

LW Chu 朱亮榮

With ageing of populations, the worldwide population of persons with dementia will reach over 81 million by 2040, of which the most common cause is Alzheimer's disease. In recent years, there have been major advances in the understanding of its pathogenesis, methods to diagnose it, and treatment. Magnetic resonance brain imaging, cerebrospinal fluid biomarkers, and Pittsburgh compound B and fluorodeoxyglucose positron emission tomography of the brain can facilitate an accurate diagnosis of Alzheimer's disease in its early stage, and diagnose the mild cognitive impairment stage of Alzheimer's disease. At present, only symptomatic but not disease-modifying drug treatments are available. Donepezil, rivastigmine and galantamine are the currently approved cholinesterase inhibitors for the treatment of mild, moderate, and severe Alzheimer's disease. Overall, cholinesterase inhibitors show beneficial effects on cognition, activity of daily living, behaviour, and overall clinical rating. Memantine is another symptomatic treatment for moderate-to-severe Alzheimer's disease patients. It has a small beneficial effect on cognition, activity of daily living, behaviour, and overall clinical rating. Vitamin E has antioxidant properties, and may be used in some Alzheimer's disease patients without vascular risk factors. Concurrent non-pharmacological and psychosocial management of patients and their caregivers have a very important role. Disease-modifying therapies are still under development, whilst immunotherapy may be a viable option in the near future.

Prevalence and impact of Alzheimer's disease

Alois Alzheimer first described the disease in 1907. Alzheimer's disease (AD) is an age-related neurodegenerative disorder with characteristic clinical and pathological features. The most well-known neuropathological hallmarks are extraneuronal senile plaques and intraneuronal neurofibrillary tangles (NFTs). The consequent loss of neuronal synapses and neuronal death leads to decreases in acetylcholine and other neurotransmitters.¹

With ageing of our world population, the prevalence of dementia will increase globally. The number of affected persons in the world will double every 20 years, and will increase to 81.1 million by 2040.² The total worldwide societal cost of dementia is estimated to be US\$422 billion.³ Among Hong Kong elderly people aged 70 years or older, the prevalence of dementia was reported to be 6.1%,⁴ and the combined prevalence of mild and very mild dementia was 17.4%.⁵ Moreover, AD accounted for 65% of all dementia in Hong Kong.⁴ In the US, it is estimated that an intervention, which can delay the onset of AD by 2 years on average, could reduce the numbers of affected persons by 2 million after 50 years.⁶

Risk factors of Alzheimer's disease

Genes and genetic risk

The genetic risk in familial early-onset AD differs from that in the sporadic late-onset form of the disease. In the familial disease, the three genes implicated are all autosomal dominant, and include the amyloid precursor protein gene on chromosome 21, the presenilin 1 gene on chromosome 14, and the presenilin 2 gene on chromosome 1. Presenilin 1 gene mutations are most common among familial AD mutations.⁷ Mutations in these genes lead to an overproduction of beta-amyloid (A β) peptides (A β 40 and A β 42), which give rise to synaptic dysfunction, neurotoxicity, and A β deposits in the brain called neuritic or senile plaques. Familial AD, however, is rare.^{7,8}

In sporadic or late-onset AD, the apolipoprotein-E (APOE) ϵ 4 allele increases the risk of developing the disease.⁷ As a susceptibility gene, the genotypes APOE ϵ 2/ ϵ 4 or ϵ 3/ ϵ 4 increase the risk by approximately three-fold, and the genotype APOE ϵ 4/ ϵ 4 increases the risk by approximately 15-fold. The population-attributable risk (ie the proportion with

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Division of Geriatric Medicine,
Department of Medicine, Queen
Mary Hospital, Li Ka Shing Faculty of
Medicine, The University of Hong Kong,
Pokfulam, Hong Kong

LW Chu, FRCP (Lond, Edin, Glasg), FHKAM
(Medicine)

Correspondence to: Prof LW Chu
Email: lwchu@hkucc.hku.hk

late-onset AD associated with APOE) is estimated to be 20%, making it the most important risk factor.^{7,9} The APOE allelic variants may be involved in the degradation or clearance of A β from the brain. Genome-wide association (GWA) studies and a recent meta-analysis of 12 GWA studies implicated three additional genes, namely the complement receptor 1 (CR1), clusterin (CLU), and phosphatidylinositol-binding clathrin assembly protein (PICALM), which are novel susceptibility loci for late-onset AD in European ancestry populations.¹⁰ Among Southern Chinese late-onset AD patients in Hong Kong, we recently found that single nucleotide polymorphisms in CR1 and CLU were significantly associated with AD. However, the AD association for PICALM was only present in APOE ϵ 4 negative and not ϵ 4 positive persons.¹¹

Age, gender, education, lifestyle, and other risk factors

Age is a risk factor for AD. The annual incidence of AD is approximately 1% among elderly persons aged 65 to 70 years, and increases to 6 to 8% of persons older than 85 years. The prevalence of AD is below 1% for persons aged 60 to 64 years, and increases with age to 24 to 35% among persons aged 85 years or above,^{2,4,7} and is higher in women than men.^{4,12} In men, high bioavailable testosterone levels appear to reduce the risk of AD.¹³ Education may increase the 'cognitive reserve', which reduces the risk of late-life dementia. The risk of AD is highest among those with low or limited levels of education. A positive family history of AD occurs in around 15% of AD patients, and increases the risk of AD approximately four-fold.⁷ The relationship of alcohol use to AD follows a U-shaped relationship; moderate consumption is associated with a reduced risk, whilst in heavy drinkers and non-drinkers the associated risk of cognitive impairment, dementia, and AD appears to be increased. The protective effect of moderate alcohol intake may be related to the antioxidant properties of wine.^{7,14} Physical activity and exercise reduce brain tissue loss, dementia, and the risk of AD, possibly via increased neurotrophic factors.¹⁵ Smoking increases the risk 2 to 4 times. Depressive mood and cardiovascular risk factors are also associated with an increased risk.⁷ Severe head injury also increases the risk of AD, possibly via reduced brain reserve or increases in brain A β deposition. Other dietary factors may also reduce the risk of AD, including vitamin B12; folate; antioxidants including flavonoids; vitamins C and E; unsaturated fatty acids; and a Mediterranean diet pattern.^{7,16}

Pathogenesis

Presently, the dominant hypothesis for the cause of AD relies on the amyloid cascade hypothesis. Alzheimer's

阿爾茲海默氏症：早期診斷及治療

人口不斷老化，估計至2040年，全球認知障礙症患者人數會超越8100萬。當中最普遍的病因為阿爾茲海默氏症。近年對於阿爾茲海默氏症的發病原因、診斷及醫治方法有重大發展。磁共振腦成像、腦脊液生物標記物、匹茲堡化合物B及脫氧葡萄糖正子腦攝影電腦斷層掃描都可以為早期的阿爾茲海默氏症，甚至是輕度認知障礙作出準確診斷。直至目前為止，阿爾茲海默氏症的藥物只針對其症狀，並未能緩解病情。而多奈哌齊、卡巴拉汀及加蘭他敏是治療輕度、中度及嚴重阿爾茲海默氏症的認可膽鹼酯酶抑制劑。這抑制劑有助改善患者的認知能力、日常生活、行為及總臨床評分。NMDA受體拮抗劑 memantine 是另一種針對中度至嚴重阿爾茲海默氏症的藥物，對於患者的認知能力、日常生活、行為及總臨床評分有少許幫助。維生素E具抗氧化功能，可用於無血管風險因素的阿爾茲海默氏症患者身上。施藥期間同時使用非藥物治療方法，及對患者和其照顧者作出心理社會支援也相當重要。緩解病情的藥物尚在發展階段，而免疫治療或是未來可行的發展方向。

disease is characterised by excessive formation or reduced clearance of A β . Microscopically, excessive senile or neuritic plaques are found extracellularly and NFTs intracellularly in the cortex of the brain, particularly in the hippocampal cortex. Neurofibrillary tangles are composed of hyperphosphorylated forms of the microtubule-associated protein tau. Subsequent neuronal death occurs and leads to progressive loss of neuronal function. In early-onset familial AD, excessive A β is formed. In late-onset AD, there is reduced clearance of the usual amounts of A β . The excess A β aggregates to form soluble dimers, trimers, and low-ordered molecules called oligomers. Further aggregations into A β protofibrils, fibrils and neuritic plaques may also occur. While all these forms of A β aggregates account for neuronal dysfunction and neuronal death in AD, A β oligomers are particularly toxic to the neuron. Intermediate mechanisms include activation of microglia, astrocytes, and neuroinflammatory responses. Subsequent excessive oxidative stress, mitochondrial dysfunction, and disturbed ionic homeostasis could lead to neuronal death, neurotransmitter deficits, and consequential progressive decline in cognitive function.¹⁷ In AD, the second neuropathological hallmark is an intraneuronal accumulation of abnormally hyperphosphorylated tau (ie described as the tau hypothesis). Apparently, this impairs normal transport function and causes aggregation of the tubules to form NFTs within the neuronal cell in the transentorhinal regions, hippocampus, amygdala, and then neocortical association areas. The formation of NFTs, oxidation and lipid peroxidation, and glutamnergic excitotoxicity are thought to be secondary to A β accumulation.¹⁸ These hypotheses form the basis of the current search for disease-modifying therapies in AD.

Clinical features of Alzheimer's disease

Patients with AD are characterised by cognitive and functional decline, deterioration of their activity of daily living (ADL), social or occupational functioning,^{19,20} and quality of life.²¹ In AD patients, symptoms first appear insidiously after the age of 60 years. Very often, they are brought to the clinic by their family members when they observe a progressive decline in short-term memory. Common memory symptoms include repeating questions on the same matter and misplacing common personal items. These symptoms often have a negative impact on their daily lives, and alert family members to bring them for consultation. Other common clinical features include progressive decline in other cognitive functions, including abstract thinking, judgement, language, personality changes, and behavioural symptoms. With progression of the illness, the ability to make daily judgements and manage financial matters is also affected. Speech, comprehension, and expression may be affected in moderately early AD. Finally, aphasia may be present in the late/severe stages. Failure to recognise common objects (agnosia), inability to put on the clothes (apraxia), getting lost in familiar environments and mis-identification of caregivers may occur in moderate-to-severe stage of AD.²² Among Chinese AD patients, the most common clinical features are poor memory, disorientation, apraxia, errors in calculation, impaired executive function, poor abstract thinking, language problems, and agnosia. Impairment in language ability affects approximately 57% of Chinese AD patients.²³ Occasionally, in the early stages patients may present atypically with prominent language disorder. Delay in seeking medical advice is common. In Hong Kong, the delay in consultation for memory problems is estimated to be approximately 3 years, which is much longer than the 1-year delay in Caucasian AD patients.^{23,24} The course of the disease varies from person to person, as does the rate of decline; AD may last from 2 to 20 years, with a median of about 3 to 4 years.^{7,22}

Personality changes may also occur. Disturbing behaviour and emotional symptoms, such as agitation, may become more frequent in the moderate stage of AD. Behavioural and psychological symptoms of dementia (BPSD), also known as non-cognitive symptoms, are common in AD patients. Dysphoria (depressive mood, sadness), euphoria, anxiety, irritability, social withdrawal, apathy, sundowning, sleep disorders, suspiciousness, disinhibition, disturbing behaviour, delusions, hallucinations, stereotyped or repetitive behaviour, pacing and aggression (verbal or physical) are reported in 10 to 75% of AD patients.^{22,25,26} Apart from cognitive and behavioural symptoms, there may be early somatic symptoms. In particular, progressive weight loss and low body mass index are early symptoms of AD.²⁷

Diagnosis of Alzheimer's disease

In practice, a clinical diagnosis of AD is made when patients have progressive memory decline for over 6 months with a resulting impairment of self-care and social or occupational functioning. The presence of objective memory impairment should be documented by the Mini-Mental State Examination (MMSE) and other neuropsychological tests. Other essential diagnostic points include deficits in two or more areas of cognition, absence of disturbance in consciousness, disease onset between the ages of 40 and 90 years, absence of systemic disorders or other brain diseases that could account for the progressive deficits in memory and cognition, evidence of cerebral atrophy on computed tomography (CT) or magnetic resonance imaging (MRI) without other significant organic lesions, and absence of any metabolic disorder.²⁰

In most patients, the above information can be obtained after a detailed history from the carers, physical examination, and cognitive tests that measure memory, language skills, and activities of daily function related to brain functioning. An early, accurate diagnosis of AD is especially important to patients and their families. It helps them plan for the future and pursue management options, while the patient can still take part in making decisions. During the diagnostic process, it is also crucial to rule out other causes of cognitive decline, particularly other types of dementia. Vascular dementia, frontotemporal dementia, and Lewy body dementia need to be considered as possible subtypes in the differential diagnoses. Structural neuroimaging (CT or MRI) can help rule out the presence of strokes, subdural haematoma, normal pressure hydrocephalus or tumours. Serum vitamin B12 level, red blood cell and serum folate levels can help exclude these deficiencies. Abnormalities in these tests, however, are quite common in elderly persons, and may or may not be causal. Less common causes of dementia are hypothyroidism, neurosyphilis, and sedation from drugs. If the clinical history raises suspicions, chronic heavy metal intoxication (eg mercury), human immunodeficiency virus infection, and Creutzfeldt-Jakob disease have to be considered. Overall, AD accounts for 65% of all patients with dementia, while secondary causes explain a minority.⁴ Vascular dementia (VaD) and mixed AD-VaD are usually the second and third most common causes, respectively. In general, this clinical approach is often employed in conjunction with established diagnostic criteria for AD, including those in the Diagnostic and Statistical Manual of Mental Disorders (4th edition) and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for AD.^{19,20} Using the latter criteria, the term "probable AD" is equivalent to the clinical diagnosis

of AD during a lifetime, as definite AD can only be made at postmortem.²⁰ Experienced clinicians can diagnose AD with approximately 90% accuracy. The addition of biomarkers, in particular, amyloid (eg Pittsburgh compound B or PiB) positron emission tomography (PET) and fluorodeoxyglucose (FDG) PET brain scans can further improve diagnostic accuracy (Figs 1 and 2).

Biomarkers of Alzheimer's disease

Alzheimer's disease is now regarded as a chronic disease. Affected patients have neuropathology in their brains for over 10 to 20 years before symptoms

occur. With ongoing research to develop new AD treatments, an increasing need to establish an early diagnosis of AD could become important. Thus, biological markers which could allow a positive diagnosis early in the course of AD appear desirable. Amyloid PET brain imaging and low cerebrospinal

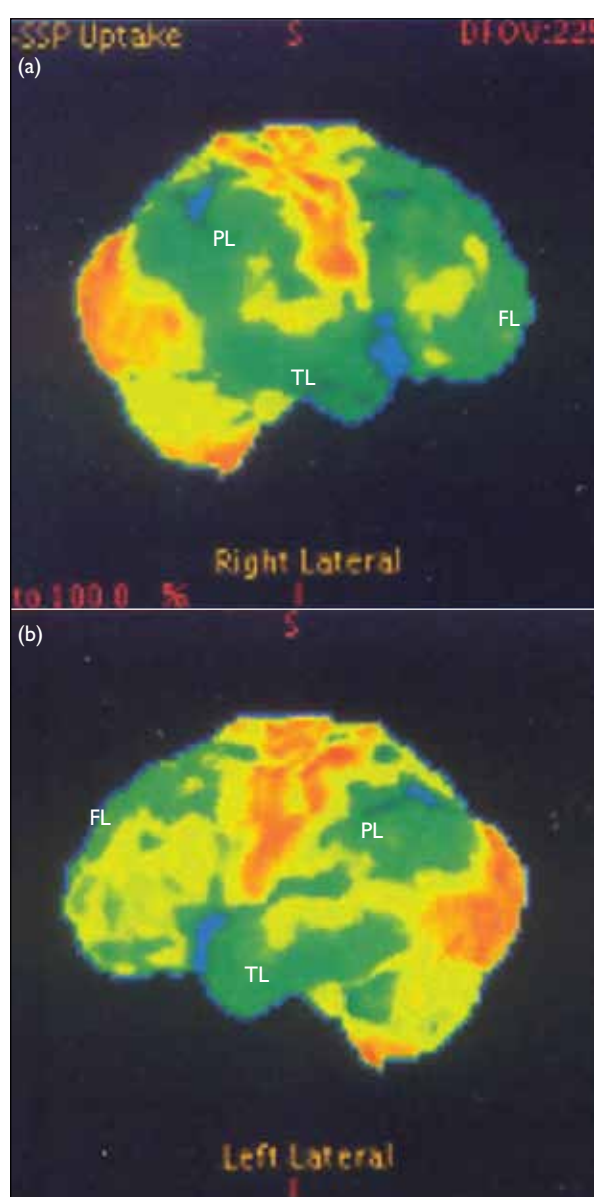


FIG 1. Fluorodeoxyglucose positron emission tomography (FDG PET) brain scan in Alzheimer's disease (AD) Brain FDG PET scan in moderately severe AD: bilateral symmetrical hypometabolism affecting temporal (TL), parietal (PL), and frontal (FL) lobes

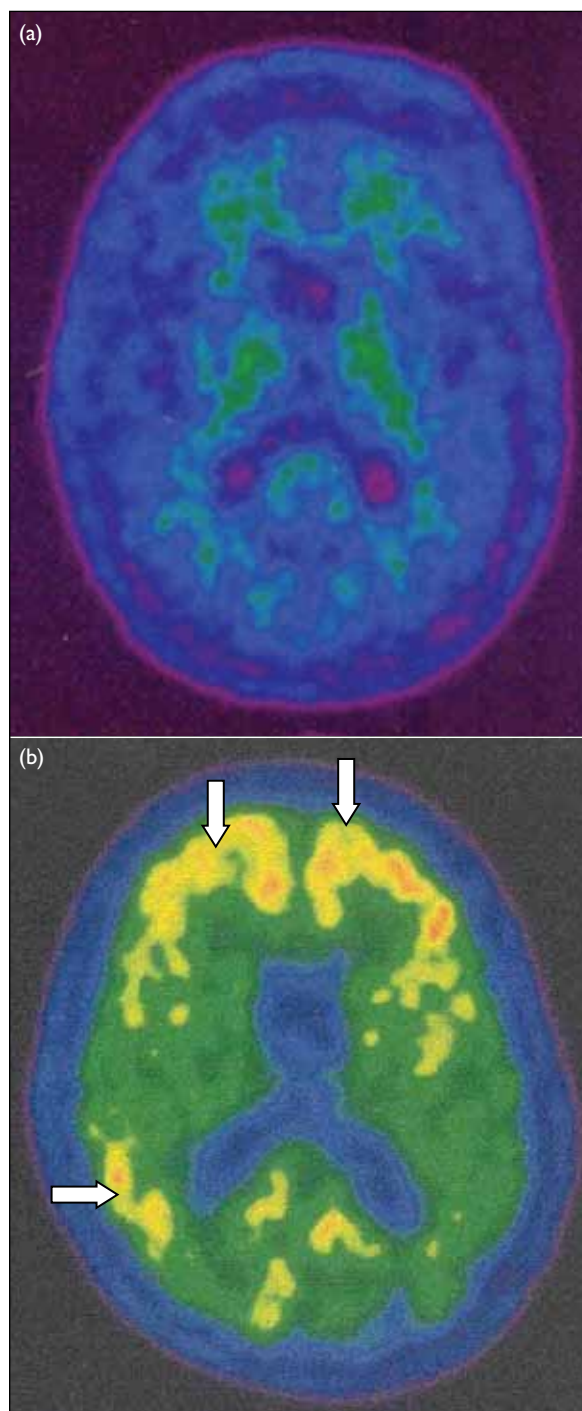


FIG 2. Pittsburgh compound B (PiB) positron emission tomography (PET) brain scan in Alzheimer's disease (AD) and normal controls (a) Normal older adults without AD: PiB-negative, with no PiB retention in cerebral cortex. (b) AD patient: PiB-positive (white arrows), with moderate PiB retention in frontal and parietal cortices

fluid (CSF) A β 42 levels constitute neuropathological biomarkers, reflecting A β protein deposition in the brain. The second group of biomarkers reflects neuronal degeneration, injury, and brain atrophy. These biomarkers include structural MRI regional brain atrophy (in the hippocampus, medial, basal and lateral lobes, and the parietal lobe), decreased [18 F]FDG PET uptake in the temporoparietal cortex, and increased CSF tau protein levels, ie total tau (t-tau) and phosphorylated tau (p-tau).²⁸

Quantitative volumetric brain MRI can differentiate AD from healthy elderly persons, with over 80% accuracy.²⁹ Semi-quantitative visual hippocampal assessment categorises hippocampal atrophy into five grades, and is also helpful with its diagnostic sensitivity of 81% and specificity of 67%.³⁰ Functional imaging by PET or single-photon emission computed tomography (SPECT) can evaluate brain function. [18 F]FDG PET is used to measure the brain metabolic energy, while 99m Tc hexamethylpropyleneamine oxime is commonly used to study cerebral perfusion. In AD patients, the characteristic change in FDG PET brain scans is bilateral hypometabolism of the superior posterior temporal and parietal lobes. In very early or mild cognitive impairment due to underlying AD pathology, FDG PET brain scans reveal hypometabolism in the medial part of the parietal cortex (posterior cingulate). In advanced AD, bilateral frontal lobe hypometabolism is also present, in addition to the characteristic hypometabolism of the temporoparietal areas (Fig 1). The sensitivity and specificity of FDG PET brain scans in the diagnosis of AD are 93% and 63%, respectively. Although SPECT brain scan is less sensitive than FDG PET, it can demonstrate the temporoparietal and posterior cingulate hypoperfusion in AD patients. The sensitivity and specificity of SPECT brain scan for the diagnosis of AD are 63% and 93%, respectively.³¹

Amyloid PET brain scans can detect A β deposit in the brain of AD patients in vivo. The most extensively reported technique is the [11 C]PiB PET brain scan. In AD patients but not in cognitively normal elderly persons, PiB is deposited bilaterally in the frontal, parietal, temporal, and occipital cortices (Fig 2). This pattern concurs with A β deposits in postmortem brain studies. In the presence of dementia, a positive PiB PET brain scan confirms the diagnosis of AD as the cause.^{31,32} However, a positive PiB PET brain scan can also be found in 10 to 30% of cognitively normal elderly persons. This is not surprising, as amyloid deposits have been reported in autopsied brains of elderly persons without dementia,³² which may represent a pre-clinical stage of AD at a time when the cognitive function is still unimpaired. In previous studies, it was found that elderly persons without dementia but high PiB positive scans have increased risks of cognitive decline and developing

AD on follow-up.³³⁻³⁵ Brain scans using PiB PET and MRI are reported to be complementary in providing neuropathological and neuronal degeneration information, respectively.³⁵

A low CSF A β 42 level is an alternative evidence of amyloid deposition which supports the diagnosis of AD. High CSF levels of t-tau or p-tau indicate neuronal degeneration and also support the diagnosis.^{28,36} The combination of CSF A β 42 and t-tau or p-tau (ie the ratio of either t-tau/A β 42 or p-tau/A β 42) has a higher sensitivity and specificity than either tau or A β 42 alone in differentiating AD from normal or other neurological diagnoses. The p-tau/A β 42 ratio is the best CSF biomarker to differentiate AD from frontotemporal dementia and semantic dementia, with a sensitivity of approximately 92% and 98%, respectively, and a specificity of approximately 93% and 84%, respectively.³⁷ In patients with mild cognitive impairment, the combination of t-tau and the p-tau/A β 42 ratio can also predict subsequent development of AD, with a sensitivity of 83 to 95% and a specificity of 87 to 88%.^{38,39}

Management of Alzheimer's disease

Pharmacological treatment

The clinical objectives in the treatment of AD are: (1) to relieve cognitive symptoms, (2) to relieve BPSD, and (3) to slow down progress of the disease. Current pharmacotherapy focuses mainly on impairment of cholinergic and glutamatergic systems, and is only symptomatic. Disease-modifying therapies are still in the developmental stage.

Cholinesterase inhibitors

Neurotransmitter enhancement therapy with cholinesterase inhibitors (ChEIs) is a clinically proven approach for patients with mild-to-moderate AD. Cholinesterase inhibitors increase cholinergic synaptic transmission by inhibiting acetylcholinesterase in the synaptic cleft, thereby decreasing the hydrolysis of acetylcholine released from the presynaptic neurons. These drugs result in small but measurable clinical benefit. The first of them approved for clinical use was tacrine (Cognex; Parke-Davis, Morris Plains [NJ], US), but is no longer used because of its liver toxicity. Donepezil (Aricept; Eisai Co Ltd, Tokyo, Japan), rivastigmine (Exelon; Novartis, Basel, Switzerland), and galantamine (Reminyl; Janssen Pharmaceuticals Inc, Titusville [NJ], US) are the three currently approved ChEIs for treating mild-to-moderate AD symptoms, ie MMSE scores between 10 and 24. Recently, such treatment has also been extended to patients with severe AD (MMSE <10; Table). Three reviews/meta-analyses on ChEIs have recently been published.⁴⁰⁻⁴² Overall, most studies on ChEIs were of good quality, and showed

that they delayed the decline in cognitive function (as measured by the AD assessment scale–cognitive subscale [ADAS-cog]), global clinical rating, as well as behaviour and ADL over 6-to-12-month periods. These benefits are applicable to mild, moderate, and severe AD patients. Compared to those on placebo treatment, patients on ChEIs generally showed an initial mild improvement in cognitive functions over the first 3 months. Thereafter, the mean decline in cognitive functions was also less rapid over the subsequent 3 to 9 months. At 6 months, the cognitive improvement (vs placebo) was 2.7 points over the mid-range of ADAS-cog.^{40,41} Symptoms that improved included attention, thinking, memory, praxis, language comprehension, and communication.⁴³

Fourteen studies reported the efficacy of ChEIs on function in mild-to-moderate AD; only one involved severe AD patients, with MMSE scores of less than 10. Overall, ChEIs showed benefit on activity of daily function versus placebo.^{40,41} There was less evidence that BPSD were better controlled after ChEI treatment; only seven studies showed a mean improvement of 4.3 points (vs 1.4 points in the placebo group) based on the Neuropsychiatric Inventory score.⁴¹

For clinicians, the most relevant outcome was the global clinical impression of change. In nine studies with this global clinical rating, ChEIs-treated AD patients showed a higher chance of improvement in the global clinical impression than placebo-treated patients. The pooled relative risks of responding to ChEIs are 1.88, 1.15 and 1.64 for donepezil, galantamine, and rivastigmine, respectively.⁴¹ There was very limited evidence regarding head-to-head comparison of the ChEIs. Only three open-label studies and one randomised controlled trial were available. Overall, there was no significant difference in the efficacy of galantamine versus donepezil, as well as rivastigmine versus donepezil. Only one short-term (12-week) study showed that donepezil appeared better than galantamine for function and behaviour. In a 2-year randomised controlled study, rivastigmine had a better outcome on function than donepezil, but effects on cognition and behaviour appeared similar.⁴¹

Alzheimer's disease is a chronic disease. Hence, the long-term effects of ChEIs are important. In open-label studies of patients treated by rivastigmine for up to 5 years, donepezil for up to 4.9 years and galantamine for up to 4 years, cognitive function and ADL showed less decline than expected.^{44,45}

In general, ChEIs (except tacrine) are well tolerated. Regarding oral prolonged release formulations, donepezil and galantamine are given once daily while rivastigmine is given twice daily. The dose titration range for rivastigmine and galantamine is broader than that of donepezil.^{40,41} Only rivastigmine has a transdermal patch formulation, which is used once daily.⁴⁵ After initiation of ChEI, regular monitoring of effects (ie cognitive, function, and behaviour) and adverse effects is recommended. Adverse effects are frequently dose-related, and often occur during the dose escalation. Slow upward titration of the ChEI dose over 3 months is therefore recommended. The commonest adverse effects are gastro-intestinal (nausea, anorexia, vomiting, diarrhoea) and weight loss. Less common ones include dizziness, headache, fatigue, malaise, muscle cramps, asthenia, bradycardia, and syncope. With the exception of allergic reactions, reduction of the dose or discontinuation leads to resolution of adverse effects. To minimise gastro-intestinal adversity, transdermal rivastigmine (Exelon patch) is recommended. The main drawbacks of transdermal rivastigmine are skin reactions (pruritus and erythema), which occur in 7 to 8% of patients.⁴⁶ Discontinuation of transdermal rivastigmine due to skin reactions is necessary only in 2% of patients.⁴⁶ Nevertheless, clinicians should avoid transdermal rivastigmine in patients with active skin diseases as such the pre-existing skin condition may become worse.

Up to 60% of AD patients respond to ChEI treatment, defined as 4 points or more benefit in the ADAS-cog compared to placebo treatments.⁴² Initiation of ChEI treatment in the early stage of AD is preferred. In a 52-week clinical trial, Farlow et al⁴⁷ reported that AD patients starting rivastigmine 6 months later (after 26 weeks) achieved lower cognitive performance than those given the drug at the beginning.

TABLE. Symptomatic drug treatments for Alzheimer's disease*

Drug	Class	Dose (mg/day)	Frequency (times/day)	Absorption affected by food	Metabolism
Donepezil (Aricept)	Cholinesterase inhibitor	5-10 [†]	1	No	CYP2D6 CYP3A4
Rivastigmine (Exelon)	Cholinesterase inhibitor	3-12	2	Yes	Non-hepatic
Galantamine (Reminyl; Reminyl PR)	Cholinesterase inhibitor	8-32	2 1 (PR)	Yes	CYP2D6 CYP3A4
Memantine (Ebixa)	NMDA-receptor antagonist	5-20	2 (one)	No	Non-hepatic

* PR denotes prolonged release, and NMDA N-methyl D-aspartate

[†] Donepezil 23 mg not available yet in Hong Kong

N-methyl D-aspartate receptor antagonist

The N-methyl D-aspartate (NMDA) receptors are abundant in pyramidal cells in the hippocampus and cortex (areas involved in cognition, learning, and memory). The mechanism involved in learning and memory entails long-term potentiation, mediated by the neurotransmitter glutamate via the NMDA receptor. However, elevated glutamate levels are also undesirable and associated with excitotoxicity of the neurons. Memantine is a moderate-affinity non-competitive, NMDA-type receptor antagonist. It is postulated to decrease the glutamate-induced excitotoxicity of the neuron, while allowing the physiological actions of glutamate on learning and memory. In clinical trials, memantine leads to a small but significant beneficial effect on cognition, ADL, behaviour, and clinical perception of change in moderate-to-severe AD, when compared to placebo. Patients are less likely to have deterioration of mood, agitation, irritability, or delusions. In mild-to-moderate AD, memantine has only a marginal beneficial effect on cognition, without any benefit in terms of ADL, behaviour and clinical impression of change.^{48,49} Memantine can also be added to ChEI in moderate-to-severe AD.⁵⁰ The recommended starting dose of memantine is 5 mg once a day. Dosing is increased weekly by 5 mg increments, to a maximum dose of 10 mg twice daily (Table). Memantine is well-tolerated; putative adverse effects occur uncommonly and are not significantly more frequent than in placebo-treated patients. Reported adverse effects include dizziness, confusion, somnolence, hallucination, and nausea. They usually subside after discontinuation of the drug or reduction in dosage.^{48,49}

Antioxidants

Only limited data are available for antioxidant treatment in AD. One randomised controlled trial showed that selegiline and alpha-tocopherol (vitamin

E) could reduce functional deterioration (ie the time to institutionalisation, loss of the ability to perform basic ADL, severe dementia, or death) in moderately severe AD patients.⁵¹ In practice, vitamin E, but not selegiline, may be used because of its lower cost and lesser liability to result in side-effects. However, vitamin E is only suitable for AD patients without cardiovascular risk factors, as it appears to increase mortality in patients with vascular diseases.⁵² Ginkgo biloba may also have antioxidant and anti-platelet properties. A recent review of four randomised controlled studies showed only a small positive effect on cognition and no consistent benefit on ADL, function, and behaviour.⁵³ Although adverse effects are not common, two case reports of serious bleeding have been reported.⁵³ Overall, ginkgo biloba is not recommended for the treatment of AD.

Antipsychotics

For troublesome aggression or in association with severe hallucinations, antipsychotics are often prescribed. Traditional antipsychotics like haloperidol give rise to severe extrapyramidal symptom (EPS) impairment and sedation. Falls, fall-related fractures, and worsening of cognitive function may therefore occur. Atypical antipsychotics have less EPS side-effects and may be preferred for short-term management of behaviour. In general, adverse events during short-term treatment with atypical antipsychotics are not more frequent than during placebo treatment. However, there is a concern of increased risk of stroke and death among elderly, atypical antipsychotic users with dementia.^{54,55} In an 18-month cohort study, we found no increase in mortality among Chinese elderly patients receiving long-term treatment with antipsychotics.⁵⁶ Nevertheless, as far as possible these drugs should be avoided, particularly for AD patients at high cerebrovascular risk.⁵⁴

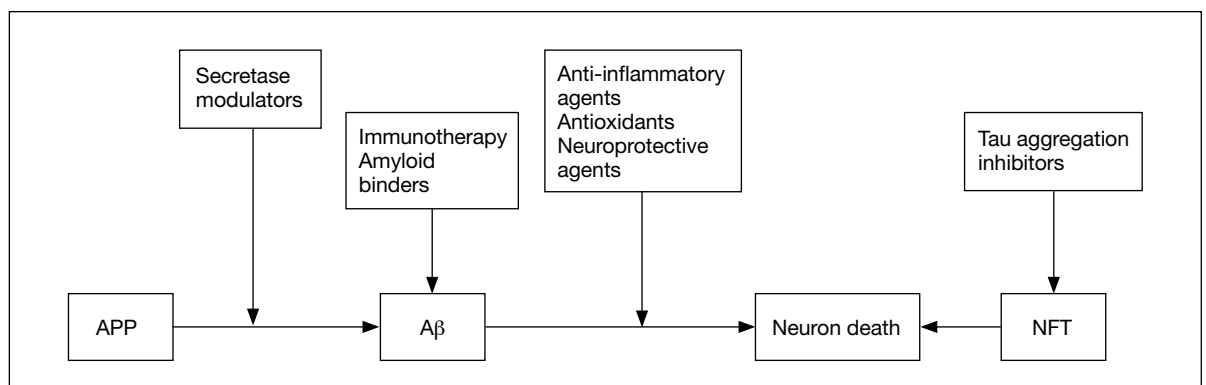


FIG 3. Research directions and strategies in the search for disease-modifying drugs
APP denotes amyloid precursor protein, Aβ beta-amyloid, and NFT neurofibrillary tangle

New strategies in the treatment of Alzheimer's disease

The current targets for disease-modifying treatment are largely based on the amyloid cascade hypothesis. Active ongoing research involves new drugs in the areas on secretase modulators, immunotherapy, amyloid binders, metal-chelating agents, anti-inflammatory agents, antioxidants, and neuroprotective agents (Fig 3). Regrettably, earlier AD treatment trials with oestrogens, corticosteroids, naproxen, ibuprofen, indomethacin, rofecoxib, tarenflurbil, rosiglitazone, xaliproden, and dimebon all yielded negative results.⁵⁷

An encouraging recent trend is the development of immunotherapy, which resulted in a reduction of amyloid plaque load in the brain. However, active immunisation (AN-1792) resulted in a serious form of encephalitis in 6% of patients.⁵⁷ Recently, Salloway et al⁵⁸ reported promising results after passive immunisation with the monoclonal antibody bapineuzumab, which resulted in cognitive benefit in the APOE 4-negative but not 4-positive AD patients. Further results of phase III trials on bapineuzumab will be available shortly. Similar encouraging results were reported from open-label use of an intravenous infusion of immunoglobulins (IVIg) that probably entails passive immunotherapy. In a previous study, Relkin et al⁵⁹ reported improvement or stabilisation of cognitive function (MMSE score) in approximately 75% of treated AD patients. A phase III clinical trial using IVIg in AD is now in progress. Other ongoing clinical trials involve a wide range of potentially useful pharmacotherapy entailing active immunisation, passive immunisation, gamma secretase inhibitors, antiaggregation and antifibrillation agents, advanced glycation end product inhibitors, tau aggregation inhibitors, and neuroprotective or neurorestorative drugs.⁵⁷ Late-onset AD is now recognised as a

multifactorial disease with multiple pathogenetic mechanisms. It is likely that a combination of several therapies targeting multiple sites may prove more useful than monotherapy.

Non-pharmacological management of Alzheimer's disease patients and psychosocial issues

Apart from drug treatments, non-pharmacological management of AD patients to improve the quality of life for both patients and caregivers is of equal importance. Caregiver stress or burnout is an important issue in AD management. Behavioural management techniques and appropriate counselling on caregiving skills should be shared with all AD caregivers. Patients with AD can be referred to dementia day-care centres. Clinicians can refer family members to join caregiver support groups, including those offered by the Hong Kong Alzheimer's Disease Association (<http://www.hkada.org.hk/ecmanage/page45.php>). The problem of mental incompetence and the possible issue of guardianship have to be discussed with the patient's family members (Guardianship Board of Hong Kong: <http://www.adultguardianship.org.hk/>). Safety issues related to wandering and poor judgement have to be considered for all dementia patients. Appropriate preventive measures (eg medic alert, personal emergency, or mobile phone alert devices) should be considered in advance. If needed, clinicians can refer AD patients and their family caregivers to medical social workers for professional psychosocial services and support.

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