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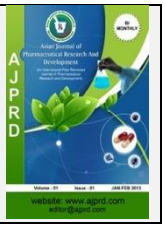

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Review Article

A Review on Alzheimer's Disease: Epidemiology, Etiology, Diagnosis, Management Strategies and Treatment Modalities

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A B S T R A C T

One of the most debilitating brain ailments that affect older people is Alzheimer's disease. It is a condition that is underdiagnosed, undertreated, and rapidly becoming into a significant public health issue. Over the past ten years, there has been a consistent increase in the amount of work done to identify the disease's etiology and create pharmacological treatments. Improved clinical diagnostic standards and better behavioural and cognitive disturbance treatments are recent breakthroughs. Randomised, double-blind, placebo-controlled, parallel-group studies assessing performance-based assessments of cognitive function, activities of daily living, and behaviour have clinically assessed symptomatic treatment, mostly focussing on cholinergic therapy. Galantamine, donepezil, tacrine, rivastigmine, and other cholinesterase inhibitors are among the medications that are advised for treating cognitive impairment in Alzheimer's patients. It is debatable and requires further research to determine the function of antioxidants, anti-inflammatory drugs, and oestrogen replacement. Behavioural disturbances are treated with antidepressants, antipsychotics, mood stabilisers, anxiolytics, and hypnotics. The development of new classes of medications that target different neurotransmitter systems (cholinergic, glutamatergic, etc.) for the treatment of behavioural disturbances and cognitive deficits, as well as the development of preventive measures like amyloid p-peptide immunisations and inhibitors of β-secretase and γ-secretase, are some of the future directions in research and treatment of patients with Alzheimer's disease.

KEYWORDS: Alzheimer's disease, apolipoprotein E4, cholinesterase inhibitor, antioxidant, anti-inflammatory agent, estrogen replacement therapy, behavioral disturbance

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INTRODUCTION

Because of the general population's increased life expectancy and growing awareness of the disease's socioeconomic effects, Alzheimer's disease (AD) has become a major public health concern. Progressive memory loss, disorientation, and pathological indicators (neurofibrillary tangles and senile plaques) were the criteria used by Alois Alzheimer in 1906 to identify it. AD was once thought to be an uncommon disorder, but as people aged, it was eventually thought to be an unavoidable side effect. Aging-related stigma and other factors prevented more thorough study into AD patients and their treatment, but these myths are dispelling and treatments though first ineffectives are starting to become accessible. We will review the diagnosis, aetiology, genetics, epidemiology, course, and management of AD in this study.

DIAGNOSTIC CRITERIA

Disorders pertaining to language and memory, higher executive function, and visuospatial orientation are among the clinical signs of AD. A few examples of noncognitive alterations are altered personalities, impaired judgement, psychosis, wandering, mood swings, anxiety, and irregular sleep patterns. When diagnosing a patient suspected of AD, the following steps are taken: (i) obtain a reliable informant's history, including general medical, neurological, neuropsychiatric, and family histories; (ii) conduct a physical and neurological examination; (iii) routine laboratory tests such as complete blood count, sequential multiple analysis-

21, thyroid function tests, vitamin B12, folate, rapid plasma reaction; (iv) optional laboratory tests like erythrocyte sedimentation rate, human immunodeficiency virus (HIV) serology, serology for Lyme's disease, urinalysis, urine drug screen, lumbar puncture, electroencephalography, and computerised tomography or magnetic resonance imaging. When using standardised criteria, such as those found in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM TV) criteria (Table I) and the National Institute of Neurological and Communicative Diseases and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (Table II), autopsy studies pertaining to neuropathological examination (looking for the hallmark senile plaques and neurofibrillary tangles) suggest a 90% accuracy rate in the clinical detection of AD [1,2].

Table - 1: Diagnostic criteria for Dementia of the Alzheimer's Type (DSM-IV)

A. The development of multiple cognitive deficits manifested by both:
(1) Memory impairment (impaired ability to learn new information or to recall previously learned information)
(2) One (or more) of the following cognitive disturbances:
(a) Aphasia (language disturbance)
(b) Apraxia (impaired ability to carry out motor activities despite intact motor function)
(c) Agnosia (failure to recognize or identify objects despite intact sensory function)
(d) Disturbance in executive functioning (ie, planning, organizing, sequencing, abstracting)
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning
C. The course is characterized by gradual onset and continuing cognitive decline
D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
(1) Other CNS conditions that cause progressive deficits in memory and cognition (eg, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
(2) Systemic conditions that are known to cause dementia (eg, hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
(3) Substance-induced conditions
E. The deficits do not occur exclusively during the course of a delirium
F. The disturbance is not better accounted for by another Axis I disorder (eg, Major Depressive Disorder, Schizophrenia)

Table –2: National Institute of Neurological and Communicative Diseases and Stroke - Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for diagnosis of Alzheimer's dementia

Definite Alzheimer's disease
• Clinical criteria for probable Alzheimer's disease
• Histopathologic evidence of Alzheimer's disease (autopsy or biopsy)
Probable Alzheimer's disease
• Dementia established by clinical examination and documented by mental status questionnaire
• Dementia confirmed by neuropsychological testing
• Deficits in two or more areas of cognition
• Progressive worsening of memory or other cognitive functions
• No disturbance of consciousness
• Onset between ages 40 and 90
• Absence of systemic or brain diseases capable of producing a dementia syndrome
Possible Alzheimer's disease
• Atypical onset, presentation, or progression of a dementia syndrome without a known etiology
• A systemic or other brain disease capable of producing dementia, but not thought to be the cause of the dementia is present
• Gradually progressive decline in a single intellectual function in the absence of any other identifiable cause
Unlikely Alzheimer's disease
• Sudden onset
• Focal neurological signs
• Seizures or gait disturbances early in the course of illness

With a loss of 3 to 4 points annually on a common diagnostic tool like the Mini-Mental State Examination (MMSE), AD tends to advance slowly over time. Different patterns of deficiency are observed; the most typical is an insidious beginning, wherein aphasia, apraxia, and agnosia occur after several years of recent memory loss. In the early stages, some individuals exhibit irritation and personality abnormalities. Patients typically experience gait and motor abnormalities in the latter stages, which lead to their final bedridden state and silent state. Although the condition can continue up to 20 years, AD patients typically live for 8 to 10 years after being diagnosed [3].

COMORBIDITIES

AD can coexist with Lewy-body or vascular dementia, despite being the most prevalent kind of dementia. Clinical information about treating individuals with this kind of comorbidity is scarce. A significant level of medical comorbidity (heart disease, diabetes, malignancies) is also seen in AD patients.

ETIOLOGY

It appears that neurofibrillary tangles and senile plaques are the primary neuropathological characteristics of AD. As the illness worsens, the senile plaques appear to start in brain regions linked to cognition before spreading to other cortical areas. Among other things, amyloid β peptide (Aβ), a piece of the amyloid precursor protein (APP), gets stuck in the senile plaques. Two separate cleavage processes produce the Aβ peptide from APP: the first end is produced by β-secretase's proteolytic activity, while the second end is produced by γ-secretase's proteolysis. Aβ seems to be divided into two species: Aβ40, which is shorter, and Aβ42, which is longer. It appears that Aβ42 is deposited first and might play a part in starting the sequence of events that eventually result in amyloid deposition. It is still not apparent if the senile plaques are the source or a by-product of AD, while there are accumulating findings showing malfunction in the metabolism of APP with consequent rise in the insoluble Aβ is responsible for AD. It appears that Aβ is either directly or indirectly harmful to the neurone by inducing inflammation or elevating the generation of free radicals. Another hallmark that sets AD apart in neurones is the build-up of neurofibrillary tangles. Tau protein, a protein involved in the production of microtubules, is primarily responsible for chemically altering (abnormally folded and phosphorylated) neurofibrillary tangles. The degree of the disease is correlated with the production of tau tangles in the brain; the more advanced the stage of the disease, the more tangles form. No instances of AD due to mutations in the tau gene on chromosome 174 have been documented, despite the fact that neurofibrillary tangles are present in AD. However, frontotemporal dementias with parkinsonism were discovered in certain families carrying that mutation. Recent research supports the conclusion that tau change occurs after Aβ buildup in AD patients [5].

GENETICS

Best evidence for the key involvement of amyloid in AD comes from the discovery of a potential mechanism shared by the four known genes responsible for familial types of the illness. In individuals with familial early-onset autosomal dominant AD, three of those particular genetic variants—APP on chromosome 21, presenilin-1 [PS 1] on chromosome 14, and prescnilin-2 [PS 2] on chromosome 1 were found. However, these mutations are incredibly uncommon, occurring in less than 1% of cases. By selectively enhancing the cleavage of APP by β or γ-secretase, all these genes seem to enhance the cellular synthesis of Aβ42. Apolipoprotein E (APOE) is the fourth gene associated with AD. It is located on the long arm of chromosome 19 and has three allelic versions (APOE-2, APOE-3, and APOE-4) that differ in the amino acid that is replaced. According to several studies, there is a dose-dependent correlation between the APOE-4 allele and a lower age at beginning of AD, as well as a disproportionate representation of this allele in individuals with both early and late-onset AD. On the other hand, a number of studies revealed that APOE-2 allele inheritance could be advantageous. One (2.2 - 4.4 higher risks) or two (5.1 - 17.9 higher risks) copies of the APOE-4 allele on chromosome 19 appear to be associated with an elevated risk for the sporadic late-onset type of AD. The presence of APOE-4 is neither required nor sufficient for the development of AD; it is only a risk factor. The APOE-4 allele is a significant risk factor for AD in both men and women from a wide range of racial and ethnic backgrounds, across all age groups between 40 and 90 years old, according to a new meta-analysis of almost 14,000 patients with the disease and controls. Between 45% - 60% of AD cases are thought to be genetically caused by APOE-4. It seems that APOE-4 functions by either improving Aβ aggregation or reducing its clearance rather than by raising Aβ production. Another potential risk factor that has been recently found is lipoprotein (a), which is also a risk factor for late-onset AD in carriers of the APOE-4 allele and appears to protect against late-onset AD in noncarriers [6]. Retrospective studies conducted as part of the EURODBM (European Studies of Dementia) initiatives revealed that women were equally at risk for vascular dementia but more likely to develop AD than males. Only partly because of their longer lifespans, women seem to be more susceptible to AD. The population with AD is twice as large in females as males because women with the condition live longer than men do. Additionally, these investigations demonstrated that whilst a history of head trauma resulting in unconsciousness and a family history of dementia did not significantly raise the risk of AD, low education did [7, 8]. As of right now, APOE-4 and age are the only known risk factors for AD. Despite this information, genotyping is not currently advised in asymptomatic people, regardless of their family history of AD, because to the unreliable predictive usefulness, the absence of a therapy to halt the illness's progression, and the possibility of prejudice [9, 10].

EPIDEMIOLOGY

There are two types of AD: sporadic and familial. It can also be classified as early-onset (before age 65) or late-onset (after age 65). In the general population, the 6-month prevalence of AD seems to range from 5.5% - 9% [11]. Every ten years, the disease's prevalence doubles. Currently, almost half of those 85 years of age and older suffer with AD. Mild cognitive impairment may be present in people with cognitive deficiency who do not match the widely

accepted clinical criteria for AD but who have a discernible decline from previous levels of cognitive function and difficulties with new learning. Forty percent of these people will get AD within three years, according to recent studies. For the purpose of cholinesterase inhibitor therapy, carer stress reduction, community support, postponing institutionalisation, lifestyle planning, and legal concerns, early detection of AD is crucial.

TREATMENT MODALITIES

Improving cognition and reducing behavioural problems (such as agitation, sleeplessness, sadness, and psychosis) are the main objectives of therapy [12].

1. **Psychosocial treatment –**
   AD sufferers can function better with the management of their environment, family support and the avoidance of other medical problems [13, 14]. A patient's surroundings should be adjusted in an effort to keep them in their homes for as long as feasible if they have AD. Everyday reminders that are written down might be useful in carrying out everyday tasks. It is crucial to have prominent windows, clocks, and calendars. There should be little change in the patient's activity. It is necessary to keep up proper hydration, diet, exercise, and hygiene. Family members are susceptible to sadness, anxiety disorders, and sleeplessness, therefore assistance is vital.
2. **Pharmacotherapy –**
   Pharmacological options now accessible to doctors treating AD include mood stabilisers, antipsychotics, antidepressants, and hypnotics for the treatment of behavioural disturbance and cognitive enhancers for the therapy of cognitive deficit [14, 15].

3. **Treatment options for cognitive disturbance –**

   i. **Cholinesterase inhibitors -** The cholinergic deficit seen in AD is the basis for the use of cholinesterase inhibitors. For AD patients, only cholinesterase inhibitors have demonstrated clinically significant improvements. By blocking the enzymes responsible for its breakdown (i.e., acetylcholinesterase), these drugs increase the concentration of acetylcholine accessible for synaptic transmission. These medications seem to be helpful at any stage of the illness, but especially in the intermediate phase [16].
   The cholinesterase inhibitors (Table III) donepezil [17–21], tacrine [22–25], galantamine [26–28], and rivastigmine are now accessible for clinical usage around the world [29–31]. Families and doctors may not notice an immediate improvement in symptoms, but patients using the medicine will appear to be losing less cognitive function when compared to controls.

   ii. Any medication used to treat AD must outperform a placebo in a randomised, double-blind, placebo-controlled clinical study using global clinical measurements and psychometric testing in order to receive approval in the US. At least three months must pass throughout the study. The Clinician Interview-Based Impression Scale (CIBIS) and the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) are two frequently used measures. The ADAS-cog assesses a person's capacity to follow instructions, build and use ideas in praxis, recall words, recognise words, name objects and fingers, and execute on basic activities. The ADAS-cog has a potential score range of 0 to 70, with a higher score signifying more disability. Based on the severity of AD, there seems to be a difference in the responsiveness to cholinesterase inhibition; individuals with mild AD (MMSE scores 18–26) do not seem to respond as well as middle-stage AD patients (characterised by MMSE values 11–17). The idea that the cholinergic deficiency initially becomes statistically significant at this stage of the illness is supported by these results [32]. In the therapy of behavioural disorder in AD patients, cholinesterase inhibitors may play a part. This family of medicines improved psychosis, agitation, and mood disorders in clinical studies [33–36]. Regretfully, there are not many researches contrasting the tolerance and safety of cholinesterase inhibitors [37]. Thus, definitive scientific information from head-to-head research is not helpful in deciding which cholinesterase inhibitor to employ.

   iii. **Estrogen replacement therapy -** A substantial body of research has been conducted on the effects of oestrogen on neuronal survival, regeneration, and plasticity in the brain. It seems to work in the brain via improving nongenomic events' transcription and mediation. Men have an inherent source of oestrogen due to the aromatisation of testosterone in the brain; it has been proposed that postmenopausal women's rapid reduction in oestrogen production raises their chance of acquiring AD. Based on many open-labeled clinical studies, there is growing evidence that oestrogen replacement treatment (ERT) in postmenopausal women may help postpone AD by enhancing cognitive performance and lowering the risk for both AD and cognitive impairment [38 – 40] and at least one double-blind, placebo-controlled trial [41]; nevertheless, a significant, double-blind, controlled research conducted recently on individuals with AD revealed no impact of oestrogen [42, 43]. In one of the latter investigations [42], oestrogen showed a time-limited advantage (two months) on the MMSE, consistent with earlier data, but failed to enhance cognitive or functional outcomes after a year of usage. Women's Health Initiative such as Memory Study; Women's International Study of Long Duration Oestrogen for Menopause; Preventing Postmenopausal Memory Loss and Alzheimer's with Replacement Oestrogens Study are among the current studies that are being conducted to determine whether oestrogen can be used as a primary preventive measure in patients with AD. While subsequent trials will demonstrate if ERT can slow the advancement of the illness, these investigations should demonstrate whether ERT is useful in preventing AD. Currently under investigation for AD are drugs belonging to an intriguing family called selective estrogen-receptor modulators. These (raloxifene, tamoxifen, droloxifene, and tiboline) function as

antagonists in certain tissues and as agonists of oestrogen in others.

iv. **Anti-inflammatory agents -** Some retrospective epidemiologic studies have provided evidence for the concept that anti-inflammatory medication can decrease the course of AD [44 – 46]. Nonsteroidal anti-inflammatory medication (NSAIDS) prospective double-blind clinical studies are rare in AD. Promising outcomes were shown in nonrandomized investigations using NSAIDS (indomethacin, ibuprofen, diclofenac, naproxen), steroids (low-dose prednisone) and other anti-inflammatory drugs (hydroxychloroquine, colchicine) to modify the disease's progression [47 -49]. Unfortunately the sample sizes in these researches were small. Past successful outcomes have not been repeated in more recent research. In 138 AD patients receiving prednisone for 16 months, a double-blind, low-dose, placebo-controlled research revealed no slowing of the pace of cognitive deterioration as compared to placebo.50 Long-term usage of high-dose steroids can result in serious health issues, even if some prior high-dose prednisone trials demonstrated benefit [51]. The cyclooxygenase-2 (COX-2) inhibitor class of anti-inflammatory drugs includes celecoxib and rofecoxib. They are now preferred in clinical trials for people with AD because they are more selective for the brain than the NSAIDs that are presently on the market. Now that a significant double-blind, placebo-controlled study comparing rofecoxib with naproxen and placebo has concluded, the findings were unfavourable [52].

v. **Antioxidant agents (Selegiline and Vitamin E) -** According to current hypotheses, AD may see an increase in free radical production, which might have a direct harmful effect. Due to the high quantity of catecholamines and low concentration of antioxidative enzymes (superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase), the brain may be more susceptible to the harmful effects of oxidative stress. Moreover, Aβ has been connected to a rise in the production of free radicals. By functioning as free-radical scavengers, vitamin E at dosages of 1000 IU orally twice day and selegiline, a monoamine oxidase B inhibitor, in doses of 5 to 10 mg orally every morning [53 - 55], seem to reduce free-radical damage. Delays in nursing home placement and loss of daily living activities were shown to be associated with selegiline alone, vitamin E alone, and selegiline and vitamin E plus placebo in patients with AD, according to a recent large double-blind study [56]. But as compared to a placebo, neither selegiline nor vitamin E enhanced cognition. When vitamin E and selegiline were combined, there was no additive impact.

Table - 3: Cholinesterase inhibitors

Drugs	**Dosage**	**Side effects**
Donepezil	5-10 mg PO qhs	nausea, vomiting, diarrhea
Tacrine	20-40 mg PO qid	nausea, vomiting, diarrhea, hepatotoxicity
Galantamine	8-12 mg PO bid	nausea, vomiting, diarrhea
Rivastigmine	2-6 mg PO bid	nausea, vomiting, diarrhea

1. Treatment of behavioral disturbance -

Most AD patients suffer from a wide spectrum of dementia-associated behavioural disorders, with depression and psychosis being the most often researched from a therapy perspective. AD patients who suffer from depression should receive strong treatment and their cognitive performance should be closely monitored. Due to a lack of clinical trial evidence, antidepressant therapy for depression in AD is still empirical and involves titrating up the dosage of the medication gradually. For depressed people without dementia to experience a clinical response, an appropriate dosage and length of therapy are required. Antidepressant medication may take up to six weeks to start working in depressed senior people and patients with AD should anticipate a similar length of time. Patients with depression and dementia seem to benefit from reversible monoamine oxidase inhibitors such as brofaromine and moclobemide [57], which don't have the serious possible side effects of the traditional monoamine oxidase inhibitors (tranylcypromine, phenelzine). Since nortriptyline and desipramine have less anticholinergic qualities than their parent chemicals, imipramine and amitriptyline their use as tricyclic antidepressants is restricted to these two medications [58]. Both of them were successful in treating depression in AD patients and were investigated in double-blind, placebo-controlled studies. All of the more recent antidepressants, such as venlafaxine, fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, nefazodone, bupropion, and mirtazapine seem to help with depression in AD patients, though only the three of them were examined in double-blind, placebo-controlled trials. Currently people with AD who suffer from depression are treated with selective serotonin reuptake inhibitors (SSRIs) as the standard of care [62]. Psychosis and behavioural abnormalities can also be independent features of the illness and can exacerbate depression in these people. In AD patients, psychosis occurs 25% to 50% of the time [63]. Although several therapies have been suggested, there are not many available controlled trials. Atypical antipsychotics such risperidone [65, 66] and olanzapine [67], which have been used in double-blind placebo controlled studies, should be the mainstay of treatment for psychosis [64] in AD patients. A comprehensive, double-blind, placebo-controlled research including 625 patients was conducted to assess the safety and effectiveness of risperidone [63] as an atypical antipsychotic for the treatment of behavioural symptoms and psychosis in

individuals with AD. In this experiment, the administration of 1 mg of risperidone daily resulted in a considerable improvement in psychosis without the appearance of typical antipsychotic side effects. A different recent double-blind, placebo-controlled study [66] examined the effects of risperidone, haloperidol, and placebo in patients with AD. It found that while both drugs were equally effective at treating AD symptoms (with a 1-mg dose of each compound), the atypical agent caused significantly fewer extrapyramidal side effects. Olanzapine [67] has also been proven in a double-blind, placebo-controlled experiment to significantly improve psychosis in AD patients as compared to placebo, with little adverse effects. Recent research seems to support the use of quetiapinc, a novel medication, in the treatment of psychosis; nonetheless, the study lacked control [68]. Low doses of typical antipsychotics should be utilised to prevent extrapyramidal symptoms; the addition of atypical medicines can further reduce this risk [69]. Treatment for both the behavioural and cognitive disturbances appears to improve morbidity and mortality, postpone admission to a nursing home, and have a major financial impact on AD [70, 71].

ECONOMIC IMPACT

Despite the fact that half of AD patients receive their treatment at home, AD is quickly rising to the top of the medical expense list, with yearly expenses exceeding $50 billion in the US. The potential financial burden of treating AD is significant, given that there were around 70 million persons in the globe who were 80 years of age or older in 1988 and that number is expected to surge to 370 million in 2050 according to recent forecasts. In addition, AD has a detrimental indirect effect on carers who go through financial, physical, and emotional strains. There are currently no prospective studies on the financial impact of treating AD, particularly in relation to cholinesterase inhibitors. There are just unregulated data accessible. According to a recent retrospective cost-analysis study [70], tacrine usage saved patients $10,000 on average from the time of diagnosis until their deaths. A further recent study [71] found that, after six months, 5% of AD patients treated with donepezil were institutionalised, but 10% of patients who did not get donepezil were.

FUTURE PERSPECTIVES

Future therapeutic approaches [72] for treating AD patients will involve developing preventive measures like Ap immunizations [74] and inhibitors of β-secretase [75] and γ-secretase, as well as using functional brain imaging techniques for early diagnosis and treatment efficacy evaluation (in vivo measurements of cholinesterase function) [76]. APP transgenic mice immunised with Aβ repeatedly develop antibodies that appear to facilitate the removal of Aβ deposits from the brain. Phase 1 clinical studies are now employing this strategy.

DISCUSSION AND CONCLUSION

The various degrees of scientific evidence that underpin current dementia treatment strategies reflect our inadequate understanding of the fundamental biology of AD. The data supporting cholin-esterase inhibitors (donepezil, tacrine, rivastigmine, and galantamine) as the suggested treatment for cognitive impairment in AD patients is sufficiently consistent and the cholinergic impairments have been well-described. Randomised, double-blind, placebo-controlled, parallel-group studies assessing performance-based assessments of cognitive function, activities of daily living, and behaviour have clinically assessed symptomatic treatment, mostly focussing on cholinergic therapy. Behavioural disorders may be treated with cholinesterase inhibitors. Although clinical researches investigating the efficacy of antioxidant, anti-inflammatory, and oestrogen replacement therapy treatments are underway, these interventions remain contentious. Mood stabilisers, antidepressants, antipsychotics, anxiolytics, and hypnotics are used to treat behavioural disorder symptoms.

ABBREVIATIONS

Aβ	amyloid β-peptide
AD	Alzheimer's disease
ADAS-cog	cognitive subscale of the Alzheimer's Disease Assessment Scale
APOE	apolipoprotein E
APP	amyloid precursor protein
CIBIS	Clinician Interview-Based Impression Scale
COX-2	cyclooxygenase-2
ERT	estrogen replacement therapy
MMSE	Mini-Mental State Examination
NSAID	nonsteroidal anti-inflammatory drug
PS 1 & 2	presenilin-1 & -2
SSRI	selective serotonin reuptake inhibitor

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