



A COMPREHENSIVE REVIEW ON TREATMENTS OF ALZIMER DISEASE

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ABSTRACT

A new paradigm is needed that focuses on minimizing the symptoms of Alzheimer's disease and related dementias rather than focusing only on a search for a cure. To include Alzheimer's in the same class of diseases as cancer, multiple sclerosis, diabetes, congestive heart failure, and degenerative arthritis places Alzheimer's in the realm of medically and psychosocially understandable and manageable. A critical first step toward making this shift is to examine carefully the way in which we define the disease. An approach to care for people with Alzheimer's disease results in treatment when it systematically compensates for functional losses of dementia by linking caregiving actions and environments to specific brain dysfunctions; namely the neuropathology of the disease. The ultimate measures of success of such a treatment approach are improved quality of life, delayed institutionalization, slowed rate of progression of the disease, people who achieve their potential, and reduced need for medication.

KEYWORDS:

INTRODUCTION

ALZHEIMER DISEASE (AD), the most common of the dementing disorders, affects an estimated 4 million people in the United States.^[1,2] It causes anguish to millions more caregivers and family members, who must cope with their loved one's steady and irreversible decline in cognition, functioning, and behavior. Patients and caregivers often mistake early symptoms for normal aging changes and physicians may fail to recognize the initial signs of dementia or misdiagnose them, perpetuating myths and fallacies about the disease--in particular that the early signs of dementia are "just old age" or "just senility." Alzheimer disease and aging, however, are not synonymous. Expected cognitive changes of aging--for example, a slowing of information processing--are benign, while dementia is progressive and disabling, not an inherent part of growing old. Recent progress in understanding the diagnosis and treatment of AD and related disorders has benefited many. Dementia is a syndrome characterized by disturbance of multiple brain functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied and occasionally preceded, by deterioration in emotional control, social behavior, or motivation.^[3,4]

Alzheimer disease is the most common form of dementia and possibly contributes to 60 to 70% of cases. Other types of dementias include vascular dementia, dementia

with Lewy bodies and a group of diseases that contribute to front temporal dementia. The boundaries between subtypes are indistinct and mixed forms often co-exist. Dementia can affect a person in different ways, and progression of the disease depends upon the impact of the disease itself and the person's personality and state of health. Dementia can be divided in three stages:

Early stage iV first year or two.

Middle stage iV second to fourth or fifth years.

Late stage iV fifth year and after patients.

Age

The more individuals advance in age the higher is the risk they will develop Alzheimer disease. Most patients develop AD after the age of 65 years old. The risk of developing AD reaches 50% for individuals beyond age 85. Because more and more people live longer lives this disease is becoming a serious concern. The age-specific incidence rates. disease demonstrate a doubling of incidence for about every six years of added life, which indicates an exponential increasing risk with increasing age. This exponential risk is fairly similar across studies, regardless of geographic region, even if the underlying absolute incidence rate differs.

Genetics of AD

The vast majority of Alzheimer disease is not genetically inherited although some genes may act as risk factors.¹⁴ Genetically identified forms of Alzheimer disease, which usually have an onset before the age of 65, have been

identified and account for 0.1% of disease cases.¹⁵ The current thinking is that there are sporadic/late onset and familial/early onset cases of Alzheimer disease.

Familial/Early onset When Alzheimer disease is caused by these deterministic variations, it is called “autosomal dominant Alzheimer disease (ADAD)” or “familial Alzheimer disease”. Many members in multiple generations are affected. Symptoms develop before age 60, and may appear among persons between 30 and 40 years old. Most of autosomal dominant familial AD can be attributed to mutations in the amyloid precursor protein (APP) and/or presenilins 1 and 2 gene.¹⁶ Mutations in the APP and presenilin genes lead to the production of protein A β 42 (beta amyloid 1-42) that accumulates into amyloid plaques and cause death of neurons by increasing the production of protein.

Sporadic/late onset

Other cases that do not exhibit autosomal-dominant inheritance are termed sporadic AD. Genetic risk factors have been identified such as the inheritance of the allele of the lipoprotein (APOE).¹⁸ Risk genes increase the likelihood of developing a disease, but do not guarantee it will happen. To 15 times increase risk of developing Alzheimer disease.

Role of environment for AD

Several studies indicate a role for environmental effects on AD development. In a recent review Richard Mayeux and Yaakov Stern summarized the role of diet, activities, or diseases that potentially play a role in the onset of Alzheimer disease. Diabetes, hypertension, smoking, obesity, and dyslipidemia have all been found to increase risk as well as a history of brain trauma, cerebrovascular disease, and vasculopathies. A higher level of education, as well as Mediterranean diet was shown to decrease the risk of developing AD.

Diagnosis

Diagnostic Criteria

The only method of definitively diagnosing AD is a brain autopsy. However, mental and behavioral tests and physical examinations allow physicians to make an accurate diagnosis of AD in 90 percent of cases.^[5] The criterion for diagnosing mental disorders can be found in

the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), published by the American Psychiatric Association. In this manual, AD falls into the category of primary degenerative dementia. The diagnostic criterion includes dementia, insidious onset with progressive deterioration, and exclusion of all other types of dementia by history and physical examination.^[6] A diagnosis of dementia includes a loss of intellectual abilities severe enough to interfere with social or occupational functioning, memory impairment, and a variety of other symptoms. The first step in finding a diagnosis is obtaining the patient history. During this time, the physician will determine what symptoms are present, when they began and how they have progressed over time. The family history of illness is also pertinent. The physician will perform a physical examination, including blood tests and urinalysis. This is done to rule out other potential causes of dementia, such as hormone imbalance, vitamin deficiency and urinary tract infections. Brain scans may also be performed to exclude tumors, cerebrovascular accidents, traumatic brain injury, and infections. These scans are also helpful in identifying the characteristic tangles and plaques seen in AD. Structural imaging scans, including magnetic resonance imaging (MRI) and computed tomography (CT), provide information about the shape and volume of the brain.

Treatment for Cognitive Symptoms

Treatment of cognitive symptoms involves altering the effect of chemical messengers in the brain. The Food and Drug Administration (FDA) has approved two types of medication for this purpose.^[7] The first type is called a cholinesterase inhibitor, which hinders the enzyme responsible for the breakdown of acetylcholine in the brain. Acetylcholine is an important neurotransmitter involved in learning and memory. Normal aging causes a slight decrease in acetylcholine concentration, causing periodic forgetfulness. However, in AD, the concentration can be decreased by as much as ninety-percent, resulting in significant memory and behavioral decline.^[9] The function of these drugs is to support communication between nerve cells, therefore increasing the concentration of acetylcholine. There are currently three cholinesterase inhibitors commonly prescribed: donepezil, galantamine and rivastigmine.

Drug Name	Indication	Action	Dose
Donepezil Brand Name: Aricept	Mild to severe AD	Prevents the breakdown of acetylcholine (ACH) by inhibiting the action of acetyl cholinesterase Treats cognitive symptoms of AD	5 mg taken once daily Over time, may increase to 10 mg daily
Galantamine Brand Name: Razadyne	Mild to moderate AD	Prevents the breakdown of acetylcholine and stimulates receptors to release excess ach treats cognitive symptoms of AD	4 mg taken twice daily Over time, may increase to a maximum of 24 mg daily

Memantine Brand Name: Namenda	Moderate to severe AD	Blocks glutamatergic (NMDA) receptors and regulates the action of glutamate Treats cognitive symptoms of AD	5 mg taken once daily Over time, may increase to a maximum of 10 mg daily
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[10]

Drug treatment of Alzheimer's

There are no drug treatments that can cure Alzheimer's disease or any other common type of dementia. However, medicines have been developed for Alzheimer's disease that can temporarily alleviate symptoms, or slow down their progression, in some people. This factsheet explains how the main drug treatments for Alzheimer's disease work, how to access them, and when they can be prescribed and used effectively.^[11]

Many drugs have at least two names. The generic name identifies the substance. The brand name varies depending on the company that manufactures it. For example, a familiar painkiller has the generic name paracetamol and is manufactured under brand names such as Panadol and Calpol, among others. Occasionally, a drug with a very well-known generic name (such as paracetamol) will also be manufactured and sold using just this name.

There are two types of medication used to treat Alzheimer's disease: acetyl cholinesterase inhibitors (often shortened to just 'cholinesterase inhibitors') and NMDA receptor antagonists. The two types work in different ways. These are explained below.

- The generic names for the cholinesterase inhibitors are donepezil, rivastigmine and galantamine:
- Donepezil was originally patented as the brand name Aricept, but is more widely available now as just generic donepezil.
- Rivastigmine was patented as Exelon and is now also available as other brands, as well as generic rivastigmine.
- Galantamine was patented as Reminyl and is now also available as generic galantamine and the brands Reminyl XL, Acumor XL, Galsya XL and Gatalin XL.
- The NMDA receptor antagonist is Memantine. It was originally patented as Ebixa and is now also available as generic Memantine. Other UK brand names for Memantine include Maruxa and Nemdatine.

How do they work?

Cholinesterase inhibitors (donepezil, rivastigmine and galantamine)

In the brain of a person with Alzheimer's disease, there are lower levels of a chemical called acetylcholine. Acetylcholine helps to send messages between certain nerve cells. In Alzheimer's there is also a loss of the

nerve cells that use acetylcholine. Falling acetylcholine levels and progressive loss of these nerve cells are linked to worsening symptoms. Donepezil, rivastigmine and galantamine all prevent an enzyme called acetylcholinesterase from breaking down acetylcholine in the brain. As a result, an increased concentration of acetylcholine leads to increased communication between nerve cells. This may temporarily alleviate or stabilize some symptoms of Alzheimer's disease.

Memantine

The NICE guidance (2011) recommends use of Memantine as part of NHS care for severe Alzheimer's disease (see 'NICE guidance: a summary'). NICE also recommends Memantine for people with moderate Alzheimer's disease who cannot take the cholinesterase inhibitor drugs (this is usually because of side effects). Memantine is licensed for the treatment of moderate-to-severe Alzheimer's disease. In people in the middle and later stages of the disease, it can slow down the progression of symptoms, including disorientation and difficulties carrying out daily activities. There is some evidence that Memantine may also help with symptoms such as delusions, aggression and agitation. For more information see factsheet 408, Drugs used to relieve behavioral and psychological symptoms in dementia a generally, cholinesterase inhibitors and Memantine can be taken without too many side effects. Not everyone experiences the same side effects, or has them for the same length of time (if they have them at all). The most frequent side effects of donepezil, rivastigmine and galantamine are loss of appetite, nausea, vomiting and diarrhea. Other side effects include muscle cramps, headaches, dizziness, fatigue and insomnia. Side effects can be less likely for people who start treatment by taking the lower prescribed dose for at least a month (see 'Taking the drugs'). The side effects of Memantine are less common and less severe than for the cholinesterase inhibitors. They include dizziness, headaches, tiredness, raised blood pressure and constipation. It is important to discuss any side effects with the factsheet 509, Dementia and aggressive behavior. The cholinesterase inhibitors were developed specifically to treat Alzheimer's disease. There has been relatively little research into whether they (or Memantine) are helpful for people with other types of dementia. There is evidence that the cholinesterase inhibitors are effective in people with dementia with Lewy bodies, and dementia due to Parkinson's disease. Rivastigmine is licensed for Parkinson's disease dementia. Acetylcholine levels are often even lower in people with dementia with Lewy bodies than in those with Alzheimer's disease.

Questions to ask the doctor when starting the drugs

It is important that someone who has been prescribed one of these drugs understands what it does and how to take it. The following are things that they may wish to ask the doctor about. It can help for the person with dementia or their care to write down these questions and any answers the doctor gives.

- Why have I been prescribed this drug specifically?
- What are the potential benefits of taking this drug?
- How long will it be before I see a result?
- If I get side effects, should I stop taking the drug immediately?
- What will happen if I stop taking the drug suddenly?
- Can I drink alcohol while taking the drug?
- How might this drug affect other medical conditions?
- What changes in health should I report immediately?
- How often will I need to visit the clinic or surgery?
- If this drug doesn't suit me, can I try another drug?

Stopping treatment

Medication should be reviewed regularly, and continued for as long as the benefits outweigh any side effects. If the person with Alzheimer's decides to stop taking a drug, they should speak to the doctor first if possible, or as soon as they can after stopping treatment. Treatment may also be stopped by agreement with the doctor if the person becomes unable to take the medicines in the prescribed way, even with support. If someone stops taking their prescribed drug, their condition may get worse more quickly. If someone has stopped and thinks they should restart their medication, it is important that they contact their doctor as soon as possible. For someone who is taking a cholinesterase inhibitor, a decision will need to be made when their Alzheimer's disease becomes severe. There is now good evidence that cholinesterase inhibitors continue to bring benefits even when someone's Alzheimer's is severe. Many doctors therefore continue to prescribe a cholinesterase inhibitor for severe Alzheimer's until the above criteria for stopping treatment are met, if ever. The issue of whether to add Memantine to the cholinesterase inhibitor for someone with severe Alzheimer's disease (known as combination treatment) is less clear cut. The two drugs work in different ways and there is research evidence that, for someone who is already on donepezil, adding Memantine might bring additional benefit. However, NICE guidance (2011) does not recommend combination treatment. Tacrine is a centrally active amino acridine with reversible nonspecific cholinesterase inhibitor activity and duration of action of less than 7 hours. In clinical trials involving approximately 2000 patients with mild to moderate AD, between 20% and 30% of Tacrine patients showed clinically observable improvement compared with placebo, representing on average about 6 months of deterioration.^[12] However, approximately one fifth experienced cholinergic adverse effects, most frequently gastrointestinal distress.^[13-14] In addition, 29% had reversible elevations of serum transaminase levels 3 times above normal. After rechallenge, nearly 90% of patients can tolerate the compound.^[15] The starting dose

for Tacrine is 10 mg 4 times daily, which can be increased up to a maximum dose of 40 mg 4 times daily. Patients receiving.

Treatment of Depression in Dementia

Pharmacotherapy

Patients with AD and depressive symptoms (e.g., depressed mood, appetite loss, insomnia, fatigue, irritability, and agitation) should be considered for pharmacotherapy, even if they fail to meet the criteria for a depressive syndrome. The physician should carefully evaluate for indexes of major depression, suicidal ideation may indicate the need for intensive monitoring or hospitalization. The choice of an antidepressant agent should be based on the drug's profile of adverse effects and the patient's general medical and psychiatric status. Many specialists favor the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline as first-line treatment because they have fewer adverse effects than other antidepressants. Tricyclic antidepressants are effective drugs for depression, but these agents, especially amitriptyline, imipramine, anafanil and clomipramine, have significant anticholinergic activity, can cause orthostatic hypotension and delayed cardiac conduction, and are risky in overdose. Nortriptyline, desipramine, bupropion, trazodone, and nefazodone are alternatives. Monoamine oxidase inhibitors (MAOIs), including tranylcypromine and phenelzine, can cause postural hypotension and have complex drug interactions with sympathomimetic agents, narcotics such as meperidine, and serotonergic agents. The MAOIs also require dietary modifications. These agents should be considered only for patients who are unresponsive to or unable to tolerate other antidepressant medications. If they are used, adequate supervision should be arranged modifications.

Fluid Biomarkers

CSF-based and blood plasma-based protein biomarkers are also being investigated for diagnosis of AD. Several studies have used immunoassays to measure the levels of various proteins in the CSF, finding that patients with AD show decreased levels of the 42 amino acid isoform of the Ab (Ab-42) peptide and elevated levels of the phosphorylated tau (P-tau) peptide. A recent longitudinal study showed that baseline Ab-42/ P-tau ratio could accurately predict the progression from MCI to AD.^[16] In 2007, plasma biomarkers were proposed as a promising alternative to CSF biomarkers for early detection of AD.^[17] In recent years, other studies have examined the clinical utility of cell-signaling, immune, metabolic, and disease-related plasma proteins, but findings have been inconsistent.⁶⁵⁶⁷ Overall, further work must be done to standardize the measurement of CSF and plasma proteins and to determine clinical utility of protein biomarkers for diagnosis of AD.

"Habilitation" therapy^[18]

An important conceptual stepping stone towards recognizing treatment Possibilities and shifting the

caregiving paradigm away from hopelessness is Called “habilitation” therapy. The term reflects the realization that the brain of a Person with Alzheimer’s and its function cannot be restored to its prior condition hence therapy is not “re” habilitative. The term also implies that effective Treatment aims to help people “live and work through everyday life”; namely, is “Habilitative.” In the definition of this unique and pioneering therapy, “using mood to bring about a person’s ability to live and work to their full potential’ is a central Feature.

Research into new treatments

No new drugs have been licensed in the UK for Alzheimer’s disease since Memantine in 2002. However, there is a lot of research into new drug treatments. These aim either to give better relief from symptoms or – if possible – to slow down or stop the underlying disease in the brain. The aforementioned considerations suggest the following research questions: What barriers contribute to the delivery of inadequate or untimely medical services in primary care settings?.

Areas of investigation might include the following Physician knowledge about diagnosis and treatment, and the skills required to assess patients; attitudes and beliefs about dementia held by the public and medical professionals.

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. 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. Recognizing the urgent need to develop clinically useful neuroimaging and other biomarkers for the early detection of AD, the NIA sponsored the ongoing Alzheimer’s disease.

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