SECTION-III

CHAPTER 1.
INTRODUCTION

1. INTRODUCTION

According to the English Dictionaries the definition of **Dementia** is *"severe impairment or loss of intellectual capacity and personality integration, due to the loss of or damage to neurons in the brain*." "Dementia" word is originally taken from Latin, meaning "madness", from *de-* "without" + *ment*, the root of *mens* "mind".[1] Dementia is a serious loss of global cognitive ability in a previously unimpaired person, beyond what might be expected from normal ageing. Dementia is not a specific disease. It's an overall term that describes a wide range of symptoms associated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform everyday activities.[2] It may be static as a result of unique global brain injury or progressive, resulting in long-term decline due to damage or disease in the body. Dementia is a non-specific syndrome (i.e., set of signs and symptoms). Affected cognitive areas can be memory, attention, language, and problem solving. Normally, symptoms must be present for at least six months to support a diagnosis. Especially in later stages of the condition, subjects may be disoriented in time (not knowing the day, week, or even year), in place (not knowing where they are), and in person (not knowing whom they and/or others around them are). Some of the most common forms of dementia are: Alzheimer's disease, vascular dementia, frontotemporal dementia, semantic dementia and dementia with Lewy bodies.[3,4]

1.1. Alzheimer's Disease (AD)

Alzheimer's disease is the most common form of dementia. It was first described by German psychiatrist and neuropathologist Alois Alzheimer[5] in 1906 and was

named after him. Most often, AD is diagnosed in people over 65 years of age, although the less-prevalent early-onset AD can occur much earlier. In 2006, there were 26.6 million sufferers worldwide. AD is predicted to affect 1 in 85 people globally by 2050.[6,7]

Although Alzheimer's disease develops differently for every individual, there are many common symptoms.[8] Early symptoms are often mistakenly thought to be 'age-related' concerns, or manifestations of stress. The most common symptoms associated with Alzheimer's are as follow:

- One of the most common signs of Alzheimer's is memory loss, especially forgetting recently learned information. Others include forgetting important dates or events; asking for the same information over and over; increasingly needing to rely on memory aides (e.g., reminder notes or electronic devices) or family members for things they used to handle on their own.
- Some people may experience changes in their ability to develop and follow a plan or work with numbers. They may have trouble following a familiar recipe or keeping track of monthly bills. They may have difficulty concentrating and take much longer to do things than they did before.
- People with Alzheimer's often find it hard to complete daily tasks. Sometimes, people may have trouble driving to a familiar location, managing a budget at work or remembering the rules of a favourite game.
- People with Alzheimer's can lose track of dates, seasons and the passage of time. They may have trouble understanding something if it is not happening immediately. Sometimes they may forget where they are or how they got there.

- For some people, having vision problems is a sign of Alzheimer's. They may have difficulty reading, judging distance and determining colour or contrast, which may cause problems with driving.
- People with Alzheimer's may have trouble following or joining a conversation. They may stop in the middle of a conversation and have no idea how to continue or they may repeat themselves. They may struggle with vocabulary, have problems finding the right word or call things by the wrong name (e.g., calling a "watch" a "hand-clock").
- A person with Alzheimer's disease may put things in unusual places. They may lose things and be unable to go back over their steps to find them again. Sometimes, they may accuse others of stealing. This may occur more frequently over time.
- People with Alzheimer's may experience changes in judgment or decision-making. For example, they may use poor judgment when dealing with money, giving large amounts to telemarketers. They may pay less attention to grooming or keeping themselves clean.
- A person with Alzheimer's may start to remove themselves from hobbies, social activities, work projects or sports. They may have trouble keeping up with a favourite sports team or remembering how to complete a favourite hobby. They may also avoid being social because of the changes they have experienced.
- The mood and personalities of people with Alzheimer's can change. They can become confused, suspicious, depressed, fearful or anxious. They may be

easily upset at home, at work, with friends or in places where they are out of their comfort zone.

The cause and progression of Alzheimer's disease are not well understood. Research indicates that the disease is associated with plaques and tangles in the brain.[9-11] Current treatments only help with the symptoms of the disease. There are no available treatments that stop or reverse the progression of the disease. As of 2012, about 1050 clinical trials[12,13] have been or are being conducted to find ways to treat the disease, but it is unknown if any of the tested treatments will work. Because AD cannot be cured and is degenerative, the sufferer mainly relies on others for assistance.

The disease course is divided into four stages, with progressive patterns of cognitive and functional impairments.[14]

- **Pre-dementia:** Memory problems are typically one of the first signs of Alzheimer's disease. Sometimes, other thinking problems, such as trouble finding the right words or poor judgment, are most prominent early on.
- **Mild AD:** As the disease progresses, memory loss worsens, and changes in other cognitive abilities are evident. Problems can include:
    - getting lost
    - trouble in handling money and paying bills
    - repeating questions
    - taking longer to complete normal daily tasks
    - poor judgment
    - losing things or misplacing them in odd places
    - mood and personality changes

Alzheimer's disease is often diagnosed at this stage.

- **Moderate AD:** In this stage, damage occurs in areas of the brain that control language, reasoning, sensory processing, and conscious thought. Symptoms may include:
  - increased memory loss and confusion
  - problems in recognizing family and friends
  - inability to learn new things
  - difficulty in carrying out tasks that involve multiple steps
  - problems in coping with new situations
  - hallucinations, delusions, and paranoia
  - impulsive behaviour
- **Severe AD:** People with severe Alzheimer's cannot communicate and are completely dependent on others for their care. Near the end, the person may be in bed most or all of the time as the body shuts down. Their symptoms often include:
  - inability to communicate
  - weight loss
  - seizures
  - skin infections
  - difficulty in swallowing
  - groaning, moaning, or grunting
  - increased sleeping
  - lack of control of bowel and bladder

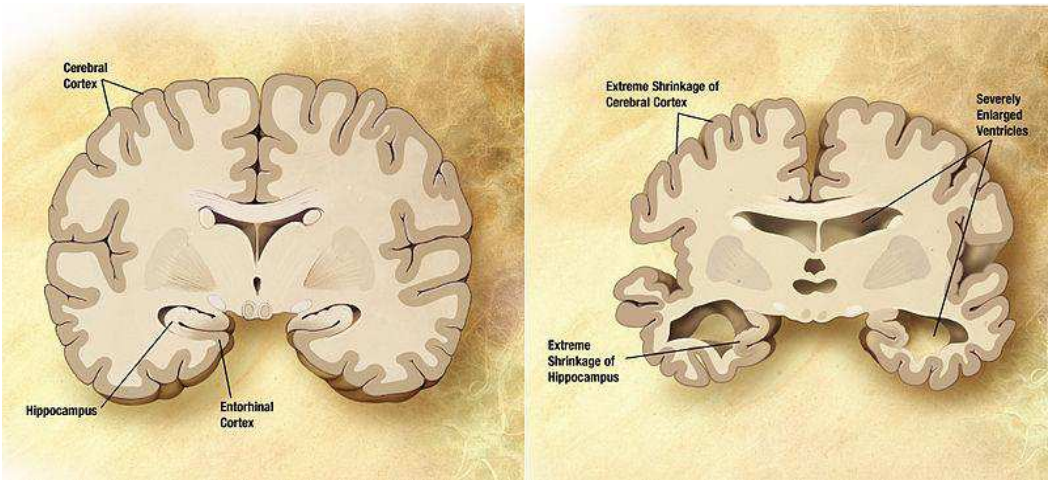


Figure 1 Comparison of a normal aged brain (left) and the brain of a person with Alzheimer's (right). Differential characteristics are pointed out.

The cause for most Alzheimer's cases is still essentially unknown (except for 1% to 5% of cases where genetic differences have been identified).[14-22] Several competing hypotheses exist trying to explain the cause of the disease:

1.1.1. Cholinergic hypothesis

The oldest, on which most currently available drug therapies are based, is the *cholinergic hypothesis*, which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine.[23] The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective. Other cholinergic effects have also been proposed, for example, initiation of large-scale aggregation of amyloid, leading to generalised neuroinflammation. There are two types of ChE present in AD patient's brain: acetyl cholinesterase and butyryl cholinesterase. BuChE is thought to arise at advanced stage of AD.[24-26]

1.1.2. Amyloid hypothesis

In 1991, the *amyloid hypothesis* postulated that beta-amyloid (βA) deposits are the fundamental cause of the disease. Alzheimer's disease has been identified as a protein misfolding disease (proteopathy), caused by accumulation of abnormally folded amyloid beta proteins in the brain.[27] Plaques are made up of small peptides, 39–43 amino acids in length, called beta-amyloid (Aβ). Beta-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that penetrates through the neuron's membrane. APP is critical to neuron growth, survival and post-injury repair.[28,29] In Alzheimer's disease, an unknown process causes APP to be divided into smaller fragments by enzymes through proteolysis.[30-34] One of these fragments gives rise to fibrils of beta-amyloid, which form clumps that deposit outside neurons in dense formations known as senile plaques (**Figure 2**).

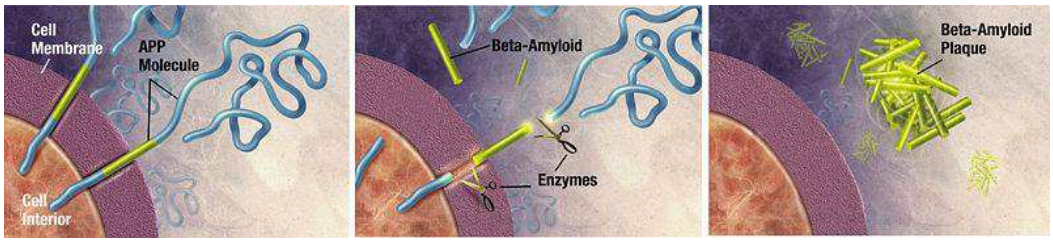


Figure 2 Enzymes act on the APP (amyloid precursor protein) and cut it into fragments. The beta-amyloid fragment is crucial in the formation of senile plaques in AD.

1.1.3. Tau hypothesis

The *tau hypothesis* is the idea that tau protein abnormalities initiate the disease cascade. In this model, hyperphosphorylated tau begins to pair with other threads of tau.[35] Eventually, they form neurofibrillary tangles inside nerve cell bodies. When this occurs, the microtubules disintegrate, collapsing the neuron's transport system.[36] This

may result first in malfunctions in biochemical communication between neurons and later in the death of the cells (**Figure 3**).

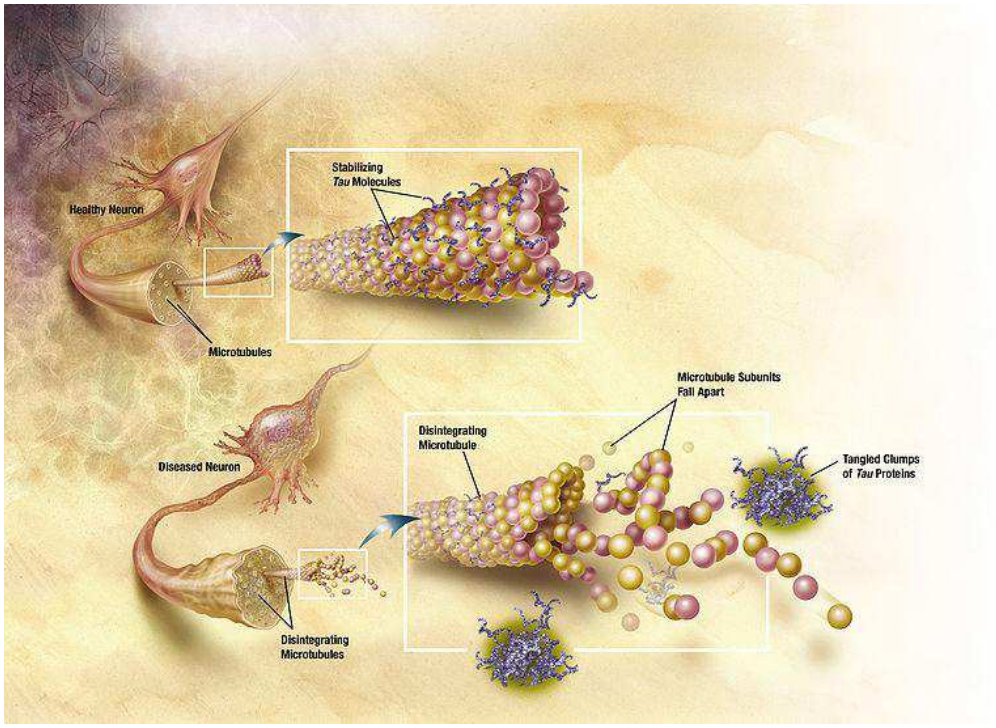


Figure 3 In Alzheimer's disease, changes in tau protein lead to the disintegration of microtubules in brain cells.

1.2. AD pathogenesis: Three current competing hypotheses

Since AD in a non-curable disease, the current treatments only delay cognitive decline by typically one year.[37] The limited efficiency of these symptom treating receptor antagonists has led to quests for more causative pathogenic targets. During the past decade, three main hypotheses on the pathogenesis of AD have emerged that focus on different features of the disease and are to some extent seen as competing: the amyloid cascade hypothesis, the metal ion hypothesis and the oxidative stress hypothesis.[38] A crude overview of some central ideas of these three hypotheses is given in **Figure 4**.

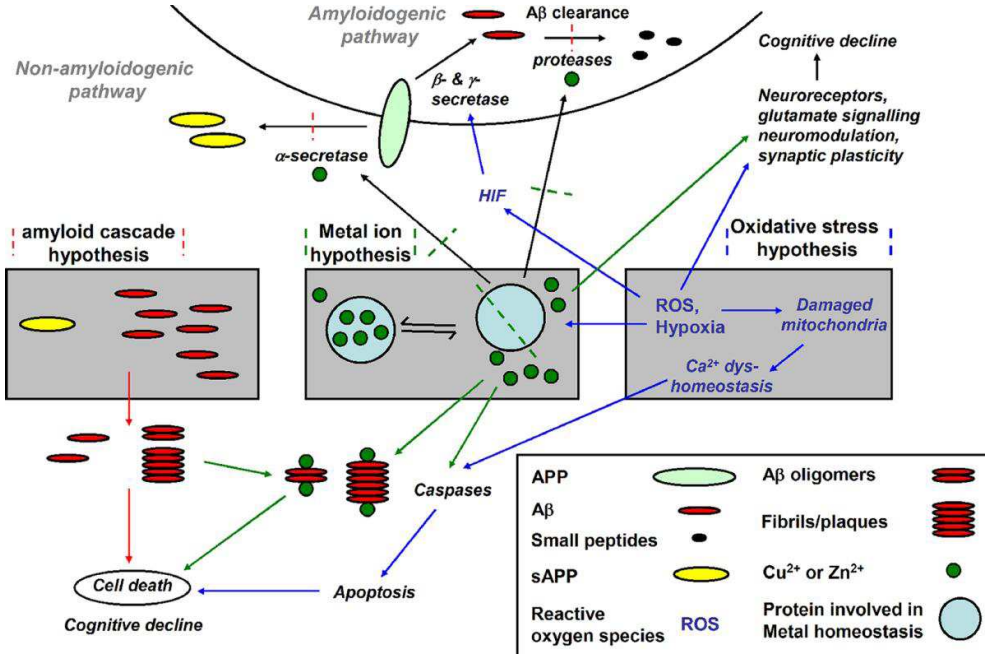


Figure 4 Simple overview of three hypotheses of Alzheimer's disease: (i) amyloid cascade hypothesis, with Aβ accumulation (red) being a main pathogenic event; (ii) metal ion hypothesis, with metal ion (green) dyshomeostasis leading to amyloid imbalance and (iii) oxidative stress hypothesis, with oxidative and general stress (blue) leading to mitochondrial damage, metal ion dyshomeostasis, apoptosis and Aβ imbalance.

The amyloid cascade hypothesis states that impaired balance between Aβ production and clearance is the main cause of AD and that amyloids are the main neurotoxic substances in AD.[39] Consequently, this hypothesis favours treatments that inhibit Aβ production or enhance Aβ clearance in the AD brain.

The metal ion hypothesis states that the underlying cause of AD is impaired metal homeostasis; in particular of Zn, Cu, and Fe, with Aβ imbalance being a consequence of this.[40] This hypothesis favours treatments such as chelators that address the metal ion imbalances supposedly causing amyloid accumulation.

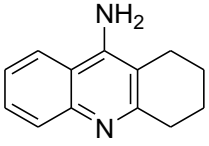
The oxidative stress hypothesis asserts that age-enhanced or genetically and environmentally enhanced oxidative stress results in accumulated gene defects and

declining mitochondrial function that subsequently leads to neurological disorders, either gradually or when reaching a critical threshold that initiates apoptosis in neurons.[41,42] Apoptosis occurs in a wide range of neurological disorders and by a range of pathways that can be triggered, for example, by lesions, misfolded proteins, oxidative stress, excitotoxicity or Ca^{2+} dyshomeostasis.

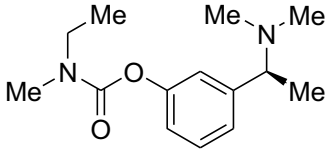
1.3. Current treatments and recent clinical research for AD

Altering the course of AD could lead to significant public health benefits. For example, an intervention that could delay the onset of AD by 2 years would decrease the incidence in such a way that in 50 years there would be nearly 2 million fewer cases than are currently projected. One can imagine that significantly altering the course of the disease would similarly sharply decrease the need for nursing home placement and could help patients remain functional for much longer.

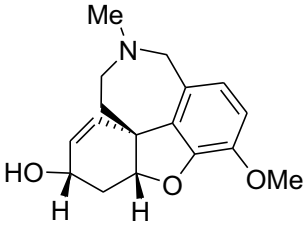
Currently there are only 5 medications approved by the Food and Drug



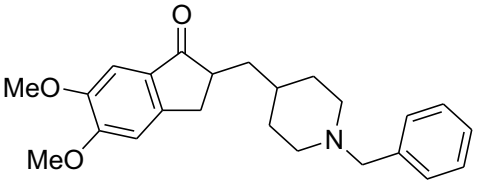
Tacrine



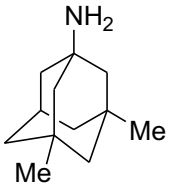
Rivastigmine



Galantamine



Donepezil



Memantine

Administration to treat AD. Four of them are acetyl cholinesterase inhibitors (donepezil, galantamine, rivastigmine, and tacrine), and the fifth memantine[43] is *N*-

methyl-D-aspartate (NMDA) antagonist. These medications ameliorate the symptoms and can improve the functioning of patients with AD, but they are not curative, nor do they significantly change the course of the illness. The most widely studied treatments aim to address the neuropathological findings over the last century and focus on acetylcholine, inflammatory markers, amyloid plaques, and tau-based neurofibrillary tangles.

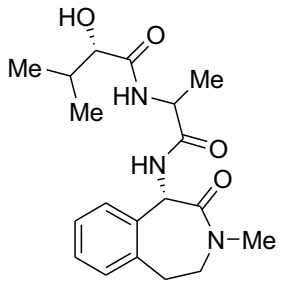
In the next section, the agents which are under investigation for the treatment of AD are discussed.

1.3.1. Interventions targeting amyloid

Researchers in Alzheimer's disease have identified five strategies as possible interventions against amyloid:

1.3.1.1. β-Secretase (BACE) **inhibitors (**also known as **beta-site APP cleaving enzyme)**: The BACE inhibitors work to block the first cleavage of APP outside the cell. There are a number of BACE inhibitors that have been described in animal models. A number of approaches, including the creation of novel antibodies to target the BACE cleavage site of APP, have been used. In April 2008, Gerald Koelsch, at the Oklahoma City site of the biotech company CoMentis, Inc., first time reported the human data on the company's β-secretase inhibitor CTS-21166.[44] In a first proof-of-concept human study, the compound appeared safe and reduced plasma amyloid-β levels substantially for an extended period of time. In April 2012 Merck reported phase I results for MK-8931.[45] Merck began Phase II/III trial of MK-8931 in December, 2012.

1.3.1.2. γ-Secretase inhibitors: The gamma secretase complex is unusual among proteases in having a "sloppy" cleavage site at the C-terminal site in amyloid beta generation; gamma secretase can cleave APP in any of multiple sites to generate a peptide from 39 to 42 amino acids long chain length, with $A\beta_{40}$ the most common isoform and $A\beta_{42}$ the most susceptible to conformational changes leading to amyloid fibrillogenesis. Inhibitors of γ-secretase enzyme block the second cleavage of APP in the cell membrane and would then stop the subsequent formation of Aβ and its toxic fragments. Semagacestat[46] (LY450139) was a candidate drug of this class. It was originally developed by Eli Lilly and Élan, and clinical trials were conducted by Eli

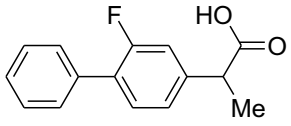


Semagacestat

Lilly. Phase III trials included over 3000 patients, but in August 2010, a disappointing interim analysis, in which semagacestat performed worse than the placebo, led to the trials being stopped.

1.3.1.3. Selective $A\beta_{42}$ lowering agents: These agents modulate γ-secretase to reduce $A\beta_{42}$ production in favour of other (shorter) Aβ versions. Tarenflurbil,[47] a single enantiomer of the racemate NSAID flurbiprofen was developed by Myriad Genetics for several years to investigate its potential as a treatment for AD; that investigation concluded in June 2008 when the company announced to discontinue development of

the compound. After Phase III testing, which included nearly 1,700 patients with mild AD treated for 18 months with either Tarenflurbil or placebo, Myrial Genetics concl-



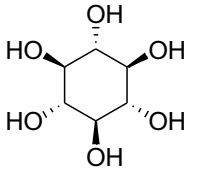
Flurbiprofen

-uded that the drug did not improve thinking ability or the ability of patients to carry out daily activities significantly more than those patients with placebo. [48]

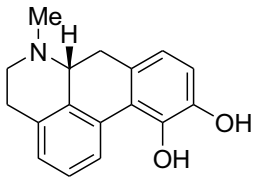
1.3.1.4. Immunotherapy: This stimulates the host immune system to recognize and attack Aβ or provide antibodies that either prevent plaque deposition or enhance clearance of plaques or Aβ oligomers. Prevention of oligomerization of Aβ has been exemplified by active or passive Aβ immunization. In this process antibodies to Aβ are used to decrease cerebral plaque levels. This is accomplished by promoting microglial clearance and/or redistributing the peptide from the brain to systemic circulation. One such beta-amyloid vaccine that is currently in clinical trials is CAD106.[49] Immunization with synthetic Aβ1-42 has been shown to be beneficial in mice and displays low toxicity; however human trials have shown no significant differences. Thus, it is not yet effective in humans and requires further research. Specific findings show that the 20 amino acid SDPM1 protein binds tetramer forms of Aβ(1-40)- and Aβ(1-42)-amyloids and blocks subsequent Aβ amyloid aggregation. It is important to note that this study was done in mice and that while it prevented further development of neuropathology it did not result in an improvement in

cognitive performance. Lastly, Aβ42 immunization resulted in the clearance of amyloid plaques in patients with AD but did not prevent progressive neurodegeneration.

1.3.1.5. Anti-aggregation agents: These prevent Aβ fragments from aggregating or clear aggregates once they are formed. Apomorphine, a non selective dopamine agonist, has been reported to be an inhibitor of beta amyloid fibril formation, and may thus have potential as a therapeutic for AD. The other interesting agent in trials is



Scyllo-inositol



Apomorphine

scyllo-inositol,[50] which is currently in phase 2 clinical studies sponsored by Elan Pharmaceuticals.[51] This agent seems to be directed at the Aβ oligomers; it binds them and prevents synaptic damage. Scyllo-inositol is a small molecule that readily crosses the blood-brain barrier by active transport. It has received fast track designation from the U.S. FDA.

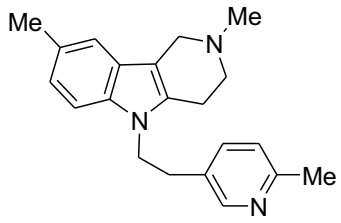
1.3.2. Advanced Glycation End (AGEs) products

Advanced glycation end products are formed endogenously during glycation and can also be ingested in a variety of foods. These AGEs have been implicated in aging through a variety of mechanisms, including increased protein crosslinking and

increased free radical formation and as proinflammatory mediators. Receptor for advanced glycation end products (RAGE) is an immunoglobulin supergene family expressed on the cell surface of multiple cell types throughout the brain and on the blood-brain barrier. In AD, RAGE is upregulated on cells in the hippocampus, such as astrocytes and microglia. Amyloid is known to bind to these receptors. This may be one way in which the inflammatory cascade is stimulated and thus may lead to cell death. Preclinical studies have suggested that blocking this receptor against amyloid binding protects the cell by decreasing plaque formation and inflammation. Pfizer and the Alzheimer's Disease Cooperative Study are working together on a phase 2 trial of PF04494700,[52] an oral RAGE antagonist.

1.3.3. NMDA receptor antagonist

Latrepirdine (Dimebon),[53] once used as a nonselective antihistamine in Russia, was studied in animal models of AD95 and was found to be beneficial in an avoidance



Latrepirdine

conditioning paradigm. The mechanism of action of latrepirdine is unclear because it may also modulate α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and NMDA receptors and weakly inhibit acetylcholinesterase.

1.3.4. Nerve Growth Factor (NGF)

The loss of acetylcholine neurons is thought to be a significant cause of the memory loss of AD. NGF is a trophic factor for acetylcholine neurons. In a mouse model of Down syndrome, it was seen that increased APP reduced retrograde transport of NGF, and this led to the loss of cholinergic neurons. It is postulated that this may be a mechanism of cholinergic cell loss in AD.[54] NGF has been shown to prevent the death of cholinergic neurons in rats in both aged and lesion models. In a search for a more effective way to target NGF at appropriate areas, genetically modified autologous fibroblasts are a focused area in clinical trial studies.

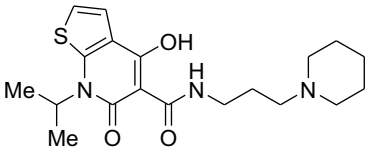
1.3.5. Targeting Tau protein

Hyperphosphorylated tau protein is the main component of the other neuropathological hallmark of AD, the neurofibrillary tangle. Mechanistically, hyperphosphorylated tau is also known to interfere with microtubule assembly, which may promote neuronal network breakdown.[55] Various avenues have been explored in animal models to address tau. One is inhibiting tau kinases and others involve supporting microtubule assembly. Another avenue that has currently passed a phase 2 trial is blocking tau aggregation with methylene blue (MTC).[56]

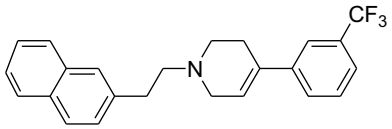
1.3.6. Serotonin receptors

The discovery of the serotonin 5-hydroxytryptamine-4 (5-HT4) receptor in the past 5 years has provided insights into the signaling pathways and the physiological roles of G protein–coupled receptors in neurons. Animal research has demonstrated the involvement of 5-HT4 receptors in cognitive processes, the protection of neurons

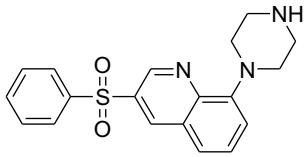
via increased secretion of the soluble form of APP and some evidence of cholinergic stimulation, and all of these are potentially therapeutic in AD. Recent 2-week clinical trials of PRX-03140[57] in humans suggest that agonists at the 5-HT4 receptor may have



PRX-03140



Xaliproden



SB-742457

a cognitive enhancing effect. PRX-03140 was in a phase 2 clinical trial, but after slow enrolment and insufficient financing, the company Epix, discontinued its development and left this as an unexplored molecule. Other serotonin receptor modulators has been or are also being explored, such as 5-HT1A (xaliproden)[58] and 5-hydroxytryptamine-6 (SB-742457),[59] which have just undergone phase I clinical trial.