Alzheimer’s disease: A review of recent developments

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Abstract

Alzheimer’s disease (AD) is the most common type of dementia in aging adults, and a substantial burden to patients, caregivers, and the healthcare system. It is an increasingly significant public health issue; with the number of people living with AD projected to increase dramatically over the next few decades, making the search for treatments and tools to measure disease progression increasingly urgent. This review is based on a search of Medline, the Cochrane Database of Systemic Reviews, and citation lists of relevant publications. The subject headings and keywords used were Alzheimer’s disease, dementia, primary neuronal degeneration and senile plagues. Only the articles written in English were included. The diagnosis is still primarily made based on history and physical and neurologic examinations. Approved treatments are few and of limited efficacy, serving mostly to slow or delay progression and not to cure the disease, despite significant research by pharmaceutical industries. Cholinesterase inhibitors offer some help in treating cognitive and global functioning, as well as behavioral abnormalities in patients with mild-, moderate-, or severe-stage disease. The N-methyl-D-aspartate (NMDA) antagonist, memantine, is similarly effective alone or in combination with cholinesterase inhibitors in moderate to severe stages of the disease. Recent insights into the pathophysiology of AD have led to promising investigational therapies, including the development of γ- and β-secretase inhibitors as well as active and passive immunization against the amyloid β-protein.

Keywords: Advancing age, Alzheimer’s disease, cognitive dysfunction, dementia, neuropsychological testing, primary neuronal degeneration

Résumé

La maladie d’Alzheimer (Ma) est le type le plus courant de démence chez les adultes de vieillissement et un fardeau considérable aux patients, les fournisseurs de soins et le système de santé. C’est un plus signiﬁcant question de santé publique. avec le nombre de personnes vivre avec AD devrait pour augmenter de façon spectaculaire au cours des prochaines décennies, faisant de la recherche de traitements et outils pour mesurer la progression de la maladie plus en plus urgente. Cette analyse est basée sur une recherche dans Medline, la Cochrane Base de données des examens systématiques et des listes de référence des publications pertinentes. Les mots-clés et les vedettes-matières utilisées étaient la maladie d’Alzheimer, de démence, de dégénérescence neuronale primaire et de fleaux séniles. Seuls les articles écrit en anglais ont été inclus. Le diagnostic est fait encore principalement basé sur l’histoire et physique et neurologiques examens. Traitements approuvés sont peu nombreux et de décou efﬁ limité, servant principalement à ralentir ou retarder la progression et ne pas de guérir la maladie, en dépít de signiﬁ cant recherche par l’industrie pharmaceutique. Offrent des inhibiteurs de la cholinestérase peu d’aide dans le traitement de fonctionnement cognitif et mondial, ainsi que des anomalies comportementales chez les patients avec légère-modérée-, ou phase sévère de la maladie. Le n- méthyl -D-antagoniste aspartate (NMDA), la mémantine, est entrée en vigueur de la même façon seul ou en combinaison avec des inhibiteurs de la cholinestérase de modérés à sévères stades de la maladie. Aperçu recents dans la physiopathologie de l’AD ont conduit à des thérapies prometteuses expérimentales, y compris le développement de γ- and - β-SECRETASE ainsi aussi actives et l’immunisation passive contre l’amyloïde β-protéine.

Mots clés: L’âge, la maladie d’Alzheimer, les dysfonctionnements cognitifs, démence, neuropsychologique tests, primaire dégénérescence neuronale
Introduction

Alzheimer’s disease (AD) is named after a German physician, Alois Alzheimer, who first described it in the early 20th century. It has rapidly emerged as a major public health issue throughout the world. It is estimated to be by far the most common form of dementia in the United States, currently afflicting over 5 million people, mainly elderly individuals, with an associated healthcare cost in excess of US$100 billion annually. The cost of caring for those afflicted is enormous and most probably beyond the capability of most developing countries, including Nigeria. A general definition of dementia is an acquired deterioration of cognitive function that impairs one’s ability to successfully perform activities of daily living (ADLs). It is characterized most notably by memory loss, and increasing age is its single most important risk factor. Memory loss and dementia, in general, are progressive and irreversible, though the rate of progression is highly variable and impossible to predict.

Epidemiology and Genetics

Advancing age is the single most major risk factor for AD, with the prevalence doubling every 5 years between the ages of 65 and 95 years and increasing from 2% at 65 years of age to 40% at over 85 years of age. While people do experience minor changes in their memory and thinking as they age, these changes do not affect daily functioning or the ability to live independently. Although the illness has been reported to occur in exceedingly rare patients in their 20s and 30s, onset of clinical symptoms in this illness is uncommon until the 50s. The second major risk factor for AD is family history, with a threefold to fourfold higher risk among individuals having a single first-degree relative with AD and a nearly eightfold higher risk among individuals with two or more first-degree relatives with AD. In contrast late-onset AD, early-onset AD is relatively rare, affecting only 5% of AD patients and developing in individuals 30–60 years of age. Some cases of early-onset AD, termed familial AD, are inherited in an autosomal dominant manner, with genetic mutations on chromosomes 21, 14 and 1, resulting in the formation of abnormal precursor proteins, presenilin 1 (PS-1) and presenilin 2 (PS-2). The presenilins have been found to operate in a complex that acts functionally as γ-secretase. Specifically, a few dozen families have mutations in the amyloid precursor protein (APP) gene, usually in the region of the gene that codes for the β-amyloid proteins. Increased levels of β-amyloid have been found in AD patients with PS-1 or PS-2 mutations. Apolipoprotein E (ApoE) gene status on chromosome 19 appears to be a major genetic susceptibility risk factor for the development of typical late-onset AD. Some evidence suggests that ε2 is protective as regards the risk for AD. The putative mechanism underlying this mechanism is currently not understood. There appears to be a racial influence and possible gene–environmental interaction with regards to ApoE and AD because ApoE ε4 showed a weak association in African-Americans and lacked an association in Nigerians.

Other possible risk factors for AD include gender, education, head trauma, memory deficit with severity of any extent, and small hippocampal volume. The very large Women’s Health Initiative Memory Study of estrogen in elderly women has shown that estrogen replacement may increase, rather than decrease, the risk for AD. Several studies indicate that lack of education is also a risk factor for AD, or alternatively, education may impart a “cognitive reserve” that delays the onset of clinical manifestations of AD. Studies have been muddled by wide differences in reported series in the criteria applied to define significant head trauma history. Further, ApoE ε4 patients have been demonstrated to recover less well from head trauma, so the greater manifestations of trauma may be a pseudo-marker for ApoE ε4 inheritance, which is a risk factor for AD. A wealth of data from various studies has suggested that a strong association between the metabolic syndrome and vascular risk factors appears to increase the risk for AD. Specifically, diabetes mellitus, insulin resistance, high cholesterol, hypertension, reduced exercise, and obesity are all risk factors with some association for AD. There is some circumstantial evidence linking aluminum with AD, no causal relationship has yet been established and, based on mounting scientific evidence, the possibility of such a relationship is becoming increasingly unlikely.

Neuropathology and Pathophysiology

Dementia is causally associated with disruption of cerebral neuronal circuits, with the amount and location of neuronal loss resulting in its characteristic symptomatology. Loss of larger neurons of the superficial cortex is a consistent feature of AD, as are synaptic alterations such as reduction of pre-synaptic terminal density. The neurotransmitter acetylcholine (Ach) appears to be particularly important for memory, and loss of cholinergic neurons may underlie memory loss in AD. Anatomically, AD begins in the entorhinal cortex and progresses to the hippocampus and the posterior temporal and parietal neocortex, ultimately resulting in diffuse...
degeneration throughout the cerebral cortex. Grossly, AD is characterized by diffuse atrophy of the cerebral cortex, reflecting loss and shrinkage of neurons, with resulting enlargement of the ventricles. In particular, the hippocampus, part of the mesial temporal lobe memory system, is damaged and atrophied in AD, even at the earliest stages of the disease. Microscopically, the two identifying features of AD are amyloid plaques and neurofibrillary tangles. In addition to amyloid plaques, wispy accumulations of an intracellular proteomous material called neurofibrillary tangles (NFTs) are present. These are the cardinal features originally described by Alzheimer 103 years ago. The so-called “amyloid hypothesis”, which ascribes a causative role in AD to abnormal amyloid processing and deposits, remains the prevailing model regarding AD causation. As AD progresses, glutaminergic, noradrenergic, and serotonergic system deficiencies develop and have been associated with further cognitive deterioration and/or behavioral abnormalities. Therapeutic efforts during the last decades have largely focused on correcting these neurotransmitter deficits, and some modest success in improving symptoms has been achieved.

Presentation and Natural History

Memory loss, particularly short-term memory loss, is also the most common presenting symptom of AD. Longer-term memory is initially preserved but will eventually deteriorate as well with disease progression. This is referred to as Ribot’s law of memory, but this is only relatively true, as it is difficult to check the accuracy of ancient memories. Impairment of cognitive function that slightly interferes with the functions of daily living is characterized as mild cognitive impairment (MCI), and many individuals with MCI will progress to AD dementia; the progression rate is about 12% per year, with faster progression in some subgroups, e.g., those with severe memory deficits especially when additional cognitive impairment is also present. Behavioral changes and psychiatric symptoms are not uncommon in AD, especially in the more advanced stages of the disease. These include agitation, paranoia, psychosis, delusions, anxiety and insomnia. Frequently reported sleep disturbances include nighttime awakening, early morning awakening; excessive daytime sleepiness and on rare occasions, a diurnal reversal of sleep–wake cycle with the main sleep period occurring in the daytime. AD is progressive and remains incurable and ultimately it is fatal, with death typically occurring 4–6 years after initial diagnosis.

Diagnosis: Clinical, pathologic and radiologic

The most commonly used clinical criteria for the diagnosis of AD are those of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and those developed in 1984 by a joint task force on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA). Normally, a neuropsychological examination explores in depth an individual’s performance in a wide range of functional domains. Various screening tests and batteries have been developed during the last years, but the Mini Mental State Examination (MMSE) is still the most widely used, despite its weakness when it comes to detecting mild dementia. The Community Screening Instrument for Dementia (CSI-D) was developed as a screening instrument for dementia use in cross-cultural studies. It is composed of the following function domains: language expression (naming, definition, repetition and fluency), registration, attention and calculation, recall, orientation to place and time, language comprehension (motor response), memory recall, memory and praxis. It was developed from existing cognitive screening instruments with a view to identifying items that were equally discriminating for subjects with high and low levels of education and literacy and for subjects from developed and less developed communities. The instrument has been used and validated in Cree American Indians, Nigerians in Ibadan, African Americans in Indianapolis, and among Chinese. The CSI-D highly correlated with the Mini Mental State Examination (MMSE) and 10-word-list–learning task.

The general neurologic examination may often be normal in the demented patient with AD. Continuing gait problems can occur in the late stages of AD, leading to substantially increased risk for falls. There is currently no laboratory test to confirm the diagnosis of AD. The prevailing neuropathologic criteria for AD are those promulgated by the National Institute on Aging (NIA) and National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). These criteria include minimal neocortical plaque densities that are age-adjusted but do not specify either the plaque type or the neocortical region involved. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) criteria requires an age-adjusted semiquantitative plaque frequency and a clinical diagnosis of dementia for the diagnosis of AD.

Both DSM-IV-Text Revision (DSM-IV-TR) and NINCDS-ADRDA criteria rely heavily on history and the neurologic examination, and recent evidence suggests that both have fallen behind due...
to the recent dramatic advances in our scientific knowledge of AD, with reliable biomarkers available now being based on structural Magnetic Resonance Imaging (MRI), molecular imaging with Positron Emission Tomography (PET), and cerebrospinal fluid (CSF) analyses. Although the revised NINCDS-ADRDA criteria remain focused on a clinical determination of memory impairment, they also stipulate that there must also be at least one abnormal biomarker among structural neuroimaging with MRI, molecular neuroimaging with PET, and CSF analysis of β-amyloid or tau proteins. Structural MRI in patients with AD or MCI shows atrophy in the entorhinal cortex and hippocampus, predictive of future cognitive decline and conversion to AD among individuals with MCI. It has been suggested, therefore, that MRI volumetry may be a useful imaging adjunct in the diagnosis of AD and may even exceed the diagnostic accuracy of clinical evaluation. PET-based imaging includes measurement of regional cerebral glucose metabolism (rCMRgic) using the partially metabolized glucose analog fluorine-18 (18F)-labeled 2-fluoro-2-deoxy-D-glucose (FDG). Significant regional hypometabolism. A reduction of glucose metabolism in the bilateral temporal, parietal and posterior cingulated region is currently the most commonly described diagnostic criterion for AD. The use of radiotracers other than FDG, including carbon-11 (11C)-labeled tracers, is increasing the applicability of PET to the study and diagnosis of dementia and psychiatric diseases generally.

PET imaging tracers which label and thus allow visualization of β-amyloid or tau (T) protein in vivo are promising approaches to improving the early diagnosis of AD. PET ligands for plaque imaging are all derived from histological staining agents and based on the favorable clinical results to date; β-amyloid imaging agents will likely enter phase-III evaluation and wider clinical use in the near future. PET will no doubt continue to be important in dementia research and increasingly important in clinical practice as new molecularly targeted radiotracers are approved for clinical use.

**Treatment**

Over a hundred years after its discovery, AD remains incurable and its progression inevitable, with the primary focus of treatment on mitigation of associated behavioral and neurologic problems. Currently no therapy has been proven to delay biological progression of disease. The development of drugs that will delay disease progression in affected individuals or primarily prevent its onset in normal older subjects remains a crucial, but far elusive goal. The currently available symptomatic therapies for AD mildly improve defects in cognitive function, ADLs and global functioning, as well as delay onset of or slightly improve behavioral symptoms. The role of family members or other caregivers is critical, and any benefits need to be weighed against adverse effects that may occur in determining an appropriate dose or deciding whether to continue therapy with a particular drug. Memory aids such as notebooks and posted daily reminders may be helpful in the early stages of the disease. The patient’s home, especially the kitchen and bathrooms, must be made as safe as possible, and eventually patients must stop driving and can no longer be responsible for their finances and other personal affairs.

A number of drugs have been approved for treatment of AD, albeit they are not curative. The current pharmacologic therapies for AD can be broadly divided into two categories: (1) symptomatic approaches based on enhancement of neurotransmitter systems and (2) neuroprotective strategies using antioxidants such as vitamin E. Many AD patients also are prescribed antipsychotics or antidepressants to manage psychiatric and behavioral symptoms, but with an apparently increased risk of mortality.

The most effective medications for AD to date are the acetylcholinesterase (AChE) inhibitors, which reduce the enzymatic degradation of the neurotransmitter Ach, deficient in the AD brain, and thus enhance the cholinergic system. The three AChE inhibitors approved by the United States Food and Drug Administration (FDA) for treatment of AD, donepezil, galantamine and rivastigmine, have been demonstrated to improve cognition, function in ADL, and behavior in patients with AD in double-blind, placebo-controlled trials. Despite the perception among clinicians of limited therapeutic efficacy and cost-effectiveness of AChE inhibitors, this class of drugs is actually highly effective in early (i.e. mild to moderate) AD in terms of symptomatic control and delay of its long-term adverse effects.

Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist also approved for use in AD and was the first drug approved for treatment of moderate to severe AD. Although its mechanism of action is not entirely understood, it works by antagonizing glutamate at the NMDA receptor, potentially improving signal transmission, and by preventing excess calcium to rush into the neurons with glutamate stimulation, and may therefore protect against toxic damage to cholinergic neurons. In a study, patients with moderate to severe AD
treated with memantine alone showed significant improvement in cognitive function and ADLs in a placebo-controlled trial.\textsuperscript{149} In another clinical study of patients with moderate to severe AD, memantine in combination with the AChE inhibitors (donepezil, galantamine, or rivastigmine) significantly slowed deterioration in both cognitive function and ADLs compared to patients treated with placebo or AChE inhibitors alone.\textsuperscript{149}

**Evidence against previously accepted therapies**

Based on evidence that free radicals may contribute to the pathologic processes in AD, antioxidants such as \(\alpha\)-tocopherol (vitamin E) and selegiline are being evaluated for its treatment. Results to date have been equivocal.\textsuperscript{150} However, herbal supplements are often used by AD patients, most notably, *Ginkgo biloba*, whose purported pharmacologic effect is likely due to flavoglycoside, a free-radical scavenger and antioxidant.\textsuperscript{151} Several double-blind, placebo-controlled studies with negative results argue against the use of estrogen or non-steroidal anti-inflammatory drugs, both of which may actually have greater risks than benefits in subjects with AD.\textsuperscript{151,152}

**Treatment of behavioral symptoms**

Treatment of these symptoms can be challenging, and none of the currently available drugs is approved by the United States FDA for treating behavioral symptoms in AD. Treatment of behavioral symptoms is of great importance to family members and caregivers because these symptoms tend to be most difficult for them to manage. Risperidone and olanzapine are effective for the treatment of aggression in AD. Selective serotonin reuptake inhibitors, although well tolerated, are only modestly effective for the management of behavioral problems and should be used at lower doses to avoid adverse effects. Insomnia may be responsive to trazodone or alprazolam or other benzodiazepines.

**Future Trends in AD Drug Therapy**

Most efforts to develop drugs that will delay disease progression have recently focused on reducing amyloid and potentially halting or reversing formation of plaques in the brain. A number of new drugs are now being evaluated clinically for safety (phase-I and -IIA trials) and efficacy (phase-IIB and -III trials) with emphasis on strategies to mitigate the pathogenicity of \(\beta\)-amyloid.\textsuperscript{142} Vaccination using the \(\beta\)-amyloid protein proved effective initially in reducing \(\beta\)-amyloid plaques in transgenic animals, and a similar vaccine was tested in a large phase-II trial\textsuperscript{139} which was interrupted when a large number of subjects developed encephalitis.\textsuperscript{154}

**Conclusion**

Currently, there is a compelling need to establish novel treatments for AD and research into AD therapy has been at least partly successful in terms of developing symptomatic treatments, but has also had several failures in terms of developing disease modifying therapies. While progress has been frustratingly slow in the development of effective treatments for AD, understanding of its underlying biology continues to advance and, with a number of promising therapies in the pipeline, there is room for some optimism.

**References**


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Announcement

Android App

A free application to browse and search the journal’s content is now available for Android based mobiles and devices. The application provides “Table of Contents” of the latest issues, which are stored on the device for future offline browsing. Internet connection is required to access the back issues and search facility. The application is compatible with all the versions of Android. The application can be downloaded from https://market.android.com/details?id=comm.app.medknow. For suggestions and comments do write back to us.