Comparison of cognitive decline medications of Alzheimer´s disease

Efficacy and safety of Donepezil, Galantamine, Rivastigmine and Memantine

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Abstract

Introduction:

Alzheimer’s disease (AD) is a chronic neurodegenerative disease, mostly caused by age-related loss in neuronal function affecting memory, thinking and behavior. Prevalence of this most common form of dementia is highest in patients over age 65. The direct cause to disease is still not known. But there are theories stating the cause of the neuronal dysfunction in AD being due to accumulation of extracellular amyloid-beta plaques and intercellular neurofibrillary tangles. These are toxic to the nerve cells and cause loss of nerve cells and synapses.

Currently there are three approved drugs Donepezil, Rivastigmine and Galantamine all functioning as cholinesterase inhibitors. These drugs cannot stop AD progression, but rather slow down the resulting dementia symptoms and improve the quality of life. These drugs interfere with the breakdown of the acetylcholine to increase the levels of the neurotransmitter at the synapse which is shown to be depleted in AD. Memantine is another approved drug that acts as a NMDA (N-methyl-D-aspartate) receptor antagonist and protects the postsynaptic neurons from excitotoxicity from the neurotransmitter glutamate which, according to some studies, have resulted cognition improvement. The aim of this study is to analyze and compare the efficacy and safety of Donepezil, Rivastigmine, Galantamine and Memantine.

Method:

The search for articles was carried out in PubMed to collect mainly clinical studies of randomized controlled trials. 6 original clinical trials were chosen mainly based on improvement of cognitive function.

Results:

All 6 studies indicated efficacy, compared to placebo and/or baseline for the above mentioned four drugs. No major adverse effects connected to the drugs have been reported in either study. All placebo-controlled studies reported similar side effects with no significant difference between drug and placebo. No clinically emergent side effect was reported in open-label studies included in this work. The adverse effects in open-label studies were similar to placebo-controlled studies and couldn’t be related to drug.

Discussion:

The magnitude of cognition improvement among the drugs were in the same range and no comparable difference could be seen from the data. Commonly observed side effects for all four drugs were reported to be diarrhea, nausea and vomiting.

Conclusion:

All four drugs have demonstrated slowing cognitive deterioration while being tolerable without any major side effects.

Keywords: Alzheimer’s disease, Donepezil, Rivastigmine, Galantamine, Memantine and randomized controlled trials.
Abbreviations:

ACh – Acetylcholine
AchE - acetylcholinesterase
Aβ - β-amyloid
AD - Alzheimer’s disease
ADAS-cog - Alzheimer’s Disease Assessment Scale - cognitive
ADL - Activities of Daily Living
ApoE - apolipoprotein E
APP - amyloid precursor protein
ChAT - choline acetyltransferase
CIBIC+ - Clinician’s Interview-Based Impression of Change Plus Caregiver Input
MMSE - Mini-Mental State Examination
SIB - Severe Impairment Battery
GBS - Gottfries-Bräne-Steen (GBS) scale
NMDA receptor - N-methyl-D-aspartate receptor
Introduction

Dementia is originated from the Latin word demens which means “without mind”. Dementia is a progressive disease causing with deterioration of cognitive function severe enough to effect normal daily activities. Such deterioration can ultimately disable the patient to perform basic daily functions, requiring care from family or other caregivers [1].

Alzheimer’s disease (AD) is the most common form of dementia and accounts 60-70 percent of the cases [2]. Vascular dementia is the secondary leading form of dementia and is caused by reduced oxygen supply to the brain due to narrowing or blockage of blood vessels. This disease can occur together with AD and is called mixed dementia. Frontotemporal dementia, Lewy body dementia and Parkinson’s disease dementia are other form of neurodegenerative diseases with cognitive deficits. All the mentioned forms of dementia, although being caused by different factors, results in deterioration of memory and cognitive functions and shortened life span of the patient [1,3].

Alzheimer’s disease (AD) is named after a German physician Alois Alzheimer who described the disease for the first time in 1906. Dr. Alzheimer discovered the disease when he examined the post-mortem brain of one of his patients, a 51-year-old woman Auguste Deter, which was suffering from progressive cognitive impairment with memory loss, spatial disorientation, and delusions. Dr. Alzheimer performed an autopsy of Auguste’s brain morphologically and histologically. He observed that Auguste’s brain was atrophied showing a reduction in its volume. He also found abnormal deposits in and around nerve cells known today as senile plagues and neurofibrillary tangles [4].

Risk factors

Aging and familial inheritance are some of the major risk factors causing AD among the patients, hence AD is observed mostly in the elderly [3]. Prevalence of AD is estimated to be 13% among patients with age 65 and increases to 45% in patients over age 85. Family history of AD also increases the chance of getting AD. Chances are greatest when at least one first degree relative (parents or sibling) have been diagnosed with AD. One reason for such high risk is genetic inheritance of three specific genes associated with Autosomal dominant familial AD. One of these genes is the amyloid precursor protein (APP) located on chromosome 21 whose mutation causes AD. Many patients suffering from down syndrome (trisomy of chromosome 21) will develop AD. Studies have also shown that a mutation in the presenilin genes on chromosome 1 and 14 are also linked to AD. Studies have also found that an allele type ε4 of apolipoprotein E (ApoE) is the main genetic risk factor of AD. ApoE protein is a plasma protein involved in cholesterol transport and has a role in neuronal repair [3,5].

Lifestyle choices and other diseases can also increase the chance of developing AD. Some population studies have shown that smoking, alcohol consumption, high blood pressure in middle age, and diabetes are associated with AD and vascular dementia [3,6]. Furthermore, studies have shown the social status and social interaction can also independently effect risk for developing AD, including: gender (females have increased risk, but also live longer); low education level; depression in young age; lack of social interaction and stimulating environment, are all associated with AD [3].

There are also some studies indicating factors which decrease the chance of developing AD. High educational level i.e. more brain activities during life is one of such factor. Individuals having used NSAID for long time, and postmenopausal estrogen
replacement therapy and statin drugs have a lower incidence to develop AD. There is however a need for more studies to confirm these findings [3,6].

**Symptoms**

The precise date of the onset is difficult to determine for AD, because the symptoms of AD come very slowly and are very mild in the beginning. It can go many years before the family of the patients can see that the everyday functioning of the patient has been sufficiently reduced to the point that they seek professional help. The progression of AD symptoms can be divided into three stages: mild, moderate and severe. The progression, and how the patient experiences the symptoms, are very individual; but there are some core symptoms in all stages of the AD [6,7].

In the mild stage of AD, the first symptoms that show are forgetfulness, specifically, memory of recent events is impaired. The patient often repeats questions and statements, and misplaces items. The patient has difficulty to recall recent conversations or events, but past memory of life events still seems to be clear. The patient also suffers from minor disorientation of places and time. Impaired problem solving, poor attention and judgment problems are also normal. The mildly AD patient can still perform self-care activities of daily living and can be normal to the casual observers [6,7].

When the patients advance to the moderate stage of AD, the memory of recent events, confusion about relationships and identifications of near relatives starts to be more severe. The daily self-care activities, inclusive of driving skills, starts to decline; and the patient’s cognitive decline starts to be more noticed by the observers. Patient can easily be lost in familiar places, the language deficits become more severe with incomplete sentences. Patients also suffers from agitation and restlessness including wandering, have difficulty with day and night orientation and get sleep disturbances and start to hallucinate [6,7].

In the severe stage of AD, the patient need total care of a caregiver for the basic daily functions. The patient has difficulty to remember its own family members properly. The patient speaks with single words. In this phase, the patients partly are in bed the whole time and suffer from seizure, weight loss, swallowing problems, urinary and fecal incontinence. An AD patient lives up to 8 to years. The cause of the death for many AD patients is due to aspiration, pulmonary embolus or infections. Infections are normally pneumonia [6,7].

**Diagnosis**

The most difficult part of diagnosing AD is that the precise onset of the disease is very difficult to predict. The neurodegenerative pathogenesis of the cognitive dysfunction may start 2-3 decades before the first symptoms of AD appears. Since the disease is most common in elderly patients, it is difficult to determine if it is a beginning of a normal age-related memory loss or the result of a neurodegenerative loss of the cognitive skills that will eventually progress [6].

The diagnostics of dementia, in general, is established by Diagnostics and Statistics Manual fourth edition (DSM-IV) of American Psychiatric Association. Dementia criteria are met when multiple cognitive deficits including memory impairment and aphasia (inability to communicate effectively), or apraxia (inability to do voluntary motor tasks), or agnosia (inability to process sensory information), or disturbance in executive
functioning are detected. Executive functioning represents the ability to plan, organize, sequence, and abstract [6].

The criteria specifically designed for AD diagnostics were published by National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRA) back in 1984. The aim of NINCDS-ADRA publication was to standardize AD diagnostics criteria. The NINCDS-ADRA are like the above mentioned DSM-IV criteria. NINCDS-ADRA is currently more used to diagnose dementia for clinical research studies [6].

Table 1. AD diagnostic criteria by DSM-IV and NINCDS-ADRA (reproduced from Zaven S. Khachaturian et al.)

<table>
<thead>
<tr>
<th>Diagnostic criteria of AD based on DSM-IV</th>
<th>Diagnostic criteria of AD based on NINCDS-ADRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of multiple cognitive deficits:</td>
<td>Dementia is documented by testing.</td>
</tr>
<tr>
<td>o Memory impairment,</td>
<td>o Deficits in at least two cognitive areas.</td>
</tr>
<tr>
<td>o And at least one of the following:</td>
<td>o Progressive worsening of memory and other cognitive functions.</td>
</tr>
<tr>
<td>• Aphasia</td>
<td>o No disturbance in consciousness.</td>
</tr>
<tr>
<td>• Apraxia</td>
<td>o Age between 40 and 90 years.</td>
</tr>
<tr>
<td>• Agnosia</td>
<td>o Absence of systemic disorder or other brain diseases that could cause progressive memory loss and cognition.</td>
</tr>
<tr>
<td>• Disturbed executive functioning</td>
<td>o Diagnosis is supported by:</td>
</tr>
<tr>
<td>Continued gradual cognitive decline.</td>
<td>o Progressive deficit of aphasia, apraxia, and agnosia.</td>
</tr>
<tr>
<td>Deficits have effected social and occupational function compared to past.</td>
<td>o Impaired daily activities.</td>
</tr>
<tr>
<td>All other causes which could introduce the above cognitive deficits are excluded.</td>
<td>o Family history of AD.</td>
</tr>
<tr>
<td></td>
<td>o Laboratory results.</td>
</tr>
</tbody>
</table>

As shown in table 1, both methods for diagnosing AD require some laboratory examinations and tests to exclude all other possible causes which can impair the cognitive function of AD.

These laboratory examinations include (Zaven et al):
- Blood and urine tests
- Brain imaging using CT, MR, PET, or SPECT
- Functional imaging e.g. functional MRI. This method is very helpful in distinguishing between the different types of cognitive disorders, excluding vascular dementia.

Many patients deny their condition and therefore the physicians have to see the condition decline from other people’s view. Interviews with family members or others closely associated with the patient must be taken to make a decision of the cognitive decline of the patient. Therefore, many follow up examinations should be done to estimate the cognitive progression of the disease [6].

Some processes have to been gone through to evaluate if a patient might have a dementing illness. The evaluation process includes the patients history (interview with the patient and their close associates, present illnesses, family history, social history) an thorough physical (blood pressure, pulse, respiratory rate, attention to heart condition, checking the baroreflex, liver and spleen) and neurological examination (mental status,
cranial nerves, motor system, reflexes and sensation) and some screening laboratory tests (blood count, electrolyte panel, screening metabolic panel, thyroid function tests, levels of vitamin B12 and folate, tests for syphilis and HIV, urinalysis, electrocardiogram and chest X-ray) is required to be done and taken [6,8].

Brain imaging tests are also a part of the screening laboratory tests such as computed tomography (CT) to exclude for instance hemorrhage, infarctions, tumor and abscess. Magnetic resonance (MR) can detect recent infarctions, plaques of multiple sclerosis and can detect focal pathology in sites which cannot be visualized by CT scans. PET and SPECT are types of MR imagining that can, with help of injected pharmacological agents that work as source of radiation, give an image of the brain condition. This provides information that can be helpful to differentiate among certain types of cognitive disorders. In most cases, neurophysiological tests are done to test the patient’s memory, attention, language, judgement, control of movement and other cognitive abilities that are impaired by brain disease. These tests are also useful for keeping track of changes in the patient’s cognitive status over time [6,8].

Neurophysiological evaluation

Neurophysiological evaluation tests are commonly used as a method to measure the progression of AD over time as the cognitive function normally deteriorates with time. Such time related deterioration can be used to measure the efficacy of a treatment and whether the patient should continue, or switch the prescribed drug. Some of the commonly used neurophysiological tests are summarized below [9]:

**MMSE**
The Mini-Mental State Examination (MMSE) is commonly used to screen cognitive impairment and cognitive function deterioration over time. This test is used both clinically and in research, however in clinical research this test is commonly used as secondary outcome. MMSE is a 30 points questionnaire with the highest score indicating no cognitive impairment and takes around 10 minutes. Questions in the MMSE evaluate the patient’s orientation, registration (immediate memory), short-term memory, and language functioning. Individuals scoring MMSE scores of 24 or below indicates cognitive impairment [3,9].

**ADAS-cog**
ADAS-Cog (Alzheimer´s Disease Assessment Scale-Cognitive Subscale) is commonly used in pharmacological clinical trials as a primary outcome instrument to measure cognitive changes. The instrument contains 70 points, with higher points indicating severity in cognitive impairment [3,9].

**SIB**
SIB (Severe Impairment Battery) is a method specifically developed to measure progression and thereby efficacy of a treatment on severely impaired AD patients, as the name implies. SIB is a 100 points scale with a low number indicating cognitive impairment [10].

In addition to the above evaluation methods, specific to measuring cognitive function, there are other evaluation tests designed to measure e.g. the global change in an AD patient. One of the most commonly used methods is the CIBIC-plus or CIBIC+ (Clinician’s Interview-Based Impression of Change Plus Caregiver Input). CIBIC+ is
performed as a semi-structured interview which covers cognition, behaviour, and function. It is commonly used as a primary outcome in clinical research [3,9].

Furthermore, since the motoric function of an AD patient is also normally reduced by cognitive impairment, an evaluation test to measure the motoric functions is also necessary. One of the commonly used method to evaluate motoric function is the ADL (activities of daily living) method and is mostly used as secondary outcome measurement in clinical research. Basic ADL evaluation examines the ability of the patient to perform daily tasks such as taking a bath, brushing hair, getting dressed, use of toilet and the corresponding afterward cleaning, mobility, and eating [3,9,10].

Pathology

The underlying cause of the neuronal dysfunction in AD is still not well understood, however there are several suspects. The pathology of AD is mainly due to loss of nerve cells and altered synaptic function. The cause behind this neuronal dysfunction is associated with two main hypotheses that describe the cause of the Alzheimer’s disease: the β-amyloid hypotheses and the hypotheses of hyper-phosphorylation of tau protein [11].

AD is characterized by neuropathological microscopic lesions. β-amyloid plaques and neurofibrillary tangles are associated to cause these lesions. The β-amyloid plaques originate from β-amyloid proteins that aggregates with each other and forms misfolding plaques between nerve cells. Tangles, on the other hand, originates from the tau protein that undergoes an abnormal hyperphosphorylations and form neurofibrillary tangles which aggregates inside the nerve cell bodies. Both the β-amyloid plaques and the neurofibrillary tangles are neurotoxic and cause loss of nerve cells and loss of synapses [12].

The amyloid Hypothesis

The Amyloid Hypothesis is the theory of accumulation of a small protein fragment namely β-amyloid (Aβ) which initiate the neurodegenerative events of Alzheimer disease. Aβ consists of approximately 40 – 42 amino acids. Aβ is a cleavage product of the amyloid precursor protein (APP). This protein is found on the membrane of many types of nerve cells. Large part of this protein is embedded in cells membranes but its exact function is still largely unknown. There are however theories about its role in the plasticity of neurons. To yield Aβ, the APP is cleaved by the enzymes β secretase and γ secretase. When Aβ molecules are released from APP these form soluble oligomers which later aggregate with other Aβ with β sheet structures to insoluble toxic fibrils being resistant to degradation. The aggregation of the Aβ is toxic to the neurons and cause neuronal loss due to activation of damaging inflammatory cascades [13,14].

There are also genetic factors that can cause the Aβ protein pathology cascade in AD. Mutations in the genes located on chromosome 21, 14 and 1 have a role in onset of AD at early age. The above mentioned APP gene is located on chromosome 21 and a mutation in this gene can start onset of AD already in age of 40-50 years.

Onset of early age AD due to mutations in genes include presenilin 1 (PSEN1) and presenilin 2 (PSEN2), 2 of the 4 components of the catalytic subunits of γ secretase – both having a role in cleavage of APP and located on the chromosomes 14 and 1. PSEN1 can have a penetrance at age of 25 years; while PSEN2 can have a penetrance at 45 years [13,14].
Another genetic risk factor coupled to AD is Apolipoprotein E (ApoE) which is located on chromosome 19. It might have a role in the late onset of AD and is associated with familial and sporadic cases of AD. Sporadic cases refers to those not having any familial history of AD. There are two isoforms of ApoE, namely ApoE2 and ApoE3. APOE gene code is represented by three alleles (ε2, ε3, and ε4). The APOE ε4 allele is a common genetic risk factor for AD and has a possible involvement in Aβ deposits [13,14].

The Tau – protein hypothesis

Tau proteins are microtubule associated proteins (MAP). These proteins are mostly abundant in neurons and stabilize microtubules in axons of the neurons. In its phosphorylated form, it is also present to some degree on the somadendritic compartments. Tau gene is encoded on the long arm of the exon 17. This gene codes for six isoforms of the Tau protein which are generated by alternative splicing. The isoforms are distinguished by their number of binding domains. Three of the six isoforms have three binding domains and the remaining have four binding domains. The binding domains are positively charged and are located in the carboxy-terminus of the protein. The positively charged domains bind to the negatively charged microtubules. Tau protein is hydrophobic and is unfolded in its native form. In AD, the Tau protein hyperphosphorylates when the balance between kinases and phosphatases is tipped in favour of phosphorylation. The phosphorylated Tau protein then loses attachment to the microtubules and destabilizes the structure of axons; hence transportation within axons is disrupted. Altered and aggregated forms of Tau proteins act as a toxic stimulus to start neurodegeneration [15,16].

Treatment

Today there is still no treatment for curing AD. Studies have shown that the decline of the memory is a result of an impairment of acetylcholine (ACh) and glutamate producing neurons and their associated synapses.

Reports from the 1970s indicated a deficit of choline acetyltransferase enzymes (ChAT), in AD, which is responsible for the synthesis of the neurotransmitter ACh. ACh has a role in the peripheral and central nervous systems and is the neurotransmitter of the cholinergic neurotransmission. Cholinergic hypothesis is the oldest hypothesis that stated a reduction of the cholinergic neurons activities causes AD [17].

The synthesis of Acetylcholine

ACh is synthesized from the enzyme choline acetyltransferase (ChAT) in the cytoplasm of the cholinergic neurons. This neurotransmitter is then transported by the vesicular acetylcholine transporter (VACHT) from the cytosol into synaptic vesicles. ACh is exocytosed and released into the synaptic cleft when the presynaptic neuron is depolarized. From the synaptic cleft ACh binds to the nicotinic or muscarinic receptors and activates them. These receptors are located on the postsynaptic neurons. The remaining ACh that is present in the synaptic cleft is inactivated by the enzyme acetylcholinesterase (AChE) to choline and acetate. The AChE is normally associated on the plasma membrane of the postsynaptic neuron. The choline that is released by breakdown of ACh is taken back to the presynaptic neuron by active transport. This choline is resynthesized to ACh by the ChAT [18].
Acetylcholine inhibitors

Cholinesterase is a family of enzymes that catalyzes the hydrolysis of the neurotransmitter acetylcholine (ACh) into choline and acetic acid. It is a reaction which is necessary to allow a cholinergic neuron to its resting state after activation. There are two types of cholinesterase inhibitors namely acetylcholinesterase (AchE) and Pseudocholineesterase (BuChE) also known as butyryl cholinesterase. AChE inhibitors can act both reversibly and irreversibly. The reversible inhibitors can act as competitive or noncompetitive inhibitors. These are the ones which are mostly used in therapeutic application. The irreversible AChE activity is more associated with toxic effects (18).

Acetylcholine inhibitors in Alzheimer’s disease treatment

Treatment of AD interferes with cholinesterase enzyme of the breakdown of the acetylcholine to result in an increase of the neurotransmitter at the synapse. Acetylcholine is normally depleted in AD. The result of this gives a slowdown and improvement of dementia symptoms [19].

Medication currently approved by the U.S food and Drug Administration (FDA) and the European Medicines Agency (EMA) to treat the cognitive decline symptoms of AD are Donepezil, Rivastigmine and Galantamine [18]. Memantine is another approved drug which protects neurons from excitotoxicity. It acts as an antagonist on the as NMDA (glutamate) receptor. According to some studies Memantine gives improvement results at the severe stage of AD [20].

Donepezil

Donepezil is sold under the trade name Aricept and is a noncompetitive selective fast reversible inhibitor of AChE that binds to the anionic site of the enzyme. This drug is prescribed for symptomatic treatment of mild and moderate AD. Some studies have shown that donepezil can also relieve symptoms of severe AD patients. The drug is available in 5 and 10 mg dose strengths. The initial dose of treatment is 5 mg/day before bedtime. The patient is evaluated after one month of treatment and the dose is then, normally, increased to 10 mg/day [18,21].

Rivastagamine

Rivastagamine is sold under the trade name Exelon and is a slow reversible carbamate inhibitor that binds to the esteratic site of the AChE to inhibit the enzyme action. Rivastagamine doesn’t selectively bind to AChE, it also binds to BuChE to inhibit its action. This drug is used in the symptomatic treatment of mild to moderate AD. The drug is administered orally as capsules or liquid formulations. The treatment starts with doses of 1.5 mg twice a day. One dose should be taken in the morning together with breakfast and the later dose with late evenings meal. An evaluation of the drug tolerability is done after two weeks and if tolerable the dose is doubled. The dose can further be increased to 4.5 mg and 6 mg twice a day. An evaluation should be done after two or four weeks after each dose increase. The patient can stay on a dose that is well tolerated without any severe side effects [18,22].

This drug is also available as patches enabling transdermal administration. This type of administration provides a continuous and steady delivery lasting for up to 24 hours. The patches are available in 3 doses; 4.6 mg, 9.5 and 13.3 mg. Lowest doses are prescribed initially and subsequently titrated. The highest dose (13.3 mg) is only prescribed if it is well tolerated, otherwise 9.5 mg is the most recommended daily dose. One patch contains 24 hours dose [22].
**Galantamine**

Galantamine is sold under the trade name Reminyl and this substance is isolated from the plant *Galanthus woronowii* and is an alkaloid. It is a selective competitive rapidly-reversible AchE for the treatment of mild to moderate AD. The drug binds to the anionic subsite and the aromatic gorge. The drug also binds as an allosteric ligand to the nicotinic receptors inducing modulation. It also binds to the sites separate from those that the ACh binds to and acts to enhance the activity of nicotinic receptors in the presence of ACh. The treatment of the drug is started at a dose of 4 mg twice daily and can be increased to 12 mg twice daily after four weeks. The patients should stay on the dose of 8 mg per day for 4 weeks. If this dose was well tolerated the dose can be increased to 12 mg twice a day. The dose can be lowered back to 16 mg per day if the 24-mg dose was not tolerable. The doses should be taken with meals, morning and evening times [18,23].

**NMDA receptor in severe AD treatment**

Another theory that is involved in AD pathogenesis is excessive activation of glutamate receptor—a process that is called excitotoxicity and cause neuronal damage because of excessive Ca2+ influx inside the cell. This overload of Ca2+ impairs the neuronal plasticity causing its damage [20].

**Glutamatergic Hypothesis**

Glutamate is a neurotransmitter associated with learning. It has been shown that there is an excessive stimulation of the glutamate neurotransmitter on the N-methyl-D-aspartate receptor (NMDA receptor) in AD. NMDA receptor is found on the post synaptic nerve cells. This receptor works as ligand gated ion channel for Ca2+ ion influx. The receptor consists of four subunits. So far three of the four subunits of this receptor have been described NR1, NR2 and NR3. NR1 and NR2 are involved in the channel activation, where NR2 has an agonist site for the neurotransmitter glutamate and the NR1 subunit has the co-agonist subunit for the neurotransmitter glycine. Both neurotransmitters must bind to the receptor for its full activation. Full opening of the channel is voltage dependent because the endogenous part of the channel is blocked by Mg2+. Another receptor called AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) which is also located on the postsynaptic neuron also has an agonist site for glutamate. Binding of glutamate mediates the activation of AMPA so Na2+ ions can flow through the channel. This inflow of Na2+ changes the membrane potential and depolarizes the postsynaptic neuron and mediates the releasing of the interior Mg2+ ion from the NMDA receptor. This gives the full activation of the NMDA receptor and opening of the channel so Ca2+ ions can flow through the channel [20].

In AD, there is an overstimulation of glutamate which overexcites the NMDA receptor. The hyperexcitation removes the blocking Mg2+ for a longer period, thus a large influx of Ca2+ ions are induced. The excess of the Ca2+ damages the neurons. One approved drug to stop overexcitation of the NMDA receptor is Memantine [20,24].

**Memantine**

Memantine is sold under the trade name Ebixa and is an uncompetitive antagonist of the NMDA receptor. Memantine works by blocking the open channel of the NMDA receptor and decreases the overflow of the Ca2+ ions inside the postsynaptic neuron. It blocks the channel like the Mg2+ ions and it is not voltage dependent when there is excess overstimulation of glutamate. In normal physiological conditions this drug dissociates from the channel when it is depolarized [20,24].
The drug treatment starts with a dose of 5 mg taken once per day. The dose increases by 5 mg per week to a maximum dose of 20 mg per day. If the patients suffer from side effects, such as confusion, the dose is reduced again [34].

**Objective**

Although the use of the drugs for treatment of AD symptoms are common, their efficacy is not necessarily comparable and their effect might be different for different patient groups. Health professionals should therefore have an overview and common understanding of efficacy of the different drugs which can enable them to better prescribe and treat the patients.

The aim of this project is to investigate the efficacy and safety of Donepezil, Galantamine, Rivastigmine and Memantine for AD symptomatic treatment.

The project intends to clarify some research questions regarding AD drugs:

- Is there any comparable difference between the four drugs in term of their efficacy and side effects?
- How long do the treatment benefits last?

**Method**

The search for articles was carried out in PubMed database identifying original research articles of clinical randomized controlled trials that have been published mainly the latest 10 years. However, for the drug Donepezil a search was done from year 2000-2017, to find an article to mainly to find a long-term study that was done for mild-to-moderate stage of AD. In latest 10 years, no new clinical trials have been done for this beginning stage of AD so therefore a longer historical search was made. For the drug Memantine a search from 2002-2017 was done to find a clinical study that could give some good efficacy value on cognition improvement.

The relevant articles were chosen based on the title, reading the abstract and the limits were randomized controlled trials. Some inclusion criteria were included when the articles were chosen. The population to be studied should have been diagnosed with AD based on standardized criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, or the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association. Therapeutic doses should be given for at least minimum 12 weeks to make a conclusion of the treatment effect. There should also be relevant validated scale to measure the outcome of cognitive and global function.

Mesh keywords such as: Alzheimer’s disease, Donepezil, Rivastigmine, Galantamine, Memantine and randomized controlled trials were used to filter for relevant articles.

Table 2 shows the search terms, filtering keywords (Limitation) and the number of articles as result of each search. The articles were briefly reviewed, for each search, and the most relevant articles were identified and selected which are also indicted in Table 2.
For the introduction one book was chosen for getting clarification of the cause, diagnosis and treatment of the AD. Google and google scholar were searched for key words such as: Alzheimer’s disease, Pathology, drug therapy, cholinesterase inhibitors, Donepezil, Galantamine, Rivastigmine and Memantine.

Table 2. Literature search in PubMed.

<table>
<thead>
<tr>
<th>Date</th>
<th>Search Terms</th>
<th>Limitations</th>
<th>Number of Items</th>
<th>Selected References</th>
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<td></td>
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Results

Efficacy and safety

Donepezil

1. Efficacy and Safety of Donepezil in Chinese Patients with Severe Alzheimer’s Disease: A Randomized Controlled Trial [25]

A recent study that was published 2017 by J. Jia et al. to study efficacy and safety of donepezil in patients with severe AD. The multicenter randomized double blinded placebo-controlled parallel group study was 24 weeks long. 38 investigational hospitals in china was involved in the study. The age of the patient was between 50-90 years. The inclusion criteria were that the diagnosis of AD should have been confirmed by brain computed tomography (CT) or magnetic resonance imaging (MRI) scans and some laboratory test to rule out other causes to the condition. The Mini-Mental State Examination (MMSE) scores should be between 1 and 12, and SIB scores from 10 to 90. The exclusion criteria were as follows: all disorders that might have affected the cognition
of the patients was excluded. Patients who had difficulty to swallow a tablet, taking treatments of other cholinesterase inhibitor or memantine were also excluded. This was if these drugs were taken within 3 months prior to the study start and aswell if the patient had received a poor response to the donepezil. The patients were randomly divided into two equal groups. The control group got the test drug and the placebo group a tablet looking similar to donepezil. For 6 weeks, they got a dose of 5 mg of the test drug and the remaining 18 weeks they got a dose of 10 mg. The safety parameters were monitored throughout, and the test drug was not reduced to a lower dose if the patient felt intolerant of the drug.

The primary efficacy endpoint was chosen as the change of SIB score from baseline to week 24 of the trials. The secondary endpoints were the overall score in CIBIC+ and the change of total MMSE from baseline to week 24 of the trial. Missing values in SIB were adjusted with last observation carried forward (LOCF) method.

The trial results claimed that the total SIB score favored the Donepezil group compared to Placebo group. SIB score for drug group was improved by 4.8 compared to placebo group at week 24.

The trails result also show that CIBIC+ showed improvement for drug group from baseline to week 24 while the Placebo group showed unchanged CIBIC+ score between baseline and week 24 measurements.

The MMSE score showed no significant difference between the drug and placebo group. Both groups had improved MMSE scores at week 24 compared to baseline.

The study also reports that 43.4% of all participants experienced at least one adverse effect (AE) during the trial period (26.7% of placebo group and 16.7% of drug group). Most AE were mild to moderate in severity.

Five AEs namely sinus bradycardia, anorexia, Q-T interval prolongation, dizziness, diarrhea was considered, by investigators, to be caused by the drug. Severe AEs were more common in placebo group. 4 people died during trial period (1 in drug group and 3 in placebo group) which the investigators considered to be not related to the drug.

**A long-term study on efficacy and safety of donepezil**


Subbiah et. al. have performed a long-term study on efficacy and safety of donepezil treatment for patients with mild to moderate AD published in 2001. The study was carried out for 52 weeks at 28 sites in five European countries (Denmark, Finland, Norway, Sweden, and The Netherlands).

In total 286 patients participated in the studies which was randomized to two groups (donepezil n=142, and placebo n=144). The participants were both men and women between the age of 40-90 years with mean age 72.5 years.

Inclusion criteria consisted of diagnosis of AD based on DSM-IV as well as NINCDS-ADRDAs diagnostics methods. The patients had to have a mild to moderate AD confirmed by the MMSE score between 10-26.

Exclusion criteria consisted of some significant clinical conditions as well as other chronic diseases such as diabetes and asthma.

The donepezil group was treated with doses of 5 mg/day during the first 28 days of study followed by an increase to 10 mg/day for the remaining study period. If required, in some cases, the dose was reduced to 5 mg/day for some patients. Efficacy measurement were taken for both groups at screening, baseline, week 4, 12, 24, 36, 52 of the study.
The primary outcome of efficacy was measured by the Gottfries-Bråne-Steen (GBS) scale which according to the authors is a comprehensive global assessment for rating dementia symptoms. The authors argued to choose GBS, instead of the commonly used AD Assessment Scale-cognitive sub-scale (ADAS-cog), as GBS is a more comprehensive global rating of dementia symptoms and sub-domains measures which are missing in the ADAS-cog.

GBS assesses patients over four domains:
- Intellectual impairment (GBS-I),
- Motoric which includes basic functions related to activities of daily living (GBS-ADL),
- Emotional reaction/function (GBS-E),
- and dementia symptoms which represent pathological aspects of behavior (GBS-S).

The above mentioned four domains contain, in total, 27 assessment items each being scored from 0 to 6 meaning a patient can get a GBS score between 0 and 162 with high numbers indicating deterioration of symptoms. Mini-Mental State Examination (MMSE), Progressive Deterioration Scale (PDS), Neuropsychiatric Inventory (NPI), and Global Deterioration Scale (GDS) were included as secondary assessment of efficacy.

The safety of drug was assessed by monitoring, among other things, the adverse effects, changes in vital signs, and EKG abnormalities. All efficacy variables at the above mentioned measurement points and at the end which including Last Observation Carried Forward (LOCF) were analyzed by a covariant model (ANCOVA) to estimate the effect of treatment. All tests were two-sided with a p value of 0.05 considered to be statistically significant.

Efficacy results: The results indicate that both donepezil and placebo groups were comparable at baseline with GBS score for donepezil being 29.51±17.33 and for placebo 29.77±17.84 (p=0.014).

The study indicates that least squared (LS) mean value (±SE) of GBS score for donepezil group at week 52 has declined half as much (±SE=3.6±1.1) as the placebo group (±SE=7.3±1.1). This means both groups have experienced a deterioration of the symptoms but the deterioration in donepezil group has been slower.

±SE of MMSE score, the secondary assessment of efficacy, also indicated difference between the two groups. The score of the donepezil group remained close to the baseline i.e. no deterioration of cognition symptoms while the score of placebo group has dropped by more than 2 points.

More interestingly, the study indicates that the GDS score of the donepezil group had improved, indicating some sort of recovery while GDS score of placebo group has indicated deterioration of symptoms. The authors argue the GDS results might either indicate that such score, to be correct, should be carried out for an even longer period, as it is not as sensitive an assessment tool compared to e.g. MMSE.

Safety results: The study was completed by 66.9% of donepezil and 67.4% of placebo participants. Most of the dropouts, according to the study, were due to withdrawal of consent. Other reasons of discontinuation were AEs and insufficient clinical response. The study indicates that 81.7% of donepezil and 75.5% of placebo groups experienced at least one treatment-emergent AE over the course of the study. Although these numbers are rather high but still comparable in both groups.
Efficacy and safety of Galantamine

Galantamine efficacy and safety when switched from Donepezil.

3. Two galantamine titration regimens in patients switched from donepezil [27].

The main objective of this study was to study the efficacy and safety in patients receiving galantamine at two different rates of dose increase (titration) over a period of 12 weeks. Since all subjects were individuals whom had switched from donepezil to galantamine, the study also could provide an overview of galantamine efficacy and safety for switching donepezil to galantamine.

The study was a 12-week randomized, open label, flexible dose trial carried out between 2000 and 2001 at 11 centers in Norway and Sweden where 104 subjects were screened among which 89 were chosen for the study with average age of 74.6 (0.8 SE) years.

Inclusion criteria required all subjects to be diagnosed with mild to moderate AD according to NINCDS-ADRDA. Subjects were also evaluated with MMSE and were required to have a MMSE score between 10-24 and an ADAS-cog/11 score of ≥12. All subjects had received donepezil for ≥8 weeks and due to lack of efficacy or tolerability were required to switch to galantamine.

Major exclusion criteria were neurodegenerative disorders other than AD, as well as some other conditions.

All subjects went through 7 days of donepezil-washout period prior to receiving galantamine. Initial dose of galantamine was 8mg/day. The fast titration group was increased in their dose to 16mg/day with increments of 8mg/week, while slow titration group was increased to 16mg/day with increments of 8mg/4weeks. The dose was then increased to 24mg/day if tolerated, otherwise, remaining at 16mg/day for the remainder of study period.

ADAS-cog/11 and MMSE were chosen as primary efficacy measurements. Secondary outcome was measured with Alzheimer’s Disease Corporation Study – Activities of Daily Living (ADCS-ADL). Safety was measured by monitoring AE, vital signs, ECG.

In total 43 subjects in each group (86 in total) completed the study among which 74 subjects had received donepezil for over a period of 6 months. The study reports a mean change in ADAS-cog/11 scores to be -2.6 (-4.3; 0.8) at fast titration group and -0.6 (-2.1; 1.0) at slow titration group, while the negative score indicating improvement in cognitive function (95% CI). No significant difference was observed between the subjects who had received donepezil shorter or longer than 6 months.

MMSE score, at week 12 compared to baseline for the whole population, were improved slightly by 0.9 (0.3; 1.4; P=0.002).

A higher percentage (81.4%) of the fast titration group had improved CIBIC+ score at week 6 compared to the 66.0% slow titration group. This difference, however, became smaller at week 12 (69.8% fast titration and 62.8% slow titration with improved CIBIC+ score).

No change in ADCS-ADL score was registered between screening and week 12 nor was there any different in subjects who had received donepezil for shorter or longer than 6 months.

The study reports that 48.3% of the participants experienced AE with nausea and bradycardia being the most common form of AE. The study claims that none of the AE has been caused by the study drug.

The study claims switching from donepezil to galantamine will maintain or improve the cognitive function. Efficacy of galantamine for fast and slow titration seemed to be similar.
The study authors admit that the lack of a placebo group and continued donepezil group could not provide a comprehensive comparison between the efficacy of galantamine compared to placebo or donepezil subjects continuing treatment. One justification being that discontinuation of donepezil for over 6 weeks will cause a non-reversible deterioration which cannot be treated even if the treatment is re-established.

The study reports a maintained or slightly improved cognitive function in subjects. Other donepezil study also shows that continuation of donepezil might results in maintenance of the cognitive function. So, it is difficult to claim that switching to galantamine alone is causing the maintenance or slight improvement of cognitive function. Therefore, it would have been helpful if there was a donepezil group whom had continued with their normal dose for the 12 weeks of study. Comparison of donepezil group with galantamine would have enabled a conclusion. However, based on this study, it seems that galantamine is also a viable drug for mild to moderate AD patients with comparable efficacy to donepezil and no side effects. If AD patients cannot tolerate donepezil, the authors argue that they might safely switch to galantamine.

**Efficacy and safety of galantamine for long term**

4. **Cessation versus Continuation of Galantamine Treatment after 12 Months of Therapy in Patients with Alzheimer’s Disease: A Randomized, Double Blind, Placebo Controlled Withdrawal Trial** [28].

The objective of this study was to examine the efficacy of galantamine for long term (>12 months) treatment in subjects with mild to moderate AD. The study was designed in two phases with the first phase being an open label 12 months’ period followed by a period of an additional 24 month of randomized, double blind, placebo controlled withdrawal trial. This study was carried out at 29 sites between 2001 – 2005 in Italy.

Inclusion crietial considered subjects above age of 50 diagnosed with NINCDS-ADRDA mild and moderate AD, and having an MMSE score between 11 and 24. Main exclusion criteria were presence of other neurodegenerative disorders than AD, serious clinically significant illness, history of previous cerebral infarction, or having used acetylcholinesterase inhibitors within 3 months from inclusion point.

244 subjects were included in the study among which 176 completed the first 1 year open label period. Out of the 176 subjects only 126 were included in the second phase (n=69 galantamine and n=57 placebo). Only 36 galantamine subjects and 19 placebo subjects completed the second phase of the study, hence a large dropout has been experienced in the second phase.

The efficacy of the drug was measured by ADAS-cog/11 and the overall assessment was measured with CIBIC+. The safety of the drug was assessed by monitoring of AE, vital signs, laboratory tests.

Results after first phase:
The study measured an improvement in ADAS-cog/11 score from 24.1±8.7 at base line to 22.9±9.6 at month 7 with 95% CI. The mean difference was therefore calculated to –1.2 (-2.3 to -0.1, p<0.01).

However the ADAS-cog/11 score at month 12 declined to 24.7±11.3 i.e. ADAS-cog/11 score at month 12 was similar to baseline. Almost 1/3 of the subjects had an improved CIBIC+ score at month 12, while almost 1/3 had unchanged CIBIC+ score, and the remaining had worse CIBIC+ evaluation compared to baseline.
Results of second phase:
The criteria to measure efficacy of the drug in the second phase was defined by withdrawal rate due to cognitive deterioration by ≥4 points in ADAS-cog scale. This criterion could possibly show the efficacy of galantamine to preserve or delay the deterioration of cognitive function compared to placebo group. However, the study seems to have experienced a very large number of dropouts due to other reasons than cognitive deterioration. The study report that no statistically significant results were achieved in the likelihood of premature discontinuation of the trial due to change in ADAS-cog score of ≥4 between the two groups.

34% of galantamine subjects and 27% of placebo subjects had at least one emergent AE during phase 2. 10.5% in galantamine and 6.4% in placebo group discontinued the study due to AE.

Efficacy and safety of Rivastigmine

5. A 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease [29].

The main objective of this study was to investigate the efficacy, safety, and tolerability of rivastigmine drug administered transdermal with use of patches. It is claimed that this type of drug administration might reduce the adverse effects as the patches enable an even and sustained drug concentration in plasma and thereby have less fluctuation as it the case with orally administered drugs. The study therefore has included two comparison groups, a drug treated group using rivastigmine capsules and a placebo group. The rivastigmine group treated with patches was further divided in two titrations, each being treated with different size of patches, i.e. different daily doses.

The study was conducted in 21 countries between 2003 – 2006. A total of 1,195 patients were included in the study:
- 293 treated with 10cm^2 rivastigmine patch delivering 9.5 mg/24 hours,
- 303 treated with 20cm^2 rivastigmine patch delivering 17.4 mg/24 hours,
- 297 treated with rivastigmine capsules of 6 mg BID,
- 302 placebo treated.

Inclusion criteria were patients between the age of 50 – 85 years with an MMSE score between 10 – 20). Furthermore, the patients had to be either living with someone or could perform daily visits to a caregiver.

The primary efficacy outcome was measured with ADAS-cog and Alzheimer’s Disease Cooperation Study – Clinical Impression of Global Change (ADCS-CIGC). Secondary efficacy outcome was measured with ADCS-ADL, MEMS, and NPI. Adverse events (AE) were monitored throughout the study. Furthermore, due to use of adhesive patches, skin irritation and patch adhesion were also monitored with their corresponding methods. 970 patients (81.2%) completed the study, and the intended to treat last observation carried forward (ITT-LOCF) number being 1,053 patients.

All three treatment groups indicated cognitive improvement at end of Week 24 (ITT-LOCF) in ADAS-cog scale. Mean ADAS-cog scale for the 10 cm^2 and capsule groups had improved by 1.6 (p ≤ 0.05) compared to placebo, while the corresponding score for 20 cm^2 was 2.6 (p ≤ 0.001). Similarly, mean improvement in ADCS-CIGC for 10 cm^2 and capsule groups were identical (0.3; p ≤ 0.05) compared to placebo group. The corresponding value for 20 cm^2 was measured to be 0.2 but had marginally missed its statistical significance (p ≤ 0.054).

The secondary efficacy measures (MMSE, ADCS-ADL, and NPI) all indicated improvement at (ITT-LOCF) compared to placebo group (p ≤ 0.001 to p ≤ 0.05).
Tolerability and AE were measured from mild to moderate with nausea, vomiting, and diarrhea being most common. The study observed no statistically significant different in AE between 10 cm\(^2\) group and placebo. The study reports higher tendency of AE in capsule and 20 cm\(^2\) groups compared to placebo. The safety of drugs was measured by monitoring serious AE which was compared between all four groups (7.9% at 10 cm\(^2\) group, 11.9% at 20 cm\(^2\) group, 7.1% at capsule group, and 8.6% at placebo group).

**Efficacy and safety of Memantine**

6. Memantine in Moderate-to-Severe Alzheimer’s Disease [30].

The main object of this study was to evaluate the efficacy and safety of memantine in AD patients at moderate to severe stage. The study was carried out between 1999 (screening of patients) to 2003 (publishing the results), however the exact time of the trials are not reported. The study included 252 patients from 32 treatment centres in USA. The patients were divided into a placebo group and a drug group receiving 20 mg/day of memantine for 28 weeks.

Inclusion criteria were patients with age of 50 years and above being diagnosed with DSM-IV and NINCDS-ADRDA. Furthermore, the patients had to have an MMSE score between 3 – 14 and having a stage of 5 or 6 in Global Deterioration Scale (GDS). Exclusion criteria were patients being diagnosed with other forms of dementia or having another clinically significant condition.

Primary efficacy measure was chosen to be CIBIC-plus and a modified version of ADCS-ADL designed for the severely impaired AD (ADCS-ADLsev). Secondary efficacy measures were chosen to be SIB, MMSE, and four others. Efficacy measurements were performed at baseline, mid-term (week 14), and end of the study (week 28) or those who remained in study or at point of premature termination. The intended to treat (ITT) group was defined as those who had been assessed at least once after baseline. ITT scores for premature termination were included at end point assessment with last observation carried forward method (LOCF).

To ensure consistency, the CIBIC-plus assessment was performed by the same clinician for each patient throughout the trial period. Safety was measured by monitoring adverse events, and assessment of neurologic and physical examination at specified intervals.

Of the 126 patients in each group, the placebo group experienced 42 dropouts while 29 dropped out from the drug group. The remaining 181 patients completed the trials.

The study measured improvement in drug group in both primary efficacy measures. CIBIC+ score, set to 4 at baseline by default, was measured to be 4.5±1.12 for memantine group and 4.8±1.09 for placebo group (p = 0.06) at end point (higher values represent worsening). ADCS-ADLsev score for both groups had declined from baseline indicating worsening. ADCS-ADLsev score at end point had declined by -3.1±6.79 at memantine group and -5.2±6.33 for placebo group (p = 0.02) with lowest value indicating worsening.

Cognitive assessment based in SIB scores indicated slower deterioration in drug group (-4.0±11.34) compared to placebo (-10.1±13.50) with confidence interval of p<0.001. Similarly, MMSE score, although having no statistical significance (p = 0.18), also indicated slower deterioration in drug group (-0.5±2.40) compared to placebo group (-1.2±3.02).

The study claimed to expect higher AE in study population and report that 84% of drug group and 87% of placebo experience AE during the study. Although the percentage of the patients with AE being high, both groups are comparable and therefore the AE was determined not to be related to or caused by drug.
Summarization of the results

Table 3 shows a summary of the results. All scores in Table 2 are relative to placebo groups or baseline (in open label studies) and indicates improvement relative to placebo and/or baseline. Improvement relative to placebo doesn’t necessarily suggest cognitive improvement, it rather represents a slower rate in cognitive impairment.

**Table 3.** Summarization cholinesterase inhibitors and the NMDA-receptor antagonist efficacy.

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Drug</th>
<th>Dose mg/day</th>
<th>Duration</th>
<th>SIB</th>
<th>GBS</th>
<th>ADAS-cog</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Donepezil</td>
<td>5 to 10</td>
<td>24 weeks</td>
<td>4.8</td>
<td></td>
<td></td>
<td>Improvement</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>5 to 10</td>
<td>52 weeks</td>
<td>-3.7</td>
<td></td>
<td></td>
<td>Improvement</td>
</tr>
<tr>
<td>3</td>
<td>Galantamine</td>
<td>8 to 24</td>
<td>12 weeks</td>
<td>-2.6</td>
<td></td>
<td></td>
<td>Improvement</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>8 to 16</td>
<td>1 year</td>
<td>-2.6</td>
<td></td>
<td></td>
<td>Phase 1: Improvement.</td>
</tr>
<tr>
<td>5</td>
<td>Rivastigmine</td>
<td>6mg BID</td>
<td>6 months</td>
<td>-1.6</td>
<td></td>
<td></td>
<td>Capsules: Improvement.</td>
</tr>
<tr>
<td>6</td>
<td>Memantine</td>
<td>5 to 20</td>
<td>28 weeks</td>
<td>-2.6</td>
<td></td>
<td></td>
<td>200cm² 2 patch: Improvement.</td>
</tr>
</tbody>
</table>

* Efficacy of the drug in second phase of the study is not reported. The study suffered from unusually large no. of dropouts unrelated to the study design.

** The main efficacy outcome was measured with CIBIC+ which didn’t provide any statistically significant results. However, the secondary outcome parameter (SIB) indicates slow deterioration in cognitive impairment compared to placebo.

The overall drug effects, based on results of Table 2, seem to be in few percent of the full scale for all drugs. Caution must be taken when comparing full scale numbers compared to the relative changes caused by a drug.

For example, 2-3 points in ADAS-cog scale might indicate just a few percent of its full scale (70 point), but according to the European Medicine evaluation Agency (EMEA) 4 points in ADAS-cog scale represents significant clinical effect. A difference of 4 points in ADAS-cog scale might results in a patient’s ability to recognize family members and perform daily living activities (33).

There are limited number of literature to investigate the long-term efficacy (beyond 1 year) of AD drugs. A general trend for the included literature indicated higher efficacy in the initial phase of treatment (up to ca. 6 months) where after the efficacy of the drugs reduced. In some cases, the cognitive scores improved compared to baseline suggesting “cure”, but after the initial peak of improvement the cognitive function begin to deteriorate over time despite the continuation of the drug.

Discussion

Method and aim

The aim of this study is to investigate efficacy and safety of Donepezil, Galantamine, Rivastigmine and Memantine. In order to compare efficacy and safety of the four-approved clinical drug for the symptomatic stages of AD a literature study was conducted to identify any possible variations between efficacy and safety. Since most of the literatures are concerned with one type of the drug, literatures for all drugs had to be screened and subsequently compared.

6 articles were included in the analysis. Relevant articles were chosen for each drug. Most studies were randomized placebo controlled trials and some of them were open label studies. Studies that were done for longest duration for each drug were also included.
There are many randomized control studies done for these four drugs. The old clinical studies that have been done were not very compelling and time was not put to harvest the oldest studies. Therefore, the search limit was done for the most recent clinical trials that have been done for the recent 10 years and would have been more useful for contemporary evaluation. However, for some drugs are wider historical search was done to find a good clinical study that gave some good efficacy on the cognition improvement.

**Results**

*Do the drugs have measurable efficacy and side effects, and is there any correlation between efficacy and treatment duration, titration, and switching?*

**Donepezil**

Donepezil is approved for symptomatic treatment for all stages of AD. To clarify the efficacy and side effects of donepezil for all the stages of the symptomatic treatment of AD, PubMed was searched for relevant recent articles. Search was limited to clinical randomized controlled trials. A recent study published 2017 by J. Jia et al. concerning the efficacy and safety of donepezil in Chinese patients with severe AD was chosen. Another study from Subbiah et. al. which had performed a long-term study on efficacy and safety of donepezil treatment for patients with mild to moderate AD published in 2001 was chosen. The study was carried out for 52 weeks. This study was chosen because that is the only long-term study that has been done to study the efficacy and safety of donepezil and it also gives an idea about the efficacy this drug has on the mild-to-moderate stage of AD.

In the study done in 2017 by J. Jia et al. the trial results claimed that the total SIB score which was the primary outcome favored the Donepezil group compared to Placebo group. In this study, the Donepezil group improved in SIB scores up to 4.8 (95% CI). The CIBIC-plus scores improved with -0.4, (95% CI) which shows an indication of improvement in global change. The MMSE scores between drug and placebo groups did not differ significantly. The study also reported that 43.4% of all participants experienced at least one adverse event (AE) during the trial period (26.7% of placebo group and 16.7% of drug group). Most AEs were mild to moderate in severity. Five AEs namely sinus bradycardia, anorexia, Q-T interval prolongation, dizziness, diarrhea were considered, by investigators, to be caused by the drug. Severe adverse events were more common in placebo group. 4 people died during trial period (1 in drug group and 3 in placebo group) which the investigators considered to be not related to the drug. Based on the findings of this trial, there are clear indications that Donepezil resulted in measurable improvement of severe AD patients in both SIB and CIBIC+ scores. The safety aspects do not provide noticeable difference in adverse effects between drug and placebo groups which indicate the drug is possibly safe.

Another 52-week long study done by Subbiah et. Al at 2001 used Gottfries-Bråne-Steen (GBS) scale as a primary outcome of efficacy which according to the authors is a comprehensive global assessment for rating dementia symptoms compared to the commonly used ADAS-cog scale. This study indicates that donepezil does have a positive effect in patients with mild to moderate AD. The study indicates that the GBS score among donepezil group deteriorated by 3.6±1.1 least squared mean value, while the corresponding value for the placebo group deteriorated by 7.3±1.1 GBS point. The MMSE score for the donepezil
group remained close to baseline after 12 months, while the placebo group deteriorated by 2 points in MMSE score. Although the study indicates a difference between the two groups, it also shows that the donepezil treatment does not completely stop the deterioration of cognitive function in AD patients. It rather slow down the deterioration process. The study results do not indicate any noticeable safety issues with the drugs, which could be regarded as safe for the AD patients. The study indicates that 81.7% of donepezil and 75.5% of placebo groups experienced at least one treatment-emergent AE over the course of the study. Although these numbers are rather high, they are still comparable between the two groups. The high percentage of subjects with AE could be the results of relatively longer period of the study and therefore not related to treatment drug.

Based on the two above mentioned studies, it seems that donepezil can be prescribed to AD patients at all stages with the confidence that it is tolerable by most of the patients and it can also slow down the process of deterioration. Ongoing research is, however, needed to advance other AD medications to the point of complete stop or curing of the disease.

**Galantamine**

Galantamine is another drug approved to treat AD at its mild-to-moderate stages. It has a dual action, it inhibits AChE to increase ACh levels at the synaptic cleft and in the same time causes a conformational change of the nicotinic receptor on the postsynaptic neuron to increase its response to acetylcholine [31].

In this study, PubMed was searched for relevant articles concerning efficacy and safety of Galantamine. Focus was on finding recent randomized control trials, and resulted in identification of two relevant studies.

The first study published in 2011 by K. Engedal et.al. was chosen as it examined an interesting and practiced aspect of AD treatment namely switching from donepezil to galantamine, since donepezil is mostly the first prescribed drug. The main objective of this study was determining the efficacy and safety of galantamine in two titration groups for a period of 12 weeks. In the meantime, it provided an overview of any possible changes in patient’s condition when switching from donepezil to galantamine due to e.g. lack of efficacy or tolerability of donepezil.

The study reports improvement in ADAS-cog/11 scores in both titration groups compared to baseline. However, the study measured better improvement in the fast titration group -2.6 (-4.3; 0.8) compared to the slow titration group -0.6 (-2.1; 1.0) (95% CI). No significant difference was observed between the subjects who had received donepezil for longer or shorter than 6 months. MMSE score, at week 12 compared to baseline for whole population, were improved slightly by 0.9 (0.3; 1.4; P=0.002).

The study reports that 48.3% of the participants experienced AE with nausea and bradycardia being the most common form of AE. The study claims that none of the AE had been caused by the study drug. Although the study indicates improvement caused by galantamine compared to baseline, it is still questionable whether the improvement is a natural results of AD treatment which would be achieved by any other drug e.g. continuation of donepezil, or whether the improvement is specific to use of galantamine. The study therefore could greatly benefit from including a 3rd group which continued with donepezil. Any improvement in galantamine compared to donepezil could then be credited to galantamine or switching to galantamine. Nevertheless, the study does show that galantamine could be an
alternative drug should the subject not want to continue with donepezil for any efficacy or tolerability reasons.

The second study published in 2011 by E. Scarpini et.al. was chosen as it aimed to examine another interesting aspect of galantamine, namely the long term (beyond 1 year) efficacy and tolerability of the drug in patients with mild to moderate AD. This study was of particular interest since almost all other trial studies are of short term (max. 1 year) and therefore the efficacy and tolerability of AD medicine in long term is still not adequately explored.

The study was designed to have two phases; an initial 12 months open labelled phase followed by a 24 months’ placebo controlled phase. ADAS-cog/11 was used to measure the efficacy of galantamine throughout the study.

In the open labelled phase, the ADAS-cog/11 score was reported with a mean improvement of -1.2 (-2.3 to -0.1, p<0.01) at month 7. At month 12 (end of open label phase) the study report ADAS/cog-11 score very close to the baseline. This indicates that the patients cognitive function seemed to improve initially with galantamine but had started to deteriorate and dropped back to baseline level at month 12.

Based on the above results and results of the 12 weeks study from Engedel et.al. it seems that galantamine improves cognitive function for a short period of time, but cannot maintain the improvement. This hypothesis could be validated or rejected by the second phase of the study which continued the treatment for additional 24 months and compared the results with placebo.

In the placebo controlled phase the efficacy of galantamine was controlled by monitoring the deterioration of ADAS-cog/11 score ≥4 point which was also the criteria for exclusion. By defining this exclusion (dropout) criteria, an increased number of dropouts in placebo group would have indicated that galantamine maintained or delayed the deterioration of cognitive function.

Unfortunately, the study has experienced an unusually high percentage of dropouts unrelated to deterioration of the cognitive function. Out of 69 galantamine and 57 placebo subjects only 36 galantamine and 19 placebo subjects completed the study. The study report that no statistically significant dropouts due to the deterioration of ADAS-cog/11≥4 was measured between the two groups. This limits the validity of the study to conclude whether galantamine can maintain or reduce the deterioration of cognitive function beyond 1 year.

It is still unclear why the study didn’t record ADAS-cog/11 scores among the 126 subject whom started the placebo controlled phase. A frequent measurement of ADAS-cog/11 and using the last observation carried forward (LOCF) of the many dropouts might still have provided some indication of the long-term efficacy of galantamine.

Based on the results of the second phase, the long-term efficacy of galantamine, is still in question remains to be further investigated.

**Rivastigmine**

Rivastigmine is another clinically approved drug prescribed for mild-to-moderate stages of AD. The drug is commonly administered transdermal with the use of patches, and provides continuous delivery over 24 hours.

In this study, PubMed was searched for relevant articles concerning the efficacy and safety of Revictimize. Yet again some search criteria were chosen to restrict the results only to randomized control trials.

A study published in 2007 by B. Winblad et.al. was chosen due to its scope of investigation. The study did not only aim at measuring efficacy and safety of rivastigmine
compared to placebo, it also sought to evaluate efficacy and safety between two modes of rivastigmine administration, oral and transdermal. Within the transdermal group the study further divided the patients between two titrations or size of patches. Since it seemed that the study’s main interest was to investigate efficacy of the drug with transdermal administration, it implicitly might be providing a more objective assessment of rivastigmine by evaluating its efficacy when orally administered. This has also been the reason that only one study for rivastigmine is included in this report, since the chosen study by B. Winblad implicitly evaluate rivastigmine efficacy twice (oral and transdermal).

The study reports statistically significant cognitive improvement in all three treatment groups compared to placebo. Mean improvement in the primary efficacy measure of ADAS-cog score was measured to be 1.6 points (p ≤ 0.05) for both oral and slow transdermal titration groups compared to placebo. The fast titration transdermal group indicated more improvement of 2.6 points (p ≤ 0.001). Similarly, mean improvement in ADCS-CIGC for slow transdermal titration group and capsule groups were identical (0.3; p ≤ 0.05) compared to placebo group. The corresponding value for fast titration group was measured to 0.2 but had marginally missed its statistical significance (p ≤ 0.054). Adverse effects are reported to be lowest in the slow transdermal titration group compared to oral group while the AE between fast transdermal titration and oral groups were comparable to placebo group. Although not being the main interest of the Winblad et al. study, the efficacy of rivastigmine of the oral group is of highest importance for our study as it has the potential to be more objective. Based on the results of the oral group, indications are that rivastigmine regardless of its administration does have an efficacy in AD treatment with comparable tolerability to other drugs provided for the same category of patients.

**Memantine**

Memantine is a clinically approved drug specific to patients with moderate to severe AD. Memantine is designed to reduce the effect of NMDA receptors overstimulation which is thought to cause some symptoms of AD. In this study, the PubMed database was searched for relevant articles related to the efficacy and safety of memantine. It was observed that a majority of recent studies were concerned with evaluating a limited aspect of the drug, e.g. a recent Japanese study was focusing on evaluation of memantine efficacy in language scale improvement for Japanese patients, to determine if the western studies could be extrapolated to that demographic. It has, therefore, been decided to search in articles published more than 10 years ago as those early articles seemed to have the necessary scope of evaluating the efficacy and safety of memantine from a broader perspective.

A study published in 2003 by B. Reisberg et al. was chosen due to its scope of memantine evaluation. The study aimed to evaluate the efficacy and safety of memantine from a broader perspective and included various outcome measures. Primary efficacy outcome was measured by CIBIC+ and ADCS-ADLsev (a specific version of ADCS-ADL designed for severely impaired AD patients). Secondary efficacy outcome was measured with SIB, MMSE, and for other scales. 181 patients completed the study. CIBIC+ scores seem to be marginally improved (4.5±1.12 memantine; 4.8±1.09 placebo) however missing its statistical significance (p = 0.06). These results don’t seem to be conclusive for the efficacy of memantine in global condition improvement. The ADCS-ADLsev score (-3.1±6.79 memantine; -5.2±6.33 placebo; p = 0.02) indicate deterioration in patients’ motoric function in both groups, while the deterioration seems to be slower in the memantine group.
Cognitive deterioration with SIB score, although not being chosen as primary efficacy outcome, is probably one of the most encouraging results of the study. Here the deterioration in the memantine group was reported to be significantly lower (-4.0±11.34) compared to placebo (-10.1±13.50) with confidence interval of p<0.001. MMSE results also showed similar trend but without statistical significance.

From the above mentioned results and observation, it can be concluded that memantine is probably most effective in slowing cognitive deterioration but doesn’t necessarily have similar effect on global condition of the patients including its motoric and behavioral aspects. At severe stage of AD, the patients might be suffering from various conditions which cognitive improvement cannot be of much help to increase their CIBIC+ score. The drug seems to be tolerable based on the results of this study.

**Is there any comparable difference between the four drugs in term of their efficacy and side effects?**

Based on the results of Table 3, all four drugs indicate efficacy compared to placebo. However, the magnitude of improvement among the drugs are within same range and therefore no comparable difference can be concluded from the data.

Similar conclusion was also made by a previous report published by the Swedish Council on Technology Assessment in Health Care (the official acronym is SBU) published in 2006. Here several published literatures were reviewed for their efficacy to provide guidelines for practitioners involved in dementia specifically AD. The report concludes the cholinesterase inhibitors (donepezil, galantamine, rivastigmine) do not have significantly different efficacy affecting the progression of AD [1].

Similarly, memantine has also showed some effect on cognitive functions for the severe Alzheimer’s disease. To show a long-term effect of this drug there are very limited studies and not longer than half a year treatment [1].

The report also concludes that due to the pathology of the Alzheimer’s disease and how fast the symptoms develop or in which strength they appear is very individual for each patient. Even if a patient is untreated with a drug, the cognitive function can be preserved for several months. Each patient must test the drug to notice a positive improvement in the cognitive function, and the effect of the drug is very individual [1].

Another report from lakemdelsverket has also made some conclusions about the drug treatment of AD. The report concludes that there are differences in the mechanism of action of the inhibition of acetylcholinesterase between the different cholinergic medications. They also conclude that these differences have been shown to not be important to the clinical effect of cognitive functions. The main goal is that the patient should improve or maintain the cognitive functions. Evaluation of the cognitive function should be done after three to four months of treatment to make a decision on the deterioration course, if no deterioration is noted then the patient should continue with the drug. The side effects should also be noted if one drug is not very well tolerated it should be switched to another one [3].

The most common side effects of the use of AChEI were of the same range. the most common side effects seen in all groups were from the gastrointestinal tract. Nausea, dizziness and vomiting were the most commonly seen side effects.

Although the findings of this study suggest that the existing drugs cannot stop or reverse AD progression, there are numerous ongoing research projects addressing this
shortcoming. The main focus here is to develop drug therapies which can interfere with the pathogenic steps of the AD and halt the formation and depositional of the extracellular beta-amyloid plaques and intracellular neurofibrillary tangles, i.e. stop AD from progressing.

Many researchers work on using immunotherapy as method to utilize immune-system to destroy amyloid deposits. Many immunotherapies have already been developed and demonstrated effective clearance of beta-amyloid plaques in animal models. These therapies are currently in clinical trials on human subjects. One challenge to overcome is the safety factors of these therapies, but researchers strongly believe that these challenges can be overcome and expect to have a treatment ready within 10 years to stop the progression of AD.

**Conclusion**

Based on literature observations and collected data in this study, it can be concluded that all four drugs have demonstrated slowing cognitive deterioration while being tolerable without major side effects. There is no significant difference in the efficacy of the four clinically approved drugs for AD. Based on the result, efficacy can seem very small but any slightly improvement in the cognitive or global function makes a big difference of demented patients daily function. Based on these finding it can be concluded that all four clinically approved drugs for AD are safe and should be prescribed until a better alternative is found in future research.

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