria were lack of caregiver, expected lack of compliance and existing contraindications to tacrine treatment. 50 consecutive candidates with the clinical diagnosis of dementia and AD as defined by the clinical criteria were included.

In 21 patients CSF taps were obtained for analysis of CSF biomarkers and the outcome of this analysis is described in the Study II. The CSF control group consisting of 24 healthy volunteers with no history or symptoms or signs of psychiatric or neurological disorders, was randomly selected from Mölndal Hospital Sweden and age and gender matched.

Patients in study III

The Swedish Alzheimer Treatment Study (SATS) was started in 1997 to evaluate long-term ChEI treatment in the routine clinical setting. At this time only donepezil was licensed for AD treatment in Sweden. Patients were recruited prospectively from 10 different centres in Sweden. All centres had clinical and diagnostic experience in the field of dementia. Memory clinics (Malmö, Uddevalla, Gothenburg), Geriatric clinics (Umeå, Stockholm (Danderyd, Huddinge, Handen), Uppsala, Linköping) and one primary care setting (Kalix) provided patients for the donepezil study. The inclusion criteria were broad: patients fulfilling the clinical diagnostic criteria for dementia and AD giving their consent to participate, living at home at time of diagnosis, having a caregiver and being assessable with MMSE at baseline. Exclusion criteria were patients with contraindications to ChEI treatment or ongoing treatment with another ChEI. In study III we investigated the first 435 patients that received donepezil treatment in the SATS.

Patients in study IV

The Swedish Alzheimer Treatment Study (SATS) started in 1997 for donepezil and as other ChEIs gained approval for AD treatment in Sweden rivastigmine and galantamine treatment arms were added. The choice of drug was however, not randomised but left to the clinician to decide. In 200 out of 283 consecutive patients participating in the SATS study at the Memory clinical in Malmö CSF-taps were taken and stored before the start of treatment. These patients received ChEI treatment (donepezil, rivastigmine, galantamine) and were followed for 3 years. In 191 patients data of the patients MMSE at the first visit to the clinic were obtained and the pre-treatment progression was calculated. An analysis of CSF biomarkers was made on stored CSF in a uniform analysis in 169 of the 191 cases.

Table 3. Baseline characteristics in Study I – IV

Study	No.	Diagnosis	Gender (M/F) %	APOE e4 carrier	Presenile (%)	Age at baseline	Duration	MMSE (mean)	ADAS-cog (mean)
I	50	AD	44/56	54%	26%	71.8	3.7	20.5	26.2
II	21	AD	33/67	57%	38%	68.6	3.8	20.3	24.7
II	24	controls	41/58	29%		68.5		29.5	
III	435	AD	35/65	66%	15%	74.6	3.1	22.0	20.7
IV	191	AD	35/65	69%	13%	75.3	2.9	22.3	19.5

Clinical criteria

Patients with the clinical diagnosis of dementia as defined by DSM-IV (American Psychiatric Association 1994) and probable AD according to the NINCDS-ADRDA criteria (McKhann et al. 1984) were included in study I and II.

Patients with the clinical diagnosis of dementia as defined by DSM-IV (American Psychiatric Association 1994) and probable or possible AD according to the NINCDS-ADRDA criteria (McKhann et al. 1984) were included in study III and IV.

Controls in study II were healthy volunteers with no history or symptoms or signs of psychiatric or neurological disorders randomly selected from Mölndal Hospital Sweden.

Neurochemical methods

In study II the CSF T-tau analyses were determined, using a sandwich Enzyme-Linked Immunosorbent Assay (ELISA) constructed to measure T-tau, both normal and hyperphosphorylated tau (Blennow et al. 1995). CSF P-tau was determined using a sandwich ELISA, constructed to specifically measure tau phosphorylated at Thr-181 (Vanmechelen et al. 2000). CSF Aß42 was determined using a sandwich Enzyme-linked immunosorbent assay (ELISA), constructed to specifically measure the Aß isoforms including both the first and the 42nd amino acid (Andreasen et al. 1999a). In this study the CSF samples were analysed on stored CSF as routine clinical neurochemical analyses.

In study IV the CSF T-tau, P-tau (tau phosphorylated at threonine 181) and Aß42 levels were determined by the xMAP Luminex technology using the INNO-BIA AlzBio3 kit (Innogenetics, Ghent,Belgium), as previously described in detail (Olsson et al. 2005). The Luminex levels were standardized to match ELISA levels as former described (Olsson et al. 2005). In this study the CSF analysis was performed on stored CSF with the same technique applied for all samples

All CSF analyses were performed at the Unit of Neurochemistry at Sahlgrenska University Hospital.The *APOE* genotype was determined at the Department of clinical Chemistry at Malmö University Hospital.

Statistical methods

To avoid the possibility of skewed distributions, non-parametric methods were used in all studies. Mann-Whitney U test was performed when two independent groups were compared. Kruskal-Wallis one-way analysis of variance was used to compare 3 or more independent groups. Bonferroni correction was used to correct the significance levels when analysing pairwise comparisons if a significant difference between 3 or more groups was found. Cross tabulations with the χ^2 test were used to

analyze nominal scale variables, e.g. gender and *APOE* ε4 carrier. Spearman rank correlation coefficients were calculated as a measure of linear associations.

Study I
Kaplan-Meier survival analysis was used to examine the distribution of time from start of treatment (baseline) until a defined endpoint in different groups. A log rank test was performed to analyse the equality of the survival distributions for different groups. Discriminant analysis was used to investigate which of the predictor variables provided the best discrimination between the outcome groups.

Study II
Simple linear regression equations were calculated.

Study III
Cox Proportional Hazards Regression with backward stepwise selection was used to calculate predictors for dropout and risk ratios.

Study IV
Pair wise comparisons of two related samples were performed by the Wilcoxon matched-pairs signed-rank test (pre-treatment progression to the post-treatment progression). Binary logistic regression models were used to calculate predictors of treatment response and odds ratios. The analyses were done with and without adjustments for MMSE at baseline, gender, *APOE* ε4 carrier, age and education (if applicable).

Outcome measures

Study I and II
To evaluate change in cognition over time MMSE (Folstein et al. 1975) and ADAS-cog (0–70) (Rosen et al. 1984) were used. In addition a global rating was used. This was defined as an overall clinical observation and was performed with the aid of the responsible nurse or physician. It comprised of 3 levels: improved, unchanged or worse. The MMSE, ADAS-cog and global ratings were performed at baseline and every six months until 60 months. Additional outcome measures were time until nursing home placement (NHP) and time until death.

Study III
Cognition was evaluated using the MMSE and the ADAS-cog 0–70. The Clinician Interview-Based Impression of Change, CIBIC (Knopman et al. 1994; Schneider et al. 1997) was used as a global rating of change. The assessments of change of

global function from baseline were made using a 7-point scale that varies from 1 = very much improved to 7 = marked worsening, with 4 indicating no change since baseline.

The Instrumental Activities of Daily Living, IADL, scale (Lawton and Brody 1969) was used ranging from 8 points, indicating no difficulty, to 31 points indicating total loss of function. The eight different items of the IADL scale scored the ability to telephone, do shopping, prepare food, do housekeeping, do laundry, how to handle transportation, medication, and finances. If an item was not applicable for the individual the score of this item was 0. The IADL score was expressed as mean ± SD.

Patients were assessed at baseline, 2 months (only MMSE and CIBIC), 6 months and every six months for a total of three years.

Study IV

The same outcome measures as in study III were applied, at the same time intervals. Only the baseline IADL scores were used however, and not expressed longitudinally. Pre-treatment MMSE values were obtained for all patients before treatment. These MMSE measures were made at the first visit to the clinic. The pre-treatment MMSE progression rate was expressed as a linear coefficient, r0 (MMSE change /month) and was used to evaluate possible change of progression after treatment was started.

Models of heterogeneity of treatment response

Study I

At each follow-up three outcome groups were defined: responders, unchanged and deteriorated in a way similar to that of Minthon and colleagues (Minthon et al. 1993) (Minthon et al. 1995). The model was based on changes in the MMSE, ADAS-cog and global rating from baseline. Patients defined as responders were those who had changed for the better on at least 2 of the 3 types of ratings and had changed for the worse on none. Those defined as unchanged had not changed at all on 1–3 of the ratings and had changed on at most 1 rating for the better and 1 rating for the worse. The patients defined as deteriorated had changed for the worse on at least 2 ratings, and had changed for the better on none. A difference between ratings of 1 point in the MMSE or ADAS-cog score was defined as a change. At each follow-up, the patients' responses were compared with their baseline ratings. Only patients still treated with tacrine were evaluated. Heterogeneity of response at six months was illustrated in the different response groups in MMSE and ADAS-cog.

Study III

Heterogeneity of response at six months in the CIBIC score was illustrated. The longitudinal outcome of the response groups in CIBIC at 6 months was displayed

as MMSE change over time and ADAS-cog change over time. The three groups of response in CIBIC were CIBIC 1–3 = improved, CIBIC4 = unchanged, CIBIC 5–7 = deteriorated.

Study IV

The three models presented in the study were designed only to identify patients responding to treatment and did not address the issue of stabilisation of disease. Responses were analysed after two and six months of treatment.

In the *MMSE response model* responders were defined as patients having an improvement of 2 points or more in the MMSE at both time intervals compared to baseline.

In the *MMSE and CIBIC response model* responders were defined as patients with an improvment of 2 points or more in MMSE from baseline and a score of 1–3 in the CIBIC.

In the *ADAS-cog response model* two levels of ADAS-cog response were tested. To be considered a responder in the first model, patients had to have an improvement of two points or more from baseline and in the second model an improvement of 4 points or more.

Summary of Results

Main feature of Paper I

Five-year outcome of Tacrine treatment of Alzheimer's disease, early response predicts prolonged time until nursing home placement but does not alter life expectancy.

Positive effects of tacrine treatment in AD on cognition and the functioning of daily activities have been reported in short-term placebo controlled studies (Knapp et al. 1994; Harvey and Eagger 1995). Whether ChEI treatment in AD can postpone the time until nursing home placement (NHP) or death are issues of importance. High doses of tacrine were associated with longer time until NHP and possibly reduction of mortality rate (Knopman et al. 1996). Other investigators found no association between ChEI use and mortality rates (Lopez et al. 2002; Lopez-Pousa et al. 2006). What to expect of long-term tacrine treatment in a routine clinical setting is not known. The heterogeneity of response to ChEI treatment and possible predictors of treatment response were discussed in the first trials of tacrine (Lanctôt et al. 2003). To assess response, analyse heterogeneity of response and search for predictors of response could be useful. In 50 AD outpatients receiving tacrine treatment, MMSE, ADAS-cog and global assessments were obtained every 6th month. Patients were followed for at least 5 years.

Results

1. A heterogeneity of response to treatment was described and a response model was applied using the assessments of MMSE, ADAS-cog and a global rating.

2. Patients on tacrine treatment were better or stable in 75 % of the cases after 6 months of treatment. After 1 year 42 % and after 2 years 20 % were stable or better.

3. Patients that were responders or unchanged at 12 months lived significantly longer at home (median 1411 days) than the patients that deteriorated (median 744 days) or had stopped their tacrine treatment in the first year (median 333 days).

4. Mortality rate was not influenced by response to treatment or early dropout from treatment.

5. No predictors for a positive treatment response could be identified among the following parameters: baseline MMSE and ADAS-cog, age at onset, duration of disease, gender and *APOE* ε4 carrier.

6. The most common cause of dropout the first year was gastrointestinal side effects. The 1-year completion rate was 66 %, the 2-year 46 %, the 3-year 30%, the 4-year 26 % and the 5-year 16 %.

Comments

The cognitive outcomes of this study in the routine clinical setting were in line with previous short-term (Knapp et al. 1994) and long-term (Rogers et al. 2000; Truyen et al. 2002) studies of ChEI treatment. Comparing results between studies must be done with caution due to differences between studies in baseline severity, dropout rates and other factors, however in the section appendix of this thesis we include an overview (See Appendix Table A, Table B).

Our finding that continuous ChEI treatment delayed NHP has been reported previously (Knopman et al. 1996; Lopez et al. 2002; Geldmacher et al. 2003; Lopez et al. 2005), however the additional result that 'the treatment response' influenced time until NHP has to our knowledge not been reported.

In our study no association between tacrine use/ treatment response and death were found which is in line with other ChEIs reports (Lopez et al. 2002; Lopez-Pousa et al. 2006). This was in contrast to other studies indicating that patients on tacrine treatment lived longer (Knopman et al. 1996; Ott and Lapane 2002) .

Severity of disease has been outlined as a possible positive predictor of ChEI treatment response in AD (Pakrasi et al. 2003) but this could not be confirmed in the present study. In addition gender, age and *APOE* ε4 carrier did not predict response in our study which corresponds with conflicting results presented previously (Schneider et al. 1991; Macgowan et al. 1998; Evans et al. 2000; Almkvist et al. 2001; Winblad et al. 2001; Rigaud et al. 2002). Long-term studies all suffer from the problem of high dropout rates. The dropout rate in this study was however not larger than in other long-term studies as illustrated in the Appendix (Table C).

Main feature of Paper II

CSF biomarkers for Alzheimer's disease: Levels of β-amyloid, tau, phosphorylated tau relate to clinical symptoms and survival.

A diversity of studies have previously described different correlates between severity of symptoms and CSF biomarkers in AD. Dementia symptoms have been found *not* to correlate with either CSF Aß42 (Kanai et al. 1998) or CSF T-tau levels (Galasko et al. 1997; Andreasen et al. 1998). Other researchers have found a correlation between severity of symptoms and CSF T-tau levels in AD (Kanai et al. 1998). To investigate whether the CSF biomarkers could be supportive in the diagnosis of AD, correlate to

clinical criteria (DSM-IV and NINCD-ARDRA) or predict clinical outcomes such as time until NHP or death would be interesting. In 21 patients with the clinical diagnosis of AD participating in a 5-year treatment study with tacrine (Study I) CSF biomarkers were analysed and these questions were addressed.

Results

1. CSF biomarkers did aid the clinical diagnosis of AD in the study. The specificity was 88 % for CSF T-tau, P-tau and CSF Aß42. The sensitivity was 86 % for CSF T tau, 60 % for P-tau and 86 % for CSF Aß42.
2. P-tau and T-tau were possible markers for severity and P-tau for the abundance of symptoms in AD.
3. Time until NHP was not influenced by the levels of CSF biomarkers.
4. Low CSF Aß42 or high T-tau may indicate a higher risk of early death in AD

Comments

Although this study was limited in size, the specificity and sensitivity of the CSF biomarkers were in line with the results of other studies (Blennow and Hampel 2003). Whether the levels of CSF biomarkers reflect the severity of symptoms or disease progression in AD is still under investigation. Results from different studies have been inconclusive regarding this association (Tato et al. 1995; Galasko et al. 1997; Kanai et al. 1998; Andreasen et al. 1999a). In study II we found a positive correlation between the level of CSF-P-tau and the number of clinical symptoms at baseline (DSM-IV, NINCDS-ARDRDA criteria). No similar association was seen for CSF T-Tau and CSF Aβ42. In addition a positive correlation between severity of symptoms (ADAS-cog scores) and CSF T-tau and P-tau was seen. This could be in line with the belief that CSF -levels of T-tau and P-tau might reflect disease intensity in AD (Wahlund and Blennow 2003; Blennow et al. 2007).

The presence of the *APOE* ε4 allele has been associated with earlier death in AD (Dal Forno et al. 2002) but other studies did not find similar associations (Bonsignore and Heun 2003). Whether CSF biomarkers can predict survival has not been previously investigated. Our finding that AD patients that were dead in the 6-year follow-up had lower levels of CSF Aβ42 (higher T-tau) than the survivors was not explained by differences in the frequency of the *APOE* ε4 allele in the cohort. Other mechanisms must be involved but the limited number of patients in this study (n=21) renders further speculation uncertain. Therefore it is vital that further investigations in larger cohorts are performed.

Main feature of Paper III

Multiple short-term randomised clinical trials (RCTs) have shown positive effects of donepezil treatment in patients with Alzheimer's disease (Winblad et al. 2001; Birks 2006). Long-term extensions of previously closed trials have demonstrated cognitive stabilisation of disease compared to historic controls (Kramer-Ginsberg et al. 1988; Rogers et al. 2000), mathematical models (Grossberg et al. 2004; Small et al. 2005), or projected placebo group outcome (Winblad et al. 2006b). Three-year completion rates often vary between 20 to 30 % in AD extension studies (Rogers et al. 2000; Raskind et al. 2004; Pirtilla et al. 2004; Small et al. 2005). Donepezil slowed the rate of decline in IADL by at least six months in a placebo controlled study (Feldman et al. 2003). What to expect in continuous long-term donepezil treatment in the routine clinical setting remains to be investigated. Outcomes in cognitive scales (MMSE, ADAS-cog), functional rating (IADL) and global assessments (CIBIC) were investigated for 435 patients with the clinical diagnosis of AD in the SATS. Patients were followed for three years.

Results

1. The cognitive outcome in MMSE from baseline was above baseline level for more than six months and in subgroups of patients for 1 year.
2. Patients on donepezil treatment were better or stable in the CIBIC rating in 74% of the cases after 6 months of treatment. After 1 year 49 %, after 2 years 35 % and after 3 years 30 % were stable or better in the CIBIC rating.
3. After three years of treatment the mean change from baseline in MMSE –score was 3.8 points. This was better than expected from historic cohorts (6–12 points decline).
4. After three years of treatment the mean change from baseline in ADAS-cog score was 8.2 points. This was better than the ADAS-cog score predicted by historical cohorts (12–27 points) and the calculated decline by the Stern equation (15.6 points).
5. The IADL declined from baseline with approximately 1 point every six months.
6. The three-year completion rate was 38 %. The most common causes for dropout were nursing-home placement (NHP) (25 %) and side effects (13 %).
7. Three-year completers were younger, had better cognitive ratings at baseline, and less medication at baseline, but did not differ from the dropouts in duration of illness, gender or *APOE* genotype.

Comments

Open studies that confirm the results from short-term RCTs have been requested (Kelly et al. 1997; Waldemar 2001). An annual change in MMSE of 2–4 points has been proposed, based on historical cohorts (Mendiondo et al. 2000; Han et al. 2000) and placebo controlled trials (Winblad et al. 2001). Holmes and colleagues showed that 151 AD patients without treatment with baseline MMSE 11–27 had an annual decline of 3.4 points (MMSE, mean value) and that even without treatment 34 % were better or unchanged at 1 year, 13 % at 2 years and 14% at 3 years (Holmes and Lovestone 2003). In our study 49 % were better or unchanged at 1 year, 35% at 2 years and 30 % at three years. Comparing our results with historic cohorts, mathematical models (Stern et al. 1994) and other studies the outcome in study III is favourable both in the short-term and in the long-term (Appendix, Table A, Table B). One must not however, disregard the risk that dropout can favour patients with little decline in the long-term phase (Rockwood et al. 2008) thus over-emphasising long-term treatment effects. High dropout rates are an issue in all long-term AD studies, however the dropout rate in the current study was less than most other studies (Appendix, Table C).

Main feature of Paper IV

Can CSF biomarkers or pre-treatment progression rate predict response to ChEI treatment in AD?

The observation that some patients with ChEI treatment respond better than others has led to the search for predictors of treatment in ChEI studies. Several factors such as severity of disease (Pakrasi et al. 2003; Van Der Putt et al. 2006) and well preserved frontal blood flow (Hanyu et al. 2003; Connelly et al. 2005) have been outlined as possible predictors of good response. Age (Schneider et al. 1991; Evans et al. 2000), *APOE* genotype (Almkvist et al. 2001; Winblad et al. 2001) and gender (Macgowan et al. 1998; Winblad et al. 2001; Rigaud et al. 2002) have shown conflicting predictive effects on response. Fast pre-treatment progression rate in the placebo phase of a rivastigmine study was a predictor of response in a study by Farlow and co-workers (Farlow et al. 2001; Farlow et al. 2005). Whether CSF biomarkers could be useful as baseline predictors of response has not been investigated.

The positive outcome described in open ChEI studies has been criticised as being the result of diversity of disease progression and not an actual treatment effect (Holmes and Lovestone 2003). It would be valuable to investigate possible predictors of treatment response such as CSF biomarkers or pre-treatment progression rate in the routine clinical setting. To investigate whether the progression rate in AD is altered by ChEI treatment would also be interesting. In the present study 191 patients treated

with ChEIs participating in the Swedish Alzheimer Treatment Study were investigated. Pre-treatment progression rates, cognitive outcomes and CSF biomarkers were analysed.

Results

1. Fast pre-treatment progression rate was a predictor of treatment response even after adjusting for severity, another positive predictor of response.
2. Patients in the fastest quartile of pre-treatment progression rate were significantly more prone to be responders to treatment at 2 (adjusted odds ratio 6.6, p=0.001) and 6 months (adjusted odds ratio 10.4, p=0.000) than those in the slowest progressing quartile.
3. The levels of CSF biomarkers Aβ42, T-tau and P-tau did not predict response to treatment.
4. The pre-treatment progression-rate was significantly changed by ChEI treatment. This positive treatment effect lasted for at least 6 months.

Comments

Fast progression rate in the placebo phase of rivastigmine treatment in AD was described to predict positive response (Farlow et al. 2001). Severity of disease has also been outlined as a possible positive predictor of ChEI treatment response in AD {Pakrasi, 2003 197 /id} {Van Der Putt, 2006 196 /id} . These results were confirmed in the routine clinical setting by our study. Our results are in agreement with the conclusion reached by Lanctôt and co-workers that disease progression rate presumably is a better predictor of response than disease severity (Lanctôt et al. 2003). Neither the levels of CSF biomarkers nor the *APOE* genotype predicted treatment response in this study.

The pre-treatment progression rate in our study corresponded to an annual decline of 2.3 points in the MMSE, in the same range as previously reported in placebo-treated patients (Winblad et al. 2001). Moreover, the linearity of progression in our study was significantly changed by ChEI treatment for more than 6 months. We conclude that the additional knowledge of pre-treatment progression rates enhances the clinical relevance of the cognitive outcome in this study since the patients with the fastest progression rate actually showed the best treatment response.

When we defined responders in this study we did not include unchanged patients in this group. The "non-responder group"(n = 128) was broken down into an unchanged and deteriorated group and subanalysed at six months (analysis not included in the

manuscript). Results showed that 88 patients actually were unchanged compared to baseline (defined as MMSE-change from baseline of ±1 point). This analysis showed that 60 % were better or unchanged at 1 year, 49 % at 2 years and 36 % at three years (Appendix Figure A). In addition the three response groups were compared. In this analysis the responders and the deteriorated patients were not different in baseline demographics or levels of biomarkers but only in the pre-treatment progression rate (Appendix Table D). We conclude that it is difficult both to predict who will respond to treatment and who will deteriorate in spite of treatment.

Conclusions

AD patients in the routine clinical setting receiving ChEI treatment show a similar short-term response as patients in closed placebo controlled studies. A prompt clinical improvement in the first 2 – 6 months was observed which is in line with a fast symptomatic treatment effect. After that there is some evidence that the progression rate of the cognitive decline is reduced or at least postponed for about 6 months and in subgroups of patients for as long as 12 – 18 months. A heterogeneity of response to ChEI treatment can be demonstrated using different response models. At six months of continuous ChEI treatment approximately 75 % of patients in the studies of this thesis were assessed as better or stable using cognitive and global models of response. A positive response to ChEI treatment and length of treatment had clinical impact on long-term outcomes such as delay of time until nursing-home placement. Long-term treatment with ChEI or response to treatment did not influence mortality rate.

ChEI treatment probably stabilises groups of patients that remain on treatment in the long-term. At 1 year 42 % – 49 % – 60 % (Study I–III–IV) were scored better or unchanged compared to baseline, at 2 years 20 – 35 – 49 % (Study I–III–IV), at three years 30 – 36 % (Study III–IV). With additional knowledge of the pre-treatment progression rate we conclude that the positive outcome in these open studies probably does not simply reflect a diversity of disease progression since the patients with the fastest pre-treatment progression showed the best response to ChEI treatment (Study IV).

Large dropout rates in long-term AD studies make it difficult to evaluate possible long-term cognitive and protective effects of ChEI treatment. The approach of including patients from the routine clinical setting into clinical programs of continuous evaluation, such as in the studies of this thesis, proved to be valuable in maintaining large cohorts of patients in long-term treatment.

It is difficult to predict which patients will respond to treatment before treatment is introduced and it is equally difficult to predict who will deteriorate in spite of treatment. Fast pre-treatment progression rate and severity at baseline predicted a good treatment response in one of the studies in this thesis but biochemical markers such as *APOE* ε4 carrier or CSF Aß42, T-tau or P-tau did not predict response. CSF biomarkers were however a valuable aid in the clinical diagnosis of AD and levels of T tau and P-tau had correlations to clinical symptoms.

In the absence of substantial predictors of response to ChEIs such as CSF- biomarkers, ChEI treatment should be offered to all AD patients. Continuous evaluation of treatment response in long-term evaluation programs would be recommended. All future treatment strategies for AD will share the same methodological problems

evaluating treatment effects as the ones we have comprehended in the ChEI trials. New consensus guidelines to evaluate the outcome in AD treatment trials are needed. Guidelines providing standardised methods to assess outcomes or identify response groups are needed. There is a risk that potential protective treatment effects can be obscured in trials with non-sufficient length or efficacy measures. The ChEIs were the first treatments for AD but will not be the last.

Summary in Swedish / Svensk sammanfattning

Långtidseffekter av behandling, prediktorer för behandlingsrespons och biokemiska markörer vid Alzheimers sjukdom

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Ungefär 28 miljoner människor i världen har en demenssjukdom. Mer än hälften av alla demensfall utgörs av Alzheimers sjukdom (AD) och denna sjukdom är en av de stora folksjukdomarna. Symptomen vid AD innefattar nedsättning av kognitiva funktioner såsom minnesbesvär, nedsatt orienteringsförmåga, nedsatt språkförmåga, nedsatt praktisk förmåga och nedsatt igenkänningsförmåga men leder även till nedsatt initiativ- och problemlösningsförmåga. Även psykiska symptom förekommer i form av depressioner, oro, ångest och störd verklighetsuppfattning. Sjukdomen och symptomen innebär ett stort lidande både för den som drabbas och för de närstående.

Mikroskopiskt karakteriseras AD av uttalad nervcellsundergång i specifika delar av hjärnan samt förekomst av ansamlingar av äggviteämnen (plack) och ansamlingar av nervtrådar inne i och utanför cellerna (tangles). Idag vet man fortfarande inte vad som orsakar dessa sjukliga förändringar. Enligt en teori, den s.k. amyloidkaskadhypotesen anser man att en felaktig klyvning av ett äggviteämne, APP, leder till ansamling av beta-amyloid (Aβ42), som lagras i plack. Man tror att det är denna amyloidinlagring som ger upphov till den skadliga kaskaden som slutligen resulterar i nervcellsundergång. Enligt en annan teori, den s.k. tau-hypotesen, anses det att det är en felaktig kemisk reaktion (hyperfosforylering) av äggviteämnet tau som sätter igång sjukdomsprocessen.

Eftersom ryggvätskan står i direkt förbindelse med hjärnan kan kemiska processer inne i hjärnan avspeglas i ryggvätskan. Vid AD ser man i ryggvätskeprov sänkta halter av Aβ42 och förhöjda halter av tau (T-tau) och fosfo- tau (P-tau).

Alzheimers sjukdom beskrevs första gången 1906, men det tog nästan 100 år innan det första läkemedlet för behandling av AD kom. På 70-talet upptäcktes att det fanns en brist på signalsubstansen acetylkolin i hjärnan, vid AD. Den första s.k. kolinesterashämmaren (ChEI), läkemedlet tacrine, blev godkänd i Sverige 1995. ChEI-behandling ger ökade halter av acetylkolin och symptomen vid AD mildras. På senare år har ytterligare tre läkemedel med liknande verkningsmekanismer introducerats på den svenska marknaden: donepezil, rivastigmine och galantamine. Många studier har visat att behandling med ChEI vid AD ger positiva effekter på kognitionen samt på det globala välbefinnandet och aktivitetsnivån. Studier där man

jämför aktivt läkemedel med sockerpiller (placebo) genomförs ofta med speciellt utvalda (selekterade) patienter där många utesluts för att de samtidigt har andra sjukdomar och/eller läkemedel. Placebokontrollerade studier vid AD får numera av etiska skäl inte pågå längre än 6 månader. Man har funnit att vissa grupper av AD-patienter svarar bättre på behandlingen än andra. Vilka faktorer som orsakar detta är ofullständigt känt.

Avhandlingens syfte är att studera behandlingssvar hos AD-patienter från vår kliniska vardag som får långtidsbehandling (3–5 år) med ChEI. Andra syften är att beskriva modeller för att mäta behandlingssvar, att undersöka om behandlingen påverkar tidpunkten för flytt till annat boende eller död och att identifiera faktorer som kan förutsäga behandlingssvaret vid ChEI-behandling (prediktorer). Slutligen har vi velat undersöka hur länge behandlingen pågår och varför den avbryts samt studera om förloppet vid AD förändras med ChEI behandling?

Den första studien omfattade 50 patienter med AD som behandlades med tacrine och följdes under 5 år. Ett behandlingssvar definierades med hjälp av kognitiva och globala skattningar en gång varje halvår. Efter 6 månaders behandling var 75 % av patienterna bättre eller oförändrade och efter 12 månader 42 %. Patienterna med gott behandlingssvar kunde bo hemma längre än de som skattades som försämrade eller de som avbrutit behandlingen under det första året. Överlevnaden påverkades inte av behandlingssvaret eller av behandlingens längd. Varken patientens ålder, kön, genetisk variant av ApoE-protein eller kognitiv nivå vid behandlingsstart kunde förutse effekten av behandling med tacrine. Den vanligaste orsaken till att patienten lämnade studien under det första året var biverkningar. Efter 1 år kvarstod 66 % av de ursprungliga patienterna på behandling, efter 2 år 46 %, 4 år 26 % och efter 5 år 16 %.

I den andra studien undersöktes ryggvätskemarkörer (T-tau, P-tau och Aβ42) från 21 av patienterna som deltog i tacrinestudien. Analysen gav stöd för den kliniska AD-diagnosen. Vi fann att ju fler symptom som uppvisades vid behandlingsstart, desto högre nivå av P-tau förelåg. Hos de patienter som avlidit vid en uppföljning efter 6 år fann man lägre nivåer av Aβ42 och högre nivåer av T-tau i ryggvätskan jämfört med dem som var i livet vid uppföljningen.

I den tredje studien ingick 435 patienter med AD som behandlades med läkemedlet donepezil och följdes systematiskt under tre år (The Swedish Alzheimer Treatment Study, SATS). Patienterna rekryterades från 10 olika centra i Sverige. Medelvärdet på MMSE-förändringen från behandlingsstart var positivt i mer än 6 månader. Patienterna skattades förbättrade eller oförändrade med en global skattningsskala i 74 % av fallen efter 6 månader, i 49 % efter 1 år, i 35 % efter 2 år och i 30 % av fallen efter 3 års behandling.

Totalt sett var försämringen i skalorna MMSE och ADAS-cog efter 3 års behandling mindre än förväntat jämfört med historiska kontroller och matematiska modeller. Efter 3 år kvarstod 38 % på behandling. De vanligaste orsakerna att patienterna lämnade denna studie var flytt till annat boende eller biverkningar.

I den fjärde studien undersöktes 199 patienter med AD som deltog i SATS-programmet i Malmö. De behandlades med olika ChEI (donepezil, rivastigmine eller galantamine). Vi kunde påvisa att patienterna med stor försämringstakt i MMSE före behandlingsstart uppvisade den bästa behandlingeffekten efter 2 och 6 månader, även när hänsyn tagits till patientens kognitiva nivå vid behandlingsstart. Vi fann också att de patienter som hade lägre kognitiv nivå vid behandlingsstart hade en bättre behandlingseffekt. Varken patientens ålder, kön, genetisk variant av ApoE-protein eller nivå av ryggvätskemarkörer (T-tau, P-tau eller Aβ42) vid behandlingsstart kunde förutse behandlingseffekten av ChEI. Sjukdomens förlopp mätt som förändring i individernas MMSE ändrades signifikant till det bättre vid 2 och 6 månaders behandling.

Sammanfattning

Patienter med AD från vår kliniska vardag har nytta av behandling med ChEI. 75 % av patienterna förbättrades eller var oförändrade efter 6 månaders behandling med ChEI och vissa grupper av patienter var stabila över flera år. Vi har inte kunnat påvisa några säkra biokemiska prediktorer som kan förutse vilka patienter som kommer att ha en bra behandlingseffekt i våra studier. Ett tidigt behandlingssvar kan troligen ha betydelse för faktorer på längre sikt såsom flytt till annat boende. Vår slutsats är att alla patienter bör erbjudas behandling med ChEI. Strukturerade och genomtänkta uppföljningsprogram kan erbjuda stora patientgrupper adekvat behandling och vård över lång tid med ett mindre bortfall än förväntat. Förloppet vid Alzheimers sjukdom förändrades i minst 6 månader av ChEI-behandlingen. Olika metoder används ofta för att mäta behandlingssvar i AD-studier. Vi behöver gemensamt skapa standardiserade metoder för uppföljning och utvärdering av behandlingssvar för att bättre kunna jämföra resultat mellan olika studier. Detta kommer att bli än mer nödvändigt för att utvärdera framtida behandlingsmetoder.

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Appendix

Table A. Long-term studies MMSE change from baseline (positive value means clinical improvement)

	MMSE (mean baseline)	*Baseline (n)*	*Comments*	*6 months*	*1-year*	*2-year*	*3-year*	*4-year*	*5-year*
RCTs									
Mohs et al 2001 (donepezil)	17.1	431			–	–	–		
Winblad et al 2001 (donepezil)	19.4	286	donepezil placebo		–0.7 –2.2	–	–		
Courtney et al 2004 (AD2000) (donepezil)[1]	19 (median)	565	donepezil	0.9[a]	–	<–4	–		
RCTs with open label extensions									
Rogers et al 2000 (donepezil)	(25 mean ADAS-cog)	133		–	–0.8	–4.5	–5.9		
Doody et al 2001 (donepezil)[2]	(range 10–26)	763			–	–	–		
Grossberg et al 2004 (rivastigmine)	19.4	2010			–1.3	–4.3			
Pirtilla et al 2004 (galantamine)	19.4	1039			–	–	–		
Small et al 2005 (rivastigmine)	19.3	1998			–1.3	–4.3	–6.4	–7.6	–8.3
Winblad et al 2006 (donepezil)	19.4	286	continous treatment placebo first year		–0.7 –2.2		–4.9 –6.2		
Open studies from naturalistic settings									
Wallin et al 2008 SATS (don/riv/gal)	22.3	191		0.16	–0.86	–2.6	–3.0		
Wallin et al 2007, SATS (donepezil)	22.0	435		0.3	–0.99	.–3.2	–3.8		
Lyle et al 2007 (donepezil)	18.8	88		–	–	–	–	–	
Raschetti et al 2005 (don/riv/gal)	18.2	5462		0.5[b]	–				
Wallin et al 2004 (tacrine)	20.5	50		–0.7	–3.3	–4.9	–6.5		
Matthews et al 2000 (donepezil)[3]	19.5	80		1.9	1.52	2.5[c]			

RCT= randomised clinical trial

[1] multiple washout periods

[2] 3–6 weeks washout periods before open label study start

[3] if no effect patients stopped the treatment

[a] 12 weeks

[b] 9 months

[c] 18 months

Table B. Long-term studies ADAS-cog change from baseline (negative value clinical improvement)

	MMSE (mean baseline)	*Baseline (n)*	*Comments*	*6 months*	*1-year*	*2-year*	*3-year*	*4-year*	*5-year*
RCTs									
Mohs et al 2001 (donepezil)	17.1	431		–	–				
Winblad et al 2001 (donepezil)	19.4	286		–	–				
Courtney et al 2004 (AD2000) (donepezil)[1]	19 (median)	565		–	–	–	–		
RCTs with open label extensions									
Rogers et al 2000 (donepezil)	–	133		–	2.3	10.2	17.8		
Doody et al 2001 (donepezil)[2]	(range 10–26)	753	placebo at start don 5 mg don 10mg	– – –	3.9 –6.6 2.1 – 2.6 0.7–2.7	11.3–12.9 7.4– 9.1 7.9–10	13.3–18.0 10.5–10.2 11.6–12.2		
Grossberg et al 2004 (rivastigmine)	19.6	2010		–	2.8	8.6			
Pirtilla et al 2004 (galantamine)	19.4	1039			–	–	12.3[a]		
Small et al 2005 (rivastigmine)	19.3	1998			–	–	–	–	–
Winblad et al 2006 (donepezil)	19.4	286			–	–	–		
Open studies from naturalistic settings									
Wallin et al 2008 SATS (don/riv/gal)	22.3	191		0.22	1.9	4.4	5.4		
Wallin et al 2007, SATS (donepezil)	22.0	435		0.74	1.9	6.3	8.2		
Lyle et al 2007 (donepezil)	18.8	88		–	–	–	–		
Raschetti et al 2005 (don/riv/gal)	18.2	5462		–					
Wallin et al 2004 (tacrine)	20.5	50		–1.2	2.4	7.6	10.4		
Matthews et al 2000 (donepezil)[3]	19.5	80		–1.2	0.33	0.34[b]			

RCT= randomised clinical trial
[1]multiple washout periods
[2]3 or 6 weeks washout periods before open label study start
[3]if no effect patients stopped treatment

[a] 12 months completers, 24 mg continuous galantamine treatment
[b]18 months

Table C. Long-term studies, completion rates

	MMSE (mean baseline)	*Baseline (n)*	*1-year*	*2-year*	*3-year*	*4-year*	*5-year*
RCTs							
Mohs et al 2001 (donepezil)	17.1	431	26%				
Winblad et al 2001 (donepezil)	19.4	286	67%				
Courtney et al 2004 (AD2000) (donepezil)[1]	19 (median)	565	52%	20%	3.5%		
RCTs with open label extensions							
Rogers et al 2000 (donepezil)[2]	*27(mean ADAS-cog)*	133	75%	29%	22%	15 %	3 %
Doody et al 2001 (donepezil)[3]	(range 10–26)	763	75%	48%	7%[a]		
Grossberg et al 2004 (rivastigmine)	19.4	2010	74%	48%			
Pirtilla et al 2004 (galantamine)	19.4	1039		47%	30%[b]		
Small et al 2005 (rivastigmine)	19.3	1998	74%	52%	33%	15 %	4 %
Winblad et al 2006 (donepezil)	19.4	286	67%	49%	39%		
Open studies from naturalistic settings							
Wallin et al 2008 SATS (don/riv/gal)	22.3	191	83%	62%	44%		
Wallin et al 2007, SATS (donepezil)	22.0	435	82%	60%	38%		
Lyle et al 2007 (donepezil)	18.8	88	57%	43%	20%	12 %	
Raschetti et al 2005 (don/riv/gal)	18.2	5462	52%[c]				
Wallin et al 2004 (tacrine)	20.5	50	66%	46%	30%	26 %	16 % (4 % with MMSE)
Matthews et al 2000 (donepezil)	19.5	80	36%	15%[d]			
Without treatment							
Holmes et al 2003 (no treatment)	17.0	151	66%	44%	32%		

RCT= randomised clinical trial
[1]multiple washout periods
[2]161 patients enter 12 week RCT, 2 weeks washout, 133 enter open phase
[3]3 or 6 weeks washout periods before open label study start
[a]2.8 years
[b]64% of 12 month completers, continuous 24 mg galantamine treatment
[c] 9 months
[d]18 months

Table D. MMSE response at 6 months of treatment, subgroup analysis

	Responder n=47	Unchanged n=88	Deteriorated n=40	Kruskal-Wallis	Bonferroni-corrections
r0, MMSE/month	–0.496	–0.0941	–0.1225	p=0.000*	re–uc, p<0.001*, re–de, p<0.01*
MMSE, mean±SD	20.8 ±4.6	23.5 ±4.3	21.5 ±5.1	p=0.002*	re–uc, p<0.01*
ADAS-cog (70), mean±SD	19.6 ±10.5	17.3 ±9.5	22.9 ±10.2	p=0.005*	uc–de, p<0.01*
IADL baseline, mean±SD	16.0 ±5.6	14.2 ±5.5	17.9 ±6.3	p=0.004*	uc–de, p<0.01*

r0 = pre-treatment progression rate
re = responder, uc = unchanged, de = deteriorated
* significant

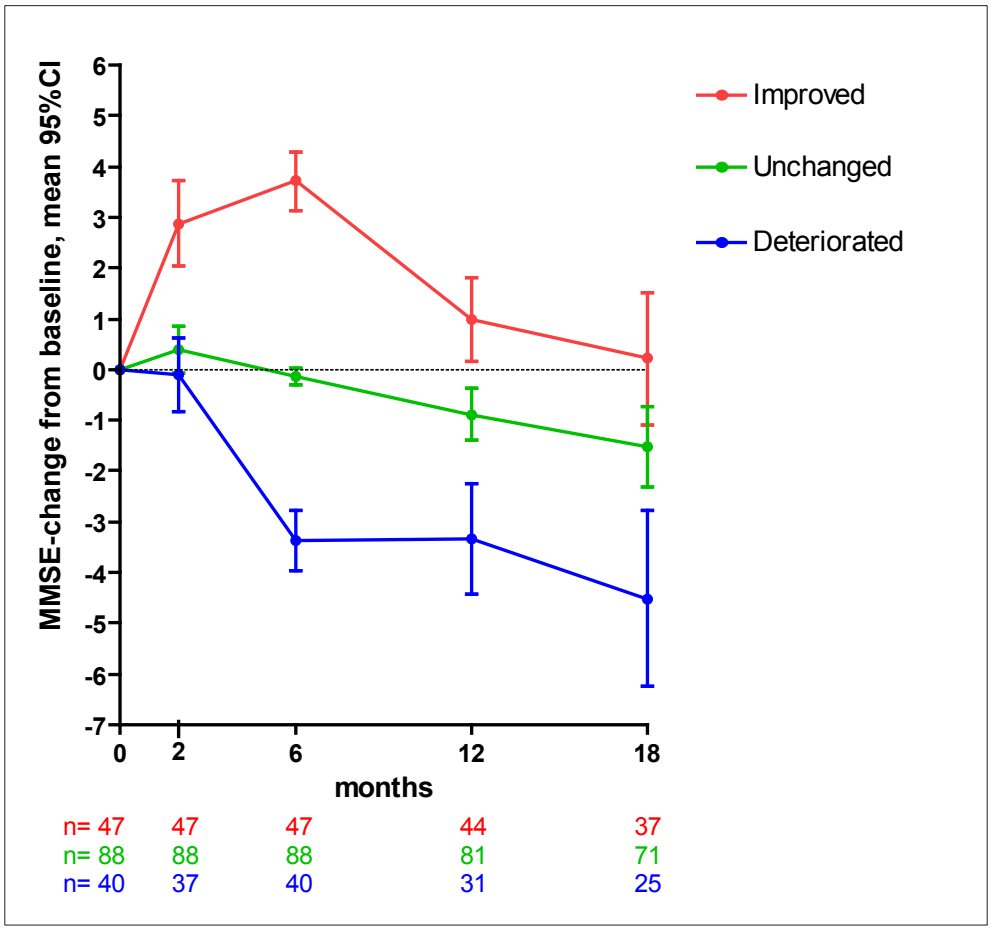

Figure A.
Mean MMSE change from baseline over 18 months in the three different response groups at 6 months of ChEI treatment. The heterogeneity of response is illustrated.