South African Family Practice 2019; 61(2):28-34

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

REVIEW

Understanding Alzheimer disease

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Abstract

Alzheimer disease (AD) is a neurodegenerative disorder with an uncertain pathogenesis. It is characterised by symptoms of memory impairment, executive dysfunction and visuospatial impairment. Management goals and interventions should be based on a solid alliance with the patient and family and on thorough psychiatric, neurological and general medical evaluations of the nature and cause of cognitive deficits and associated non-cognitive symptoms. There are currently three cholinesterase inhibitors and one N-methyl-D-aspartate (NMDA) antagonist indicated in the treatment of AD as monotherapy or in combination. Cholinesterase inhibitors remain the first-line therapy in patients with mild to moderate AD, which may stabilise the symptomatic cognitive and functional decline. Other pharmacotherapy options include the use of memantine which may be used by itself or in combination with cholinesterase inhibitors. These treatments are for symptomatic relief and are not disease modifying in preventing the progression of the disease

Keywords: dementia, Alzheimer disease, treatment of dementia, risk factors, management of Alzheimer disease

Introduction

Alzheimer disease (AD) is a neurodegenerative disorder with a pathogenesis and causes that are uncertain.[1] It affects older adults and is the most common cause of dementia.[1] AD's early clinical manifestation is selective memory impairment, but there are exceptions to this. The incidence of AD increases exponentially with age over 65 years.[2] AD before the age of 65 years is unusual and may be familial in nature. Familial early-onset AD accounts for approximately 1% of cases and follows a pattern of autosomal dominant inheritance.[3,4] Treatment is available that may ameliorate some of the symptoms but currently there is no cure or disease-modifying therapy available and the disease will inevitably progress.[1]

Pathophysiology

As discussed above, the pathogenesis of AD is uncertain.[1] Some of the early neuropathological changes in AD include the following[5-8]:

1. Neuritic plaques, which are associated with neuronal injury and may be characterised by amyloid which is formed from amyloid beta plus dystrophic neurites which frequently has phospho-tau immunoreactivity.
2. Extracellular deposits of amyloid beta peptides.
3. Neurofibrillary degeneration which is best illustrated by neurofibrillary tangles.

Table I describes other pathological changes commonly observed in association with AD.[9-16] The pathogenesis of all forms of AD seems to share the commonality of an overproduction and/or a decreased clearance of amyloid beta peptides.[17] These peptides are produced by cleavage of mature protein translated from the amyloid precusor protein (*APP*) gene and cleaved by beta-secretase and gamma-secretase. Presenillin forms part of the gamma-secretase complex and mutations of the presenilin 1 (*PSEN 1*) or presenilin 2 (*PSEN 2*) genes tend to favour the production of amyloid beta. Amyloid beta or the forms that are produced through mutations of *PSEN 1* or *PSEN 2* are neurotoxic.[17]

A second protein involved in the pathogenesis of AD is tau.[18-20] Tau is a microtubule-associated protein which aids in microtubule assembly and stabilisation. In AD, these proteins become hyperphosphorylated and aggregate to form paired

Table I. Several other pathological changes found with AD[9-14]

In addition to the essential features discussed above, several other pathological features are observed in patients with AD. These include:
1. Cerebral amyloid angiopathy is often found in patients with parenchymal amyloid beta deposits[9,10]
2. Inclusions of abnormal alpha-synucle in accumulation called Lewy bodies, are common in the setting of intermediate-to-high levels of AD neuropathologic change.[11,12] Lewy bodies may also be found in some cases of early-onset familial AD.[13,14]
3. Pathological changes of vascular brain injury are caused by oligaemia, hypoxaemia, or ischaemia involving different calibre vessels in different regions of the brain.
4. Hippocampal sclerosis (HS), defined by pyramidal cell loss and gliosis in the hippocampal formation that is out of proportion to AD neuropathological change, can be observed alone or in the context of AD, frontotemporal lobar degeneration, or vascular brain injury.[15]
5. Immunoreactive inclusions of transactive response DNA binding protein 43 kD (TDP-43) are also commonly observed in cases with AD neuropathological change[16]

helical filament (PHF) tau. These are a major component of neurofibrillary tangles within the neuronal cytoplasm. Experimental models have suggested that the accumulations of these altered proteins are neurotoxic. Additionally, pathological forms of tau between neurons have been proposed as a mechanism by which AD spreads in the brain.[18-20] Various other genes and proteins have been implicated in the pathogenesis of AD but that is beyond the scope of this review.

Risk factors for developing Alzheimer's disease

Aside from genetics as a risk factor for AD, a variety of different factors may influence a patient's risk for developing AD.[21] Risk factors for vascular disease such as hypertension, diabetes and obesity may increase the risk of developing AD, particularly if these diseases are present in midlife.[21] The exact pathogenesis of linking these cardiometabolic risk factors to AD is poorly understood and an area of active research.[22-31] Brain cholesterol metabolism may also be an important risk factor for AD.[32-36] The relationship between AD and blood lipoproteins (such as LDL-C) is complex and inconsistent.[32-36] It is clear, however, that cerebrovascular disease and AD do frequently co-exist.[37] One must also be aware that hypertension is a risk factor for cerebrovascular disease.[21,38-40] Cerebrovascular disease is associated with worse cognitive performance in patients with AD and studies have suggested that cerebrovascular disease lowers the threshold for clinical dementia in patients with a diagnosis of AD.[41-46]

Clinical features

Some of the cardinal symptoms of AD include memory impairment, executive dysfunction and visuospatial impairment.[47,48] The last two symptoms tend to present relatively early, while language and behavioural symptoms tend to manifest later in the course of the disease. Less common symptoms include language deficits and visuospatial abnormalities.[47,48] Table II describes the signs and symptoms of AD with their relevant description.[49-73]

Table II. Signs and symptoms of AD with a clinical description[49-73]

Symptom	Clinical description
	Cardinal Signs and Symptoms
Memory impairment	1. Pattern in AD is distinctive.[49] 2. Memory of events occurring at a particular time and place (declarative memory) is profoundly affected.[49] 3. Procedural memory and motor learning is spared until quite late into disease progression.[49] 4. Memory of recent events is significantly impaired in early AD.[50-52] 5. Immediate memory (e.g. mental rehearsal of a phone number) is spared early in disease progression.[50-52] 6. Consolidated long-term memory tends to be spared early in the course of the disease.[50-52] 7. Deficits develop insidiously and progress slowly over time.[50-52]
Executive function and judgement	1. In the early stages, this may range from subtle to prominent impairment.[53] 2. Family members or co-workers may notice that the AD patient is less organised or less motivated.[53] 3. Multitasking is often compromised significantly.[53] 4. Patient has poor insight and reduced ability for abstract reasoning.[54,55] 5. As AD progresses, patient may develop an inability to complete tasks.[54,55] 6. Anosognosia (reduced insight into deficits) is a feature of AD.[54,55] 7. Patients with AD may often underestimate their deficits or provide alibis or explanations for when the deficit is pointed out.[54,55] 8. Loss of insight increases overtime with disease severity. [56] 9. Loss of insight may be associated with behavioural disturbances.[57,58] 10. Patients with preserved insight tend to develop depression.[57,58] 11. Patients with lack of sight develop agitation, disinhibition and even psychotic features.[57,58]
Behavioural and psychological symptoms	1. Neuropsychiatric symptoms are in patients with AD.[57,58] 2. Neuropsychiatric symptoms tend to occur in the mid to late stage of AD.[57,58] 3. Apathy may occur in these patients and may be clinically indistinguishable from depression.[57,58]
	Other Signs and Symptoms
Apraxia	1. Occurs later in the disease after deficits in memory and language become apparent.[59] 2. Dyspraxia can be elicited by asking the patient to perform ideomotor tasks e.g. combing of hair.[60,61] 3. Dyspraxia leads to progressive difficulty with complex, multistep motor activities and later with dressing, eating and other self-care tasks.[62]
Olfactory dysfunction	1. Changes in olfactory function are common in patients with AD.[63,64] 2. Olfactory dysfunction is not a clinical symptom reported by patients or their families.[65]
Sleep disturbances	1. These are common in patients with AD.[66] 2. AD patients tend to spend more time in the bed awake and have more fragmented sleeping patterns when compared to older adults without AD.[66]
Seizures	1. Usually occurs in the later stages of AD.[67-69] 2. Younger patients with autosomal dominant forms of AD have a higher risk of seizures earlier in the course of the disease.[70,71] 3. Predominant seizure type is focal nonmotor with impaired awareness and symptoms suggest temporal lobe onset i.e. amnestic spells, unexplained emotions, metallic taste, rising epigastric sensation.[71]
Motor signs	1. Extrapyramidal motor signs and myoclonus may occur at later stages of AD.[72,73] 2. If motor symptoms occur at earlier stages of AD other diagnoses should be considered.[72,73] 3. Emergence of behavioural disturbances include agitation, aggression, wandering and psychosis (hallucinations, delusions, misidentification syndromes) may be problematic in patient management.[72,73]

Table III. The NIA-AA clinical assessment characteristics in confirming diagnosis of AD[73]

AD dementia is a syndrome of dementia defined by the following characteristics:
• Interference in functional abilities at work/usual activities
• A decline from previous level of functioning
• Not explained by delirium or major psychiatric disorder
• Cognitive impairment established by history taking from patient and knowledgeable informant; and bedside mental status examination and neuropsychological testing
• Cognitive impairment involving two of the following: ▫ Impaired ability to acquire/remember new information ▫ Impaired reasoning and handling complex tasks ▫ Impaired visuospatial abilities ▫ Impaired language functions ▫ Changes in personality/behaviour
• Other core criteria include insidious onset, history of worsening and no history of concomitant cerebrovascular disease or other active neurological/non-neurological disease or the use of medication that could affect cognition

Diagnosis

Alzheimer's disease is diagnosed based on clinical assessment and neuroimaging studies and is suspected in any older adult with insidious onset, a progressive decline in memory and in at least one other cognitive domain.[47,73] The two commonest used criteria in the diagnosis of AD include the clinical criteria established by the National Institute on Aging and the Alzheimer's Association (NIA-AA) and the Diagnostic and Statistical Manual of Mental Disorders (DSM).[73,48] Table III outlines the criteria in diagnosis of AD as established by the NIA-AA.[73]

The DSM clinical criteria for AD has been expanded beyond the previous five domains (memory, aphasia, apraxia, agnosia, and executive function) to include learning, language, complex attention, perceptual motor and social cognition.[48] While less validated when compared to the NIA-AA, the DSM criteria appear to have similar accuracy.[74,75]

The NIA-AA recent diagnostic guidelines have defined three stages of AD[76]:

- *Preclinical phase*: neuropathological changes occur, no overt (or only subtle) symptoms
- *Phase of mild cognitive impairment*: symptoms become apparent; ADLs are preserved; patient does not have dementia
- *Dementia phase*: ADLs are impaired

There may be preclinical neurologic changes in the form of cerebrospinal fluid or amyloid imaging biomarkers.[76] However, AD diagnosis is principally based on clinical criteria (Table III).[73]

Differential diagnosis

The most common disorders considered in the differential diagnosis of AD are vascular dementia and neurodegenerative dementias. The most common neurodegenerative dementias after AD include dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD).[77,78]

Pharmacological therapy

Management goals and interventions should be based on a solid alliance with the patient and family as well as thorough psychiatric, neurological and general medical evaluations of the nature and cause of cognitive deficits and associated non-cognitive symptoms. There are currently three cholinesterase inhibitors and one N-methyl-D-aspartate (NMDA) antagonist indicated in the treatment of AD as monotherapy or in combination.[79]

Pharmacological therapy: Memantine

Memantine is a NMDA receptor antagonist which is proposed to be neuroprotective by preventing glutamatergic excitotoxicity in blocking excessive stimulation of NMDA receptors.[80] This action protects the neurons from further damage and restores the physiological function of remaining neurons resulting in symptomatic improvement.[81] Glutamate stimulation of NMDA receptors has been implicated in memory processes and dementia.[82] Memantine appears to have modest benefits in patients with moderate to severe AD based on a 28-week randomised trial of 252 patients.[82] This study found that memantine reduced deterioration on multiple scales of clinical efficacy (Table V).[82] Memantine appears to have fewer side-effects than the cholinergic agents, with dizziness being the most common adverse effect.[82] However, there is a lack of evidence that patients with milder AD benefit from memantine, with no effect on behaviour or ADLs.[82] Memantine may be introduced in moderate to severe disease stages and can be used as monotherapy or in combination with a cholinesterase inhibitor.[83]

Pharmacological therapy: Cholinesterase inhibitors

Patients with AD have reduced cerebral content of choline acetyl transferase, which leads to a decrease in acetylcholine synthesis and impaired cholinergic function. Cholinesterase inhibitors used in the treatment of AD increase cholinergic transmission by inhibiting cholinesterase at the synaptic cleft and provide modest benefit in patients with dementia. Unlike memantine, cholinesterase inhibitors are considered symptomatic therapies which are not neuroprotective.[83] To date, three cholinesterase inhibitors are indicated in mild to moderate AD; donepezil, galantamine and rivastigmine, while donepezil is also indicated in moderate to severe AD (Table IV).[83] High dose rivastigmine patch is approved for mild to moderate and severe AD based on the positive findings of recent studies.[83,84,85] The cholinesterase inhibitors have demonstrated clinical benefits on cognitive

function, global clinical status, and performance of ADLs (Table V).[86-93] There are no clinically meaningful differences between the efficacy of the individual agents.[83] Efficacy and tolerability of cholinesterase inhibitors are dose-dependant, so while high doses may be efficacious, adverse events can be dose-limiting.[83-85] The agents have similar tolerability profiles, with nausea, vomiting and diarrhoea being the most common adverse effects.[94] Patients with bradycardias or bradyarrhythmia's should be carefully monitored if treated with cholinesterase inhibitors, as they have an increased risk of syncope or dizziness.[76] Treatment is individualised; patients can be switched from one cholinesterase inhibitor to another if the initial agent is poorly tolerated or ineffective.[83] Systematic reviews and meta-analyses of cholinesterase inhibitors illustrate that they delay the decline in cognitive function as measured by the AD Assessment Scale – cognitive subscale (ADAS-cog), global clinical rating, behaviour and ADLs over 6–12-month periods. These benefits seem to be applicable to mild, moderate and severe AD.[95] Pivotal six month placebo-controlled studies further highlight the beneficial effects of cholinesterase inhibitors in patients with mild to moderate AD, on cognitive and global functioning (Table V).[86-93] Extended 6–12 month trials provide evidence that patients receiving cholinesterase inhibitors can be maintained near pre-treatment baseline levels for at least 12 months of therapy and then decline, but appear to maintain higher levels of function than expected if untreated.[96]

Pharmacological therapy: Combination therapy

The combination therapy of memantine with a cholinesterase inhibitor, which affect separate neurotransmitter systems in AD, is useful in patients with advanced disease conferring independent clinical benefits. The combination leads to modest improvements in cognition and global outcomes in patients with advanced disease.[97] A study in which patients treated with memantine plus donepezil resulted in significantly better outcomes than placebo plus donepezil on measures of cognition, ADLs, global outcome and behaviour (Table V).[98] These results together with previous studies, suggest that combination therapy of memantine with a cholinesterase inhibitor represents a new approach for the treatment of patients with moderate to severe AD which may improve efficacy relative to single-agent therapy and may ameliorate gastrointestinal adverse effects of cholinesterase inhibitors.[83]

Table IV. Approved AD therapies[83]

AD stage	Class	Agent
Mild to moderate	Cholinesterase inhibitor	Donepezil (5–10 mg) Rivastigmine (6–12 mg) Galantamine (8–24 mg)
Moderate to severe	Cholinesterase inhibitor NMDA antagonist	Donepezil/Rivastigmine plus Memantine (10–20 mg) OR Memantine alone

Table V. Evidence relating to pharmacotherapy of cholinesterase inhibitors and NMDA antagonists in improving symptoms of AD[82, 86-93, 98-100]

Reference	Agent	Dose studied (mg/d)	N	Duration (wk)	Positive Outcome Measure	Comments
Early Alzheimer's disease						
Seltzer et al, 2004[99]	Donepezil	5–10	153	24	ADCS-cog	ADAS-cog: ≥ 4-point change (P ≤ 0.001)
Mild to moderate Alzheimer's disease						
Rogers et al, 1998[86]	Donepezil	5–10	468	15	ADAS-cog, MMSE CIBIC-Plus	ADAS-cog: ≥ 4-point change (P = 0.008) CIBIC-Plus: ≤ 3-point change(P < 0.001)
Rogers et al, 1998[87]	Donepezil	5–10	473	24	ADAS-cog, MMSE (CIBIC-Plus)	ADAS-cog: ≥ 4-point change (P = 0.008) CIBIC-Plus: ≤ 3-point change (P < 0.001)
Burns et al, 1999[88]	Donepezil	5–10	818	30	ADAS-cog, CIBIC-Plus (CDR-SB)	CIBIC-Plus: ≤3-point change (P<0.05)
Farlow et al, 2013[89,90]	Rivastigmine	1–4, 6–12	545	26	ADAS-cog, CIBIC-Plus	ADAS-cog: ≥ 4-point change (P < 0.001)
Rosler et al, 1999[91]	Rivastigmine	1–4, 6–12	725	26	ADAS-cog, CIBIC-Plus, PDS	ADAS-cog: ≥ 4-point change (P < 0.05) CIBIC-Plus: 2-point change (P < 0.001)
Wilcock et al, 2000[92]	Galantamine	24, 32	653	26	ADAS-cog, CIBIC-Plus, DAD	ADAS-cog: ≥ 4-point change (P < 0.001) CIBIC-Plus: 2-point change (P < 0.05)
Tariot et al, 2000[93]	Galantamine	18, 16, 24	978	21	ADAS-cog, CIBIC-Plus (ADAS-ADL, NPI)	ADAS-cog: ≥ 7-point change (P < 0.001)
Moderate to Severe						
Feldman et al, 2001[100]	Donepezil	5–10	290	24	CIBIC-Plus (MMSE, SIB, DAD, FRS, NPI)	CIBIC-Plus: ≤ 3-point change (P < 0.001)
Reisberg et al, 2003[82]	Memantine	20	252	28	CIBIC-Plus, ADCS-ADLsev (SIB)	CIBIC-Plus: ≤ 3-point change (P = 0.03, 95% CI:-0.51–0.02)
Tariot et al, 2004[98]	Memantine (added to stable donepezil regimen)	20	404	24	SIB, ADCS-ADL19 (CIBIC-Plus, NPI, BCG)	SIB: 0.9 (0.67) vs -2.5 (0.69)(P<0.001) ADCS-ADL 19: ≥ 2 point change (P = 0.02) CIBIC-Plus: 2-point change (P = 0.03)

ADCS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale, CIBIC-Plus: Clinicians Interview Based Impression of Change plus Caregivers Input, CDR-SB: Clinical dementia rating-sum of boxes, PDS: Progressive Deterioration Scale, GBS: Gottfries-Brane-Steen, ADCS-ADLsev: Alzheimer's Disease Cooperative study Activities of Daily Living Inventory modified for severe dementia, ADCS-ADL19: Alzheimer's Disease Cooperative study Activities of Daily Living Inventory, MMSE: Mini Mental Status Examination, SIB: Severe Impairment Battery, a measure of cognition, DAD = Disability Assessment for Dementia, NPI: Neuropsychiatric Inventory, BGP: Behaviour Rating Scale for geriatric patients

Nonpharmacological therapy

Behavioural disturbances can profoundly affect patients with dementia as well as their families and caregivers. Recognition and treatment of behavioural symptoms and mood disorders are important aspects of the care of patients with dementia.[83] Table VI describes the nonpharmacological approaches to manage common behavioural symptoms.

Table VI. Nonpharmacological approaches to manage behavioural symptoms and mood disorders in patients with AD[83]

Behavioural symptom	Nonpharmacological intervention
Apathy	Stimulation activities Simple tasks
Sleep disturbances	Take steps to maintain regular, good quality sleep Stimulation during the day Reduction in excessive noise/stimulation in evening
Irritability/agitation	Break down tasks into simple steps Redirection
Wandering	Visual cues Exercise Safe places to wander
Mood disorders	Exercise
Psychotic disorder	Reassurance Distraction rather than confrontation Removal of potential sources of confusion (e.g. mirrors)
Eating/appetite disorders	Offering simple, finger foods Removal of distractions from dining area Soothing music

Inadequate nutrition is common in patients with AD and is associated with increased morbidity and mortality.[101] Interventions such as oral nutritional supplements may improve weight and fat-free mass.[102] Nonpharmacological aims in helping cognitive function in AD involves cognitive rehabilitation. This involves cognitive stimulation programmes to maintain memory and higher cognitive function.[103] In terms of improving physical functioning, studies have demonstrated that formal exercise programmes may improve physical functioning or at least slow the progression of functional decline in patients with AD.[103-105] However, exercise programmes do not appear to improve any cognitive functioning in adults with AD.[104-107] In addition to exercise, individualised occupational therapy sessions focused on training patients and caregivers in the use of aids, coping behaviours, and strategies to compensate for functional deficits, demonstrated improvements in motor and process skills in daily activities.[108] These multidisciplinary, nonpharmacological approaches to management of dementia have significant advantages in having none of the side-effects that significantly complicate drug treatment in patients with AD.

Conclusion

The benefits of early investigating and diagnosis of AD include instigation of pharmacological symptomatic treatments and the initiation of psychosocial support processes. Cholinesterase inhibitors remain the first-line therapy in patients with mild to moderate AD, which may stabilise symptomatic cognitive and functional decline. Memantine, a glutamatergic partial antagonist, has shown to be beneficial in the treatment of moderate to severe cases of AD either alone or in combination with a cholinesterase inhibitor. However, these treatments are for symptomatic relief and are not disease modifying in preventing the progression of the disease.

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