AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

An Overview On Alzheimer's Disease: Causes, Symptoms, And Its Treatment

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ABSTRACT

Alzheimer's disease is a degenerative brain disease and the most common cause of dementia. Dementia is also caused by other diseases and conditions. it is characterized by decline in memory , language , problem solving and other cognitive skills that effects a person's ability to perform everyday activities. This decline occurs because nerve cells (neurons) in parts of the brain involved in cognitive function have been damaged and no longer function normally , In Alzheimer's neuronal damage eventually affects parts of the brain that enable a person to carry out basic bodily functions such as walking and swallowing . People in the final stages of the disease are bed-bound and required around the-clock care .Alzheimer's disease is ultimately fatal.[1]

Keywords: Alzheimer's disease, brain disease, dementia, memory, nerve cells, walking , neuronal damage , cognitive skills

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Received 14 January 2017, Accepted 23 January 2017

Please cite this article as: Sridhar R *et al*., An Overview On Alzheimer's Disease: Causes, Symptoms, And Its Treatment. American Journal of PharmTech Research 2017.

INTRODUCTION

The world's population is rapidly aging, the number of people with dementia is expected to grow from 35 million today to 65 million by the year 2030. In the United States alone, 5 million or 1 in 9 people over the age 65 are living with Alzheimer's disease (AD), The most common cause of dementia. For comparison, according TO Centres for disease control and prevention (2009-2016) estimates about 3 million older adults in USA has asthma. As dementia carries significant implications for patients, their families, and our society, it is imperative for well-rounded physicians to have a solid understanding of this topic.

ALZHEIMER'S DISEASE:

Alios Alzheimer and Auguste D

The German Psychiatrist and neuropathology's Dr. Alios Alzheimer is credited with describing for the first time a dementing condition which later became known as AD. In this 1906 conference lecture and a subsequent 1907 article , Alzheimer described the case of August D , a 51-year old woman with a peculiar disease of cerebral cortex , who had presented with a progressive memory and language impairment , dis-orientation , behavioural symptoms (hallucinations , delusions , paranoia) and psycho social impairment.[2,3,4]

Dementia

Dementia is a clinical syndrome (a group of co-occurring signs and symptoms) that involves progressive deterioration of intellectual function. [5]. Various cognitive abilities can be impaired with dementia, including memory, language, reasoning, decision making , attention and orientation. In individuals with dementia, cognitive impairments are often accompanied by changes in personality, emotional regulation , and social behaviours . Importantly, the cognitive and behavioural changes that occur with dementia interfere with work , social activities relationships and impair a person's ability to perform routine daily activities (eg. Driving , shopping , house- keeping , cooking managing finances , and personal care) Table 1 summarizes the clinical criteria for all causes of dementia.[5,6]

CLINICAL CRITERIA FOR DEMENTIA

Progressive impairment in two or more areas of cognition:

1. Memory (ability to learn and remember new information)
2. Language (speaking , reading , writing)
3. Executive function (reasoning , decision making , planning)
4. Visuospatial function (ability to recognize faces and objects)

5. Praxis (ability to perform purposeful movements)
6. Changes in personality , mood , or behaviour

Cognitive deficits:

1. Interfere with functioning (ability to perform activities of daily living)
2. Represent a decline from previous levels of functioning
3. Are not due to delirium or psychiatric disorders (e.g. Depression)
4. Are established history from patient , or from informant (e.g.; family member)

EPIDEMIOLOGY OF ALZHEIMER"S DISEASE

AD is a critical public health issue in many countries around the world, with a significant health, social, and financial burden on society. An estimated 5million Americans have AD with a new diagnosis being made every 68 seconds. AD is a multi factorial disease, with a no single cause known, and several modifiable and non-modifiable risk factors are associated with its developments and progression. Age is the greatest risk factor for the development of AD 8. The likelihood of developing AD increases exponentially with age, approximately doubling every five years after age 65. The vast majority of individuals suffering from AD are aged 65 or older and have late on-set. Rare genetic mutations are associated with the development of AD before age 65, which is known as early onset.[9,10]. People with Familial forms of AD have an autosomal mutation in either one of the genes located on chromosomes 1 and 14 or in the amyloidal precursor protein gene located on chromosome 21. The prevalence of AD is higher among females, reflecting the longer life expectancy of women. Family history of AD in first-degree relatives and a history of head injury with loss of consciousness are also risk factors for the development of AD. [11]

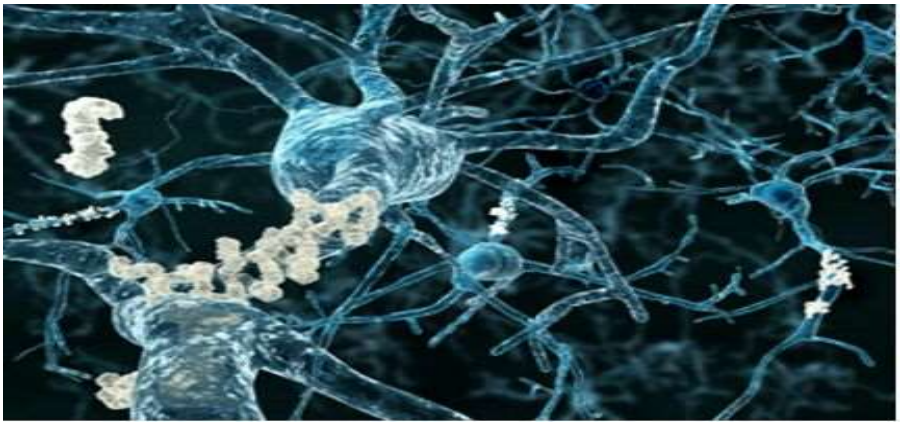
Neuropathy of AD:

AD is a progressive neuro generative brain disorder that causes a significant disruption of normal brain structure and function. At the cellular level AD is characterized by a progressive loss of cortical neurons, especially pyramidal cells that mediate, higher cognitive functions. [12] substantial evidence also suggest that AD causes synaptic dysfunction early in the disease process disrupting communication within neural circuits important for memory and other cognitive functions[13] . AD-related degeneration begins in the medical temporal lobe. The degeneration then spreads throughout the temporal association cortex and to parietal areas. As the disease progress degeneration can be seen in frontal cortex and eventually throughout most of the remaining neo-cortex.

Causes of Alzheimer"s Disease:

Like all types of dementia, Alzheimer's is caused by brain cell death. it is a neurodegenerative disease , which means there is progressive brain cell death that happens over a course of time.[14]

The total brain size shrinks with Alzheimer's- the tissue has progressively fewer nerve cells and connections.



Nerve cells (neurons) in the brain. In Alzheimer's, there are microscopic plaques and tangles between and within brain cells

While they cannot be seen or tested in the living brain affected by Alzheimer's disease, post-mortem/autopsy will always show tiny inclusions in the nerve tissue called plaques and tangles. Plaques are found between the dying cells in the brain- from-the build-up of protein called beta-amyloidal (you may hear the term "amyloidal plaques")

The tangles are within the brain neurons-from a disintegration of another protein, called tau. The abnormal protein clumps , inclusions, in the brain tissue are always present with the disease , but there could be another underlying process that is actually causing the Alzheimer's –scientists are not yet sure .[15]

This sort of change in brain nerve is also witnessed in other disorders, and researchers want to find out to know how these develop so that a cure or prevention might be discovered.

Symptoms:

Early symptoms of Alzheimer's disease may include:

- Forgetfulness
- Loss of concentration
- Language problems
- Confusion about time and place
- Impaired judgement
- Loss insight

- Impaired movement and coordination
- Mood and behaviour changes
- Apathy and depression

The early symptoms of Alzheimer's disease may be over looked because they resemble signs of natural aging- how-ever extreme memory loss or other cognitive changes that disrupt normal life are not typical signs of aging. In addition the symptoms of Alzheimer's disease do not begin abruptly: they develop gradually and worsen over the course of months or years. [16]

Older adults who begin to notice a persistent mild memory loss of recent events may have a condition called mild cognitive impairment (MCI). MCI may be a sign or early stage of Alzheimer's disease in older people. Studies suggest that some, although not all, older individuals who experience such mild memory abnormalities can later develop Alzheimer's disease.

Patients may be aware of their symptoms or may be unaware that anything is wrong. The Alzheimer's disease association recommends that everyone learn these 10 warning signs of Alzheimer's disease:

- Memory changes that disrupt daily life. Forgetfulness, particularly of recent events or information, or repeatedly asking for the same information.
- Challenges in planning or solving problems. Loss of concentration (having trouble planning or completing familiar tasks, difficulty with abstract thinking such as simple arithmetic problems.
- Difficulty completing familiar tasks at home, at work, or at leisure.
- Confusion about time or place. difficulty recognizing familiar neighbourhoods or remembering how you arrived at a location , confusion about months or seasons
- Trouble understanding visual images and spatial relationships. Difficulty reading, figuring out distance, or determining colour.
- Language problems. forgetting the names of the objects , mixing up words , difficulty completing sentences or following conversations
- Misplacing things and losing the ability to retrace steps. Putting objects back in unusual places, losing things, accusing others of hiding or stealing.
- Impaired judgement and decision making. dressing inappropriately or making poor financial decisions
- Withdrawal from work or social activities. No longer participating in familiar hobbies and interests.

- Mood and personality changes. Confusion, increased fear of suspicion, apathy and depression, anxiety. Signs can be loss of interest in activities, increase sleeping. Sitting in front of television for long period of time. [16]

Changes in the Brain That Are Associated with Alzheimer's Disease

A healthy adult brain has about 100 billion neurons, each with long, branching extensions. These extensions enable individual neurons to form connections with other neurons. At such connections called synapses, information flows in tiny bursts of chemicals that are released by one neuron and detected by a receiving neuron. The brain contains about 100 trillion synapses. They allow signals to travel rapidly through the brain's neuronal circuits, creating the cellular basis of memories, thoughts, sensations, Emotions, movements and skills.

The accumulation of the protein beta- amyloid (called beta-amyloid plaques) *outside* neurons and the accumulation of an abnormal form of the protein tau(called tau tangles) *inside* neurons are two of several brain changes believed to contribute to the development of Alzheimer's. In Alzheimer's disease, information transfer at synapses begins to fail, the number of synapses declines, and neurons eventually die. The accumulation of beta-amyloid is believed to interfere with the neuron-to-neuron communication at synapses and to contribute to cell death. Tau tangles block the transport of nutrients and other essential molecules inside neurons and are also believed to Contribute to cell death. The brains of people with advanced Alzheimer's show dramatic shrinkage from cell loss and widespread debris from dead and dying neurons. The brain changes associated with Alzheimer's may begin 20 or more years18-20 before symptoms appear. The time between the initial brain changes of Alzheimer's and the symptoms of advanced Alzheimer's is considered by scientists to represent the "continuum" of Alzheimer's. At the start of the continuum, individuals are able to function normally despite these brain changes. Further along the continuum, the brain can no longer compensate for the neuronal damage that has occurred, and individuals show subtle decline in cognitive function.[17] Later, neuronal damage is so significant that individuals show obvious cognitive decline, including symptoms such as memory loss or confusion as to time or place. Later still, basic bodily functions such as swallowing are impaired.

Risk Factors for Alzheimer's disease

With the exception of the rare cases of Alzheimer's caused by genetic mutations, experts believe that Alzheimer's, like other common chronic diseases, develops as a result of multiple factors rather than a single cause. This section describes known risk factors for Alzheimer's. Other factors that may affect risk are being studied. Age The greatest risk factor for Alzheimer's disease is age. Most people with Alzheimer's disease are diagnosed at age 65 or older. People younger than 65

can also develop the disease, although this is much more rare(see the Prevalence section). While age is the greatest risk factor, Alzheimer's is not a normal part of aging

and age alone is not sufficient to cause the disease. Apo lipoprotein E (APOE)-e4 *Gene* the APOE gene provides the blueprint for a protein that transports cholesterol in the bloodstream. 17

Everyone inherits one form of the APOE gene — e2, e3 or e4 — from each parent:

- The e3 form is the most common, with about 60 percent of the U.S. population inheriting e3 from both parents.
- The e4 form is carried by an estimated 20 to 30 percent of individuals; approximately 2 percent of the U.S. population has two copies of e4.
- The e2 form is carried by an estimated 10 to 20 percent of the population. Having the e4 form increases one's risk compared with having the e3 form, while having the e2 form may decrease one's risk compared with the e3 form. Those who inherit one copy of the e4 form have a three-fold higher risk of developing Alzheimer's than those without the e4 form, while those who inherit two copies of the e4 form have an 8- to 12-fold higher risk. In addition, those with the e4 form are more likely to develop Alzheimer's at a younger age than those with the e2 or e3 forms of the APOE gene. Researchers estimate that between 40 and 65 percent of people diagnosed with Alzheimer's have one or two copies of the APOE-e4 gene. [18]

Diagnosis

A diagnosis of Alzheimer's disease is most commonly made by an individual's primary care physician. No single, simple test exists to diagnose Alzheimer's disease. A variety of approaches and tools are available to help make a diagnosis. They include the following:

- Obtaining a medical and family history from the individual, including psychiatric history and history of Cognitive and behavioral changes.
- Asking a family member or other person close to the individual to provide input about changes in thinking Skills or behavior.
- Seeking input from a specialist, such as a neurologist.
- Conducting cognitive tests and physical and neurologic examinations.
- Having the individual undergo a magnetic resonance imaging (MRI) scan, which can help identify brain changes, such as a tumour, that could explain the individual's symptoms. Before making a diagnosis of Alzheimer's, physicians may refer to medical resources such as the *DSM-5* and published diagnostic criteria that delve even further in the disease. [19]

Medications

Acetylcholinesterase inhibitors reversibly bind and inactivate the enzyme that degrades acetylcholine, which is involved in memory. Donepezil (Aricept) is the only acetylcholine esterase inhibitor approved for use in all stages of the disease. The *N*-methyl-D-aspartate receptor antagonist memantine (Namenda) is approved for treating moderate to severe disease, and is thought to prevent excitatory amino acid neurotoxicity without interfering with the physiologic actions of glutamate, a neurotransmitter necessary for learning and memory. Studies of these drugs have usually assessed effectiveness using one of several scales, such as the Alzheimer's Disease Assessment Scale for Cognition (ADAS-cog; a 70-point scale), the Alzheimer's Disease Cooperative Study Activities of Daily Living inventory (ADCS-ADL; a 54-point scale), or the Severe Impairment Battery (SIB; a 100-point scale). In general, to be clinically significant (defined as a noticeable improvement by the patient or caregiver), an increase should be at least 10 percent of the scale length (i.e., 7 points on the ADAS-cog, 5 points on the ADCS-ADL, or 10 points on the SIB). [20]

ACETYLCHOLINESTERASE INHIBITORS

Acetylcholinesterase inhibitors are first-line agents for the treatment of mild to moderate Alzheimer disease, according to existing guidelines. Most randomized controlled trials and systematic reviews have found no notable differences in effectiveness among the various acetylcholinesterase inhibitors. Despite small variations in mechanisms of action, these agents have varying adverse effect profiles. The most common adverse effects are nausea, vomiting, and diarrhea; cardiovascular and neurologic adverse effects are comparable. [21] The incidence of adverse effects is directly related to the dose administered. Rivastigmine (Exelon) patches may be better tolerated than oral rivastigmine. Tacrine is no longer available because of safety and tolerability concerns.

A Cochrane review concluded that in patients with Alzheimer disease, treatment with donepezil, galantamine (Razadyne), or rivastigmine for six months to one year resulted in slightly improved cognitive function by an average of –2.7 points on the ADAS-cog. Improvements in behavior and activities of daily living also have been noted in patients treated with one of these three agents; however, none of the medications has a large treatment effect, and the clinical significance of these effects is questionable. [22] Another systematic review concluded that, despite statistical significance, the improvement in patients with dementia taking acetylcholinesterase inhibitors was clinically marginal (–0.1 to –5.3 points on the ADAS-cog). Additional trials are needed to determine the benefits of long-term therapy and whether these agents are effective in patients with

moderate to severe Alzheimer disease. It is reasonable to discontinue treatment if there is no improvement within six to eight weeks. [23] Therapy may be restarted if symptoms worsen after the medication is tapered, because acetyl cholinesterase inhibitors may be more effective for symptomatic control than previously recognized. [24]

MEMANTINE

Memantine prevents excessive glutamatergic activity. A Cochrane review concluded that memantine at a dosage of 20 mg per day over six months slightly improved patients with mild to moderate dementia (1 point on the ADAS-cog) but is unlikely to have clinical significance. A small reduction in agitation was seen in patients taking memantine. Seventeen patients with moderate to severe Alzheimer disease would need to be treated for six months to prevent one episode of agitation. [25] A meta-analysis concluded that memantine was ineffective for patients with mild Alzheimer disease, and the benefits for patients with moderate Alzheimer disease were inconsistent. Memantine is generally well tolerated and is often used with acetylcholinesterase inhibitors. One study randomized patients taking donepezil for moderate to severe Alzheimer disease to receive 20 mg of memantine or placebo every day for 24 weeks. Patients taking memantine showed mild improvement in cognition (+0.9 points versus –2.5 points with placebo on the SIB) and activities of daily living (2.0 points versus –3.4 points with placebo on the ADCS-ADL). Another study evaluated the effectiveness and safety of 20 mg of memantine per day for 24 weeks in patients already taking donepezil, rivastigmine, or galantamine for mild to moderate Alzheimer disease. Adding memantine was not associated with a statistically significant improvement compared with placebo. [26]The lack of adverse effects was consistent with findings in other memantine monotherapy studies. [27]Guidelines from the National Institute for Health and Clinical Excellence cite a study that found no improvement with memantine compared with placebo in patients who had moderate to severe Alzheimer disease. Patients taking memantine may have problems with adherence because it is typically taken twice per day. A once-daily extended-release formulation of memantine was approved by the U.S. Food and Drug Administration in June 2010. [28]

SELEGILINE

Selegiline (Eldepryl) is a monoamine oxidase type B inhibitor with minimal anticholinergic effects. A Cochrane review analyzed 17 double-blind, randomized, placebo-controlled trials evaluating selegiline at a dosage of 10 mg per day for the treatment of Alzheimer disease. The authors concluded that cognition improved at four to six weeks in some trials; however, there were no differences after six weeks. The benefits were found primarily in two studies; other trials did

not support these findings. No differences in adverse effects were noted compared with placebo. Currently, there is not enough evidence to recommend selegiline for the treatment of Alzheimer disease. [29]

ANTIPSYCHOTICS

Antipsychotics are not approved by the U.S. Food and Drug Administration for the treatment of Alzheimer disease, although they are commonly used to treat behavioral symptoms. Evidence suggests that olanzapine (Zyprexa) and risperidone (Risperdal) reduce aggression, and risperidone reduces psychosis in patients with Alzheimer disease. [30] The Clinical Antipsychotic Trials of Intervention Effectiveness protocol for Alzheimer disease assessed the effects of atypical antipsychotics on psychiatric and behavioral symptoms.[31] It included 421 outpatients with Alzheimer disease and psychosis or agitated/aggressive behavior. Patients were randomized to receive olanzapine, quetiapine (Seroquel), risperidone, or placebo for up to 36 weeks. There were no clinically or statistically significant differences in functioning, care needs, or quality of life between patients taking antipsychotics and those taking placebo. Some clinical symptoms improved, such as anger, aggression, and paranoia. Patients taking olanzapine experienced worsening functional ability at week 12 compared with those taking placebo. A small randomized, double-blind, placebo-controlled trial failed to demonstrate effectiveness of quetiapine or rivastigmine for treatment of agitation in patients with Alzheimer disease in care facilities after 26 weeks. At six weeks, a statistically significant decline in cognition was noted in patients taking quetiapine compared with those taking placebo.

Older patients with dementia who are treated with atypical antipsychotics have a twofold higher mortality rate than those taking placebo. One study found that new use of atypical antipsychotics was associated with an increased risk of death at 30 days both in community-dwelling patients (hazard ratio = 1.31; 95% confidence interval, 1.02 to 1.70) and in those living in long-term care facilities (hazard ratio = 1.55; 95% confidence interval, 1.15 to 2.07). Most of those deaths were related to cardiovascular or infectious causes, possibly because antipsychotics can prolong QT interval and cause sedation, which may increase the risk of aspiration. Other common adverse effects of antipsychotics include gait disturbances and extra pyramidal effects. Using atypical antipsychotics to treat behavioral symptoms such as agitation in patients with Alzheimer disease generally should be avoided because of adverse effects, although these agents may be appropriate in some situations.[32]

Ineffective Therapies

Estrogen has been studied for the prevention and treatment of dementia. A Cochrane review found no beneficial effect of long-term estrogen use on cognitive function in patients with Alzheimer disease. [33] Estrogen does not enhance the effects of acetyl cholinesterase inhibitors; no benefit was found when it was used in combination with rivastigmine. [34] An updated Cochrane review concluded that there is no evidence supporting the use of vitamin E for the prevention or treatment of Alzheimer disease, and it may be harmful in higher doses. [35] Studies have demonstrated no beneficial effect of nonsteroidal anti-inflammatory drugs for the treatment of Alzheimer disease. Statins and insulin sensitizers have not demonstrated benefit in clinical trials in patients with Alzheimer disease. Systematic reviews have found no clear benefit of lecithin or acetyl-L-carnitine. [36]

Therapies with Conflicting Evidence

TESTOSTERONE

There is conflicting evidence on the benefit of testosterone in men with Alzheimer disease. Two randomized, double-blind, placebo-controlled studies demonstrated benefit in visuospatial cognition, but it is unclear if this effect is clinically meaningful. [37]A randomized, placebo-controlled trial examined the effect of 1% testosterone gel supplementation (75 mg per day) in men with mild to moderate Alzheimer disease over a period of six months. No statistically significant benefits were detected, although testosterone treatment mildly improved patients' quality of life. A randomized, double-blind, placebo-controlled trial of men older than 65 years with limited mobility and low testosterone levels evaluated treatment with testosterone gel or placebo. The results showed a significantly increased incidence of adverse cardiovascular effects in the treatment group over six months (22 versus 5 percent in the placebo group; P = .05; number needed to harm = 6). Because of the risk of serious adverse effects and the paucity of clinically helpful effects, testosterone therapy in men with Alzheimer disease is not recommended. [38]

GINKGO

A Cochrane Review evaluated 36 studies of ginkgo for the treatment of cognitive impairment and dementia.50 All but one study used the standard ginkgo extract EGb 761, at a dosage of 80 to 600 mg per day. Ginkgo was not associated with a consistent, clinically significant benefit in persons with Alzheimer disease. A European study of 96 patients with Alzheimer disease demonstrated equal effectiveness among a prescription ginkgo extract (240 mg per day), donepezil (5 to 10 mg per day), and a combination of the two agents.51 Because ginkgo is not available as a regulated prescription product in the United States, it is possible that the variability in dietary supplement quality may account for the difference in findings. Clinical evidence appears to support the safety

of ginkgo, with no additional adverse effects reported compared with placebo. However, possible drug-supplement interactions must be considered in patients with Alzheimer disease who use ginkgo, especially the risk of bleeding with the use of aspirin, nonsteroidal anti-inflammatory drugs, or anticoagulants. This is noteworthy because many patients with Alzheimer disease take aspirin for cardiovascular health. [39]

Approach to the Patient

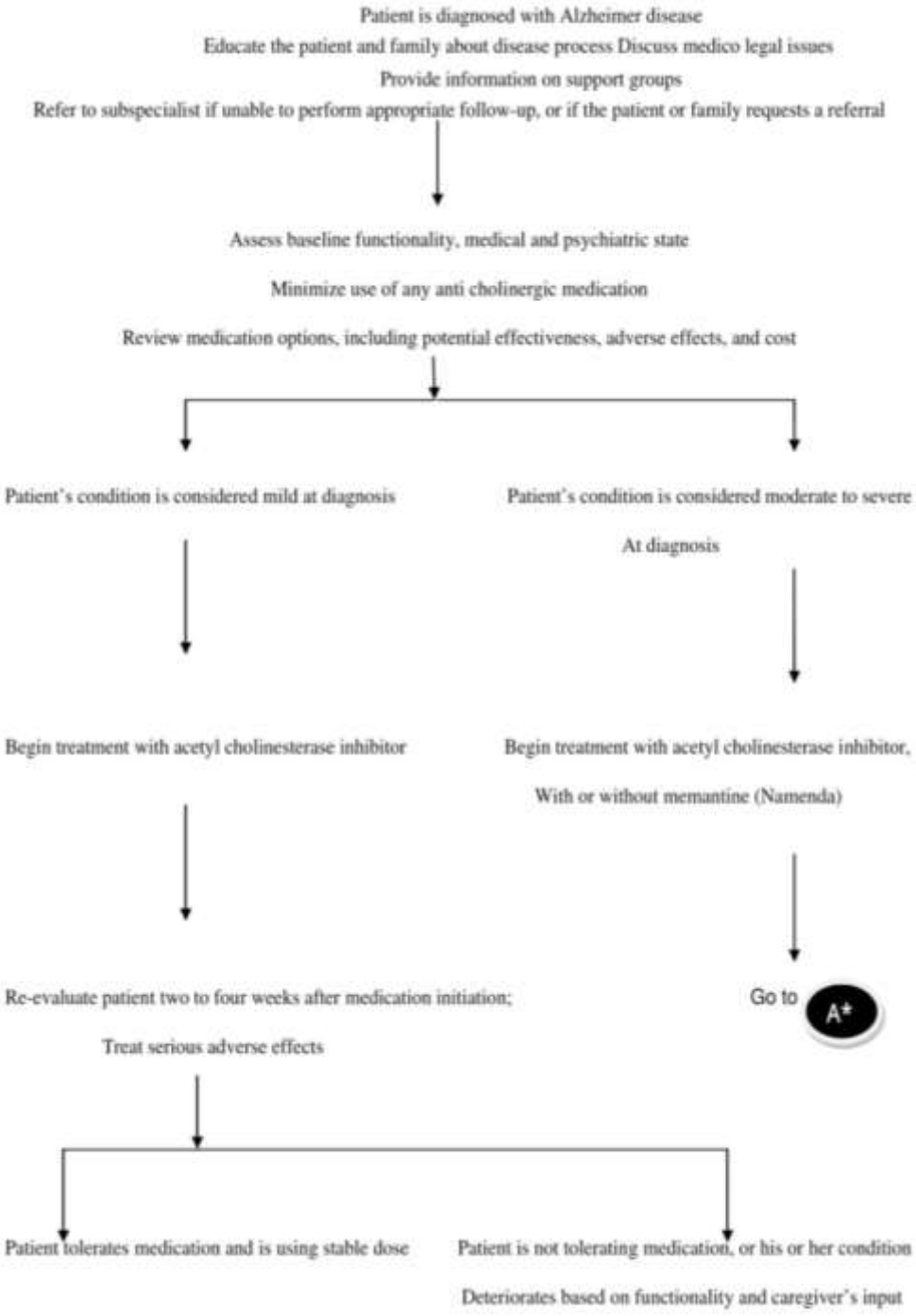
Guidelines on the treatment of Alzheimer disease are available from a number of organizations, including one developed by the American Academy of Family Physicians, in conjunction with the American College of Physicians. All guidelines emphasize the importance of educating patients and their families about the disease process and its expected course. Early referral to local support groups is recommended, and medico legal issues such as driving and end-of-life planning should be addressed. Recommendations regarding pharmacologic treatment are described and a suggested algorithm for the treatment of Alzheimer disease is presented. The decision to treat with medication should be shared with the patient and caregivers, including a discussion of the modest clinical benefit, adverse effects, and cost. Physicians should consider discontinuing therapy in patients who continue to decline despite maximal therapy. The National Institute on Aging and the Alzheimer's Association have released recommendations on the diagnosis of dementia and mild cognitive impairment from Alzheimer disease; however, these guidelines do not address the treatment of Alzheimer disease and do not recommend the clinical use of biomarkers. [40]

Possible Future Treatments

Many potential therapeutic agents are currently under investigation for the treatment of Alzheimer disease. Amyloid precursor protein and enzymes involved in β-amyloid formation are thought to contribute to genetic forms of Alzheimer disease; therefore, interventions to reduce amyloid plaque burden by altering amyloid metabolism are being evaluated. Immunotherapy to promote clearance of β-amyloid from the central nervous system is being assessed. Advanced glycation end products are associated with aging. The advanced glycation end products receptor is a potential target to decrease plaque formation and inflammation. Other potential treatments include resveratrol, a compound from the skin of red grapes that may have beneficial effects on aging in mice, and latrepirdine, a *N*-methyl- D-aspartate receptor antagonist that may also weakly inhibit acetylcholinesterase, which may improve cognitive performance and is currently in phase 3 trials. Agents targeted against tau are other possible options. [41]

Treatment of Alzheimer Disease

Treatment of Alzheimer's Disease:



Non-Pharmacological Therapy

Non-pharmacologic therapies are those that employ approaches other than medication, such as music therapy and reminiscence therapy (therapy in which photos and other familiar items may be used to elicit recall). As with current pharmacologic therapies, non-pharmacologic therapies have not been shown to alter the course of Alzheimer's disease. Non-pharmacologic therapies are often

used with the goal of maintaining or improving cognitive function, the ability to perform activities of daily living, or overall quality of life. They also may be used with the goal of reducing behavioural symptoms such as depression, apathy, wandering, sleep disturbances, agitation and aggression. Systematic reviews of published research on non-pharmacologic therapies have found that some, such as exercise and cognitive activity (for example, gardening, word games, listening to music and cooking) show promise. However, few non-pharmacologic therapies have been tested in randomized controlled studies, which provide the strongest evidence of whether a therapy is effective. In randomized controlled studies, participants are randomly assigned to receive a therapy or not receive a therapy, and results from the two groups are compared. Additional research on non-pharmacologic therapies is needed to better evaluate their effectiveness. [42]

Living with Alzheimer ’s disease

Despite the lack of disease-modifying therapies for Alzheimer’s, studies have consistently shown that active management of Alzheimer’s and other dementias can improve quality of life through all stages of the disease for individuals with dementia and their caregivers. Active management includes:

(1) Appropriate use of available treatment options,

(2) Effective management of coexisting conditions,

(3) Coordination of care among physicians, other health care professionals and lay caregivers,

(4) Participation in activities and/or adult day care programs and

(5) Taking part in support groups and supportive services.

To learn more about each of these ways of helping to manage Alzheimer’s, as well as practical information for living with the disease and being a caregiver for an individual with Alzheimer’s, visit alz.org. Alzheimer’s Association. [43]

Differences between Women and Men in the Prevalence of Alzheimer’s disease and Other Dementias

More women than men have Alzheimer’s disease and other dementias. Almost two-thirds of Americans with Alzheimer’s are women.120, A5 Of the 5.1 million people age 65 and older with Alzheimer’s in the United States, 3.2 million are women and 1.9 million are men.120, A5 Based on estimates from ADAMS, among people age 71 and older, 16 percent of women have Alzheimer’s disease and other dementias compared with 11 percent of men. There are a number of potential reasons why more women than men have Alzheimer’s disease and other dementias. The prevailing view has been that this discrepancy is due to the fact that women live longer than men on average, and older age is the greatest risk factor for Alzheimer’s.130-131 Many studies of

incidence (which indicates risk of developing disease) of Alzheimer's or any dementia have found no significant difference between men and women in the proportion who develop Alzheimer's or other dementias at any given age. However, limited new research suggests that risk could be higher for women, potentially due to biological or genetic variations or even different life experiences (for example, type and amount

of education, or occupational choices). Data from the Framingham Study suggests that because men have a higher rate of death from cardiovascular disease than women in middle age, men who survive beyond age 65 may have a healthier cardiovascular risk profile and thus a lower risk for dementia than women of the same age, though more research is needed to support this finding. Another large study showed that the APOE-e4 genotype, the best known genetic risk factor for Alzheimer's disease, may have a stronger association

With Alzheimer's disease in women than men. It is unknown why this may be the case, but some evidence suggests an interaction between the APOE-e4 genotype and the sex hormone oestrogen. Finally, because low education is a risk factor for dementia, it is possible that lower educational attainment in women than in men born in the first half of the 20th century could account for a higher risk of Alzheimer's and other dementias in women; however, this possibility has not been thoroughly investigated scientifically. [43]

CONCLUSION

Since Alois Alzheimer described the first case of AD more than a century ago, much progress has been made in understanding the biology and clinical aspects of the disease. Substantial advances have been made in characterizing pre-dementia stages of AD, such as MCI, and improving the diagnostic and therapeutic options available for managing AD. Our ability to find the 'cure' for AD ultimately depends not only on having an accurate view of the cellular and molecular processes that go awry but also on having optimal biomarkers to enable early diagnosis and timely therapeutic intervention in at-risk individuals. [44] Recognizing the urgent need to develop clinically useful neuroimaging and other biomarkers for the early detection of AD, the NIA sponsored the on going Alzheimer's Disease Neuroimaging Initiative (ADNI) beginning in 2004. The ADNI, which is akin to the Framingham Heart Study in its ambitions, is a public private partnership and the largest project of its kind that seeks to collect longitudinal neuroimaging data along with clinical data, neuropsychological assessments, and biological specimens (e.g., blood and CSF) from MCI, AD, and healthy older subjects. The ADNI and similar large-scale initiatives are likely to rapidly advance our knowledge on dementia and AD and will catalyze the development of significantly

more effective therapies for AD than exist today. To conclude, the reader is left with some important issues that must be resolved in the future as we move toward a 'cure' for AD in the 21st century:

1. What is the optimal combination of biomarkers for (a) early detection of AD; and (b) monitoring disease Progression and response to treatment?
2. What is the optimal therapeutic strategy for (a) prevention of AD; (b) treatment of AD; and (c) sporadic versus familial AD? (i.e., therapeutic targets, role of medications versus lifestyle modification, optimal time to intervene
3. What are the potential benefits and harms associated with shifting the therapeutic strategy from (a) one that involves treating people with overt AD dementia to (b) one where we treat people with MCI, and ultimately to (c) one where we treat people who are asymptomatic but show an AD-like biochemical and/or imaging biomarker pattern? Are we moving closer to treating abnormal lab results as opposed to the patient? For example, would we be abiding by the oath to 'first, do no harm' by treating an asymptomatic person who shows an AD-like biomarker pattern but is not destined to develop cognitive impairment (e.g., due to his/her high cognitive reserve or resilience in the face of AD pathology). [45]

REFERENCES:

1. Wilson RS, Segwa E, Boyle, PA, Anagnos SE, Hizel LP, Benett DA. The natural history of cognitive decline in Alzheimer's disease. Psychol Aging 2012;27(4):1008-2017
2. Alzheimer A. Uber eine eigenartige Erkrankung der Hirnridne[About a Peculiar Disease of cerebral cortex] Allg 2 psychiatr 1907;64:146-48.
3. Alzheimer A. About a peculiar disease of cerebral cortex. Alzheimer Dis Assoc Dissord 1987;1:3-8
4. Maurer K, volks, Gerbaldo H. Auguste D and Alzheimer's disease. Lancet 1997;349(9064):1546-9. doi: 10.1016/s0140-6736(96)10203-8
5. Gilman S. Oxford American hand book of Neurology. Oxford University Press: Oxford,U;2010
6. Mckhann Gm, Knopman DS, Chertkow, H, Hyman BT, Tack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimers disese: recommendations from the National Institute on Aging-Alzheimer's Association work groups on diagnostic guidelines for

Alzheimer's disease. Alzheimers Dement 2011;7(3):263-9 doi : 10.1016/s. Tal22011.03.005

7. Plassman BL, Langa KM, Fischer GG, Heeringa SG, weir DR, ofstedal MB, et al. Prevelance of Dementia in the United States. The aging, demographics 2007;29;125-32.doi : 10.1159/000109998.
8. Prince M, Bryce R, Albanese E, wimo A, Ribeirow, Ferri CP. The global Prevalence of dementia : a systematic review and meta analysis. Alzheimer's Dement 2013;9:63-75e2 doi 10.1016/j.alz.2012.11.007.
9. Querfurth HW, LaFerla FM. Alzheimer's disease : NEngl j Med 2010 ; 362;329;44.doi : 10.1056/NEJMRa 0909142.
10. Holtman DM, Morris JC,Goate AM. Alzheimer's disease: the challenge of second century. Sci Trans, Med 2011; 3; 77sr1. Doi: 10.1126/scitransmed.3002369.
11. Hebert LE, scherr PA, MC Cann jj, Beckett LA, Evans DA. Is the risk of developing Alzheimer's disease greater for women than for men? AM J Epideniol 2001;153;1326.doi:10.1093/aje/153.2.132.
12. Holtzman DM, Morris JC, Goate AM. ALzheimers disease; the challenge of the second century sci transmed 2011;3:77sr.doi:10.1126/scitransmed.3002369
13. Mann DM puradimal nerve cell loss in Alzheimer's disease. Neurodegenaration 1996:5:423-7
14. Alzheimer's disease causes by marks mac Gill.Neurology/Aging.
15. Alzheimer A.About a Peculiar disease of cerebral cortex. Alzheimer's Dis Assoc Disord 1987;1;3-8.
16. Wilson RS, segawa E, Boyle, PA, Anagnos SE, Hizel LP, Bennett DA, the symptoms in Alzheimer's disease. Psychol Aging 2012;27(4):1008-17.
17. Reiman EM, Quiroz YT, Fleisher As, Chen K, Veliz-Pardos C, Jiemenez-Del-Rio H, et al. Brain Imaging and fluid bio-marker.
18. Viswanathan A, Rocca WA, Tzourioc. Vascular risk factors and dementia.
19. American Psychiatric Association. Diagnostic and statistical manual of mental disorder.
20. Birks J.cholinesterase inhibitors for Alzheimer's disease. Cochrane Database syst Rev .2006(1) : cd005593

21. Mc Shane R, Areosasastre A, Minakaran N. Memantine for dementia Cochrane Data base syst Rev.2006:(2):CD005593
22. National Institute for health and clinical excellence [Great Britain] ; social care institute for excellence National collaborating factor for excellence for mental health . Dementia : supporting people with dementia and their careers in health and social care . NICE clinical guidelines 42 london United Kingdom: National Institute for the health and clinical evidence (or) excellence :2006.
23. American psychiatric Association :practice guidelines for the treatment of patients with the Alzheimer's disease and other DEMENTIAS 2N ED Alington va : American psychiatric Association 2007;
24. Qaseem A, snow v, cross jt jr,et al: American college of physicians/ American Academy of family physicians/panel on dementiaq. Current pharmacologic treatment of dementia a clinical practice guideline from the American College of physicians and American academy of Family Physicians. An intermediate.2008;(148.15):370-378.
25. Rock eood K, Middleton L. physical activity and the maintenance of cognitive function. Alzheimer's Dement 2007;3(2suppl) : s38-s44.
26. Daviglus ML, Bell cc, Berrettini W, et al. N1H state of the science conference statement: PREVENTING Alzheimer's disease and cognitive decline . N1H consensus. nin. gov/2010docs/a12/a12_stmt p.d.f Accessed April 29,2010.
27. MC Shane R, Areosa Sastre A, Hinakaran N. Memantine for dementia. Cochrane database.syst Rev 2006;(2):CD003154.
28. S chneider LS, Dagerman KS, Higgins JP, Meshane R. lack of evidence for the efficacy of mematine in mid Alzheimer's disease [Published ahead of print of print April 11,2011]. Arch Neurol. http://archneur.am-assn.Org/content/abstract/archneurol.2011.69.
29. Birks J, Flicker L, selegiline for Alzheimer's disease. Cochrane data base syst. Rev.2003(1):CD000442.
30. Sultzer DL, Davis SM, Tariot PN, et al ; (ATIE-AD study group. Clinical symptom responses to a typical antipsychotic medications in Alzheimer's disease Phase 1 out comes from the CATIE-AD effectiveness trail. AMJ Psychiatry. 2008:165(7):844-854.

31. Ballard C, Margallo, The effectiveness of a typical antipsychotics for the treatment of Agression and Psychosis in Alzheimer's disease Cochrane database syst Rev.2006(1):CD003476.
32. Gill SS, Bronskill SE, Normand SL,et.al. Antipsychotic drug use and mortality in older Adults with dementia. Anm Intern Med.2007;146(11):775-786.
33. Hog errorst E, yaffe K, Richards M,Huppert FA hormone replacement therapy to maintain cognitive function in woman with dementia. Chochrane database syst Rev.2009;(1);CD003799.
34. Issac Mg, Quinn R, Tablet N .vitamin E for the Alzheimer's disease and mild cognitive impairment Cochrane database syst Rev.2008;(3);CD002854.
35. Higgins JP, Flicker L. lecithin for dementia and the cognitive impairment. cochrane database syst Rev-2003;(3):cd001015
36. Hudsons, Tablet N. Acetyl-1-carnitine for dementia. Cochrane database syst.Rev.2003;(2):CD003158.
37. Tan RS, PU St. A Pilot study on the effects of Testosterone in Hypogonadal ageing male 2003;6(1):13-17.
38. Cherrier MM, Matsumoto AM, Amory JC et.al . Testosterone improves s partial memory in men with Alzheimer's disease and mild cognitive impairment. Neurology.2005:64(12):2063-2068.
39. Birks j, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Daatabase syst Rev. 2009;(1);CD003120.
40. MC Khann GM, Knopman DS, Chertkow H, et al. The diagnosis of Dementia due to Alzheimer's disease ; recommendations from the national institute of Aing-Alzheimer's Association work groups on diagnostic guidelines for Alzheimer's disease .Alzheimer's Dement 2011;7(3);263-269.
41. Neuroschl J, Sano M. Current treatment and recent clinical research in Alzheimer's disease . Mt sinaijme 2010;77(1);3-16.
42. Zarit SH. Empirically supported treatment for family care givers. In ;Qualls SH, Zarit SH, eds. Aging families and care giving. Hoboken, N.J ; John wiley and sons ,inc ;2009:p. 131-54.

43. Peng H-L, Chang Y-P. Sleep disturbance in family care givers of individuals with dementia psychiatric C 2012;19(2):135-146.
44. Jones AC, Dwyer LL, Bercovitz AR, Strahan GW. The national Nursing home surves:2004 over view. 2009;(167):1-155.
45. Neiner MW, Veitch DP, Aisen PS, Beckett(A), Cairns NJ, Green RC, et al. The Alzheimer's Disease Neuroimaging initiative : a review of papers published since its in caption Alzheimer's Dement 2012;8: S_1-68. Doi : 10.1016/j.jalz.2011.