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Treatment of Alzheimer's disease in New Zealand

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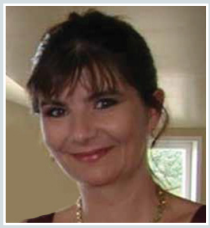

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The most common cause of dementia in New Zealand is Alzheimer's disease (AD), which results in the loss of autonomy and independence in the elderly.[1-3] Around 44,000 New Zealanders are recorded as having dementia, but the true figure is thought to be significantly higher, as up to 60% of individuals do not receive a diagnosis until late in the course of the disease, if at all.[4] The resulting "treatment gap" limits access to information, advice, treatment, care, and support. This situation worsens problems associated with the disease not only for patients, but for their families, carers and health systems. Our ageing and growing population is expected to lead to a doubling of the number of patients with dementia every 20 years, with as many as 146,000 New Zealanders predicted to be suffering from the disease by 2050.[5] The disease is associated with substantial financial liability. Around half of all New Zealanders with dementia live with family carers, affecting their ability to work, productivity in the workplace and contributions to the national economy, as well as the utilisation of treatment and support services.[5]

Some medications, including cholinesterase inhibitors and NMDA-receptor antagonists, have been found to help some symptoms of AD and slow the progression of the disease for some people for a period of time. This symptomatic therapy may be effective across the spectrum of dementia stages.[6] No cure exists for AD. New, effective therapeutic strategies are needed that alleviate and delay the adverse effects of the disease at both the individual and societal level.[7,8]

This paper is intended as an educational resource for health professionals. It presents a short background on AD in New Zealand and a review of selected peer-reviewed studies featuring medicines used to treat the condition. It is intended to help readers stay informed of developments and advancing clinical practice in the areas covered.

Alzheimer's disease

Risk factors that are associated with AD include increasing age, fewer years of education and the apolipoprotein E E4 allele.[9] Genetic predisposition is another major risk factor for AD, and most cases are polygenic, although no genetic aetiologies can be identified in many cases.[10] AD is a heterogeneous disorder with many aetiologies that involve different interactions between various genetic and environmental risk factors.[11] About 25% of all AD is familial (i.e., two or more persons in a family have AD) of which about 90% is late-onset (after age 65 years) and less than 10% is early-onset (before age 65 years).[12] Almost all cases of sporadic AD (those cases where no other cases have been seen in close family members) are late-onset.[12]

Establishing the diagnosis of AD relies upon clinical-neuropathological assessment. Clinical signs include a slowly progressive dementia, impaired memory, affective disturbance, anxiety, psychosis, and behavioural symptoms, such as aggression.[13-15] Neuropsychological features include rapid forgetting, impaired visuospatial skills, impaired naming, and no benefit of memory from recognition trials.[13-15] Neuropathological findings on autopsy examination remain the gold standard for diagnosis of AD.[16] The clinical diagnosis of AD (prior to autopsy confirmation) is correct about 80%–90% of the time.[17]

- **Clinical signs:** slowly progressive dementia
- **Neuroimaging:** gross cerebral cortical atrophy[17]
- **Neuropathological findings:** postmortem examination reveals microscopic extracellular Aβ-amyloid neuritic plaques, intraneuronal neurofibrillary tangles, and amyloid angiopathy. The plaques should stain positively with Aβ-amyloid antibodies and negative for prion antibodies, which are diagnostic of prion diseases. The numbers of plaques and tangles must exceed those found in age-matched controls without dementia.
- **Cerebrospinal fluid:** decreased Aβ amyloid 42 and increased tau.[18]

The National Institute on Aging/Alzheimer's Association Diagnostic Guidelines for Alzheimer's Disease cover three distinct stages of AD:[19]

- **Preclinical:** measurable changes in biomarkers (such as brain imaging and spinal fluid chemistry) that indicate the very earliest signs of disease, before outward symptoms appear
- **Mild Cognitive Impairment (MCI):** mildly symptomatic but pre-dementia
- **Dementia due to AD:** memory, thinking and behavioural symptoms impair a person's ability to function in daily life.

Dementia evaluation[20,21]

Evaluation of an individual for dementia should first exclude the presence of structural brain lesions that can cause dementia, such as a brain tumour or subdural haematoma; other disorders such as thyroid disease, vitamin B_{12} deficiency, and chronic infections can cause dementia. Other degenerative disorders associated with dementia, such as frontotemporal dementia including frontotemporal dementia with parkinsonism-17, Picks disease, Parkinson's disease, diffuse Lewy body disease, Creutzfeldt-Jakob disease, and CADASIL, may also be confused with AD. CT and MRI are valuable for identifying some of these other causes of dementia, including neoplasms, normal-pressure hydrocephalus, frontotemporal dementia and cerebrovascular disease.

Usually, the clinical history of AD allows it to be distinguished from other dementias. Commonly, the initial presenting symptom is progressive amnesia affecting episodic memory. This is followed by a gradual but relentless progression through successive stages of dementia severity. Disease duration is typically 8 to 10 years, with a range of from 1 to 25 years, and inevitably culminates in death. The progression of dementia is accompanied by language dysfunction, visuospatial difficulty, loss of insight, and personality changes (withdrawal, decreased initiative, and occasionally, depression). Although close friends and relatives will realise that the affected individual has deteriorated in cognitive function, the person often maintains activities in the community (including driving a motor vehicle), although generally not as well as before, and is independent in self-care. Thus, the person may appear "normal" to casual acquaintances. This early stage of mild AD dementia usually lasts from 2 to 5 years. The moderate stage (lasting 2 to 4 years) is characterised by more obvious difficulty with memory (now including long-term memory) and other cognitive functions and the loss of the ability to operate independently in the community. Functioning in routine tasks at home becomes difficult, requiring supervision or assistance with basic activities of daily living (for example, dressing, bathing, and grooming). In the severe stage of AD, individuals are totally dependent on caregivers for all activities of daily living and, in advanced disease, often become mute, nonambulatory, and unable to swallow or control bladder and bowel function.

Seven stages of Alzheimer's disease

AD symptoms vary during the course of the disease, with not everyone experiencing the same symptoms or progressing at the same rate. It is difficult to place a person with AD in a specific stage as stages may overlap. The following 7 stages provide a general idea of how abilities change during the course of the disease.

STAGE 1: ***No impairment (normal function)***

STAGE 2: ***Very mild cognitive decline (may be normal age-related changes or earliest signs of AD)***

Memory problems are only noticed by the patient, not by friends, family or co-workers.

STAGE 3: ***Mild cognitive decline (early-stage AD can be diagnosed in some, but not all, individuals with these symptoms)***

Cognitive problems are noticed by other people; there is no impact on function.

STAGE 4: ***Moderate cognitive decline (mild or early-stage AD)***

There is clear evidence of cognitive difficulties in more than one area and the person's ability to function is deteriorating.

STAGE 5: ***Moderately severe cognitive decline (moderate or mid-stage AD)***

Cognitive problems are beginning to affect all aspects of life but the person is still independent.

STAGE 6: ***Severe cognitive decline (moderately severe or mid-stage AD)***

Cognition has deteriorated such that the person now needs assistance with activities of daily living.

STAGE 7: ***Very severe cognitive decline (severe or late-stage AD)***

The person is fully dependent for all cares.

Text reprinted from the American Alzheimer's Association.

Treatment plans

Patients with dementia need a comprehensive treatment plan that includes nonpharmacological interventions – psychotherapeutic, social, and family interventions – as well as pharmacological interventions (see Table 1).[13-15] The cholinesterase inhibitors donepezil, rivastigmine and galantamine are considered to be the first-line pharmacotherapy for mild-to-moderate AD. Currently, clinical evidence is lacking in support of effective pharmacological interventions for the prevention of AD. It is thought that healthy lifestyle, ongoing education, regular physical activity, and cholesterol control all play a role in prevention of AD.

Table 1. A comprehensive treatment plan for dementia[13-15]

Biological interventions
Treatment of underlying medical disorders
Medications

Psychotherapeutic interventions
Behaviour-oriented
- Behavioural management training
- Caregiver training
- Scheduled toileting

Emotion-oriented
- Reminiscence therapy
- Validation therapy
- Supportive psychotherapy
- Sensory integration
- Simulated presence therapy

Cognition-oriented
- Reality orientation
- Skills training

Stimulation-oriented
- Recreational therapy
- Art therapy
- Exercise
- Multisensory stimulation
- Aromatherapy

Social interventions
Daytime/night-time supervision assessment
Occupational therapy functional and safety assessment
Living environment modifications
Abuse/neglect assessment
Driving assessment
Home health agency
Home cleaning service
Meals on Wheels
Financial/estate planning
Health care power of attorney/advanced directives
Long-term care facility

Family interventions
Caregiver psychoeducation
Respite care
Support groups

Cognitive deficits and noncognitive secondary symptoms present enormous challenges to patients with dementia and their caregivers. The increasing loss of independence (with a resulting need for greater care), emotional moodiness, and behaviour symptoms, may manifest in withdrawal and apathy or in so-called challenging behaviour.[22] According to NICE guidelines, patients with AD may be offered cholinesterase inhibitors for distressing behavioural and psychological symptoms, in cases where nonpharmacological approaches and antipsychotic medications have already been tried and were ineffective, or they have not been tried but are thought to be inappropriate.[22] As shown in Table 1, a broad range of nonpharmacological interventions has been developed, ranging from cognitive training,[23] music therapy,[24] sensory stimulation,[25,26] and biographical approaches[27] to training of family caregivers.[28,29] Although investigations into sensory intervention,[28,30] individualised occupational therapy[31] and behaviour therapy[32,33] appear to be promising as to efficacy, methodological procedures remain questionable. A 2006 review[34] of the effectiveness of nonpharmacological interventions for the management of neuropsychiatric symptoms in patients with dementia identified just 9 studies complying with the American Psychological Association methodological criteria, and only 3 of those studies were randomised controlled trials, all of which referred to the training of family caregivers. Furthermore, in two recent reviews, only half of the methodologically sound studies demonstrated effects with respect to psychological symptoms[35] or behavioural symptoms.[36] In all cases, the effect sizes in the effective studies were in the small to moderate range. An individually customised intervention to reduce agitated behaviour in institutionalised patients with dementia demonstrated positive effects in a cluster-randomised study in 2007.[37] Individually customised interventions appear to be particularly beneficial in severe dementia.[38] Recent evidence from German researchers indicates that a multicomponent therapy intervention known by the acronym motor stimulation, activities of daily living, and cognitive stimulation (MAKS) is associated with improvements in dementia symptoms in nursing home residents, especially in social behaviour and instrumental activity of daily living capabilities.[39]

AD medications available in New Zealand

At present, four medications are available in New Zealand for the management of AD; the orally active cholinesterase inhibitors (donepezil, rivastigmine – available also as a transdermal patch, and galantamine) and memantine, a partial antagonist of NMDA receptors. Only donepezil is funded by PHARMAC where it is available without restriction for both Alzheimer's as well as other types of dementia. Currently prescriptions for other (non-funded) AD medications cost between $100 and $200 per month, depending on pharmacy retail mark-up, dosage and the brand of medication prescribed.

Cholinesterase inhibitors (AChEI) increase the availability of acetylcholine at the synaptic cleft by preventing its breakdown by the enzyme acetylcholinesterase. Galantamine also modulates nicotinic acetylcholine receptors, and rivastigmine inhibits butylcholinesterase, but the importance of these additional properties is unknown. Cholinesterase inhibitors are indicated for mild-to-moderate AD. Cholinesterase inhibitors may help slow the progression of AD, improve cognitive ability and motivation, and reduce apathy and symptoms of psychosis such as hallucinations or delusions. Side effects may include reduced appetite, nausea, indigestion, diarrhoea, fatigue, sleep disturbance, urinary incontinence and slowing of the heart rate. Memantine is believed to act by reducing glutamate-mediated excitotoxicity. This drug is indicated for the treatment of moderate-to-severe AD. Side effects may include hallucinations, confusion, dizziness, headaches and tiredness.

While cholinesterase inhibitors and memantine provide some symptomatic relief by slowing down cognitive decline and loss of independence, they do not modify the neurodegenerative process to prevent AD progression.[40,41]

NICE Guidelines: cholinesterase inhibitors and memantine[22,42]

- Donepezil, galantamine, and rivastigmine are recommended as options for management of mild-to-moderate AD and for people with dementia with Lewy bodies who have non-cognitive symptoms that cause significant distress to the individual
- Memantine is recommended as an option for severe AD and for people with moderate AD who are unable to take cholinesterase inhibitors
- Cholinesterase inhibitors and memantine are not recommended for use in patients with vascular dementia or mild cognitive impairment except as part of properly constructed clinical studies
- Treatment should be initiated by a specialist in the care of patients with dementia, and carers' views should be sought
- Treatment should continue only if thought to be having a worthwhile effect on cognitive, functional, or behavioural symptoms
- Patients continuing with treatment should be reviewed regularly either by a specialist or according to local shared care protocols
- Assessment of the severity of AD should not rely purely on cognitive measures (such as the mini-mental state examination [MMSE])

Dosage and administration

Drug titration schedules as described by Medsafe are detailed in Table 2.

Dr Brickell tends to use donepezil as it is funded and rivastigmine patch because it is in a transdermal form and the patient does not have to swallow a pill, with slower titration schedules than those given by the guidelines:

Donepezil – 5 mg once daily for 4 weeks, then alternate 10 mg and 5 mg daily for 4 weeks, then 10 mg daily ongoing. Dr Brickell advises that patients do need to be on the maximum dose and by slowing the titration, she theorises that they will become accustomed to it.

Rivastigmine – patch 5 cm^2 for 4 weeks, then patch 10 cm^2 ongoing.

Table 2. Titration schedules for pharmacological therapies used to treat Alzheimer's disease

Drug	Pharmacological actions	Dosage	Target dosage*	Minimum therapeutic dosage†
Donepezil	Acetylcholinesterase inhibitor	Start at 5 mg once daily, taken at bedtime; after 6 weeks, increase to 10 mg once daily.	10 mg once daily	5 mg/day
Galantamine	Acetylcholinesterase inhibitor Nicotinic receptor actions	Start at 8 mg once daily with food and maintain for ≥4 weeks; an increase to the maximum recommended maintenance dose of 24 mg/day should be considered after appropriate assessment including evaluation of clinical benefit and tolerability.	12 mg twice daily	8 mg/day§
Rivastigmine	Acetylcholinesterase inhibitor Butyrylcholinesterase inhibitor	Start at 1.5 mg twice daily, taken with food; at 2-week intervals, increase each dose by 1.5 mg, up to a dosage of 6 mg twice daily.	6 mg twice daily	3 mg twice daily‖
Memantine	NMDA receptor antagonist	Start at 5 mg once daily during the first week. In the second week, the dose is 10 mg/day; in the third week, 15 mg/day is recommended. From week 4, treatment is usually continued with 20 mg/day. Memantine can be taken with or without food.	20 mg once daily	10 mg/day‡

* – Manufacturer's recommendation on the dosage that produces the best results.
† – The lowest dosage at which a statistically significant improvement in cognition over placebo was noted.
§ – This dosage can be used in patients with moderate hepatic or renal disease; galantamine is not recommended for use in patients with severe hepatic or renal disease.
‖ – If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose and titrated as described above.
‡ – A reduction in dosage to 10 mg/day is advised for patients with moderate-to-severe renal impairment; memantine is not recommended for use in patients with severe hepatic impairment.
NMDA – N-methyl-D-aspartate
Information from Medsafe Data Sheets.

Safety of cholinesterase inhibitors and memantine

A 2006 Cochrane meta-analysis reviewing the evidence on AChEI in AD showed that patients in treatment arms were more likely than those in placebo arms to report a single adverse event (number needed to harm of 7) and that donepezil was associated with fewer adverse events than the other AChEI.[40] A meta-analysis of trials of cAChEI and memantine showed that AChEI were associated with an increased risk of syncope (OR 1.53; number needed to harm=143) but not falls.[43]

Memantine is well tolerated with a side effect profile similar to placebo; a recent meta-analysis shows similar rates of withdrawal due to adverse events in memantine and placebo arms.[44]

Therapies under investigation

Clinical trials looking for alternative therapies have generally been disappointing. Trials looking at immunisation against amyloid are currently under investigation.

CLINICAL EFFICACY

Effects of FDA-approved medications for AD on clinical progression[45]

Mielke et al. began with the premise that only 40% of patients with AD on cholinesterase inhibitors and/or memantine improve (i.e., 60% of patients have no benefit on these drugs) and that these drugs have side effects. They wished to quantify medication use and benefits in a 'real world' population-based study with the aim of trying to find out if there are predictors of treatment response. They followed a cohort of 327 incident AD cases for a maximum of 9 years (average time 3 years as patients tended to die), using calculated drug exposure, gender and apolipoprotein E (APOE) as predictors of clinical progression on the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating-Sum of Boxes (CDR-Sum).

They found that about 21% of AD patients in the community take cholinesterase inhibitors or memantine; they tended to be younger, better educated and more likely to be APOE E4 carriers. Of the patients who took the medication, a prolonged duration of treatment was not associated with a better performance over time on either the MMSE or CDR-Sum. Looking at the results and focusing on cholinesterase inhibitor therapy with regards to gender, woman did better on the MMSE and CDR-Sum over time, especially if they were APOE E4-positive, while men (including APOE E4-positive) did worse over time.

Comment: In the community, many patients with AD are probably not diagnosed, and if they are, they commonly are not put on cholinesterase inhibitors. We should be more proactive in identifying people with AD, as a subgroup of these people will benefit from treatment.

Donepezil and memantine for moderate-to-severe AD[46]

295 community-dwelling patients who had been treated with donepezil for at least 3 months and who had moderate or severe AD (sMMSE 5–13) were randomised to one of 4 groups to continue treatment for 52 weeks:

1. continuing donepezil,
2. stopping donepezil,
3. stopping donepezil and starting memantine
4. continuing donepezil and starting memantine.

The primary outcomes were scores on the sMMSE and Bristol Activities of Daily Living Scale (BADLS). The minimum clinically important differences were 1.4 points on the sMMSE and 3.5 points on the BADLS.

Those patients who continued on donepezil had a score on the sMMSE of an average 1.9 points higher (met the minimum clinically important difference; 95% CI 1.3 to 2.5) and a score on the BADLS that was lower by 3 points (did not met the minimum clinically important difference; 95% CI 1.8 to 4.3) compared to those who discontinued donepezil.

Those patients assigned to memantine had a score on the sMMSE that was an average of 1.2 points higher (below the minimum clinically important difference of 1.4, with a 95% CI 0.6 to 1.8) and a score on the BADLS that was 1.5 points lower (95% CI 0.3 to 2.8, all below the minimum clinically important differences on the BADLS) compared to patients on memantine placebo.

The improvements in cognition and function associated with donepezil and memantine were small relative to the overall size of the decline in cognitive and functional status that was seen in all patients.

There were no significant benefits with combining the two drugs and the efficacy of donepezil and of memantine did not differ significantly in the presence or absence of the other. Memantine was associated with a significantly smaller worsening of the Neuropsychiatric Inventory scores.

Comment: This study originally planned to recruit 800 patients but the sample size was subsequently adjusted to 430, which the study researchers still felt gave them enough power to make conclusions. I do not think this reduction in number is important, because if a difference cannot be detected using 430 people, then the differences being looked for are very small and not likely to be clinically significant. The trial was also troubled with a high dropout rate.

The results suggest that donepezil is beneficial in moderate-to-severe AD patients on the sMMSE scale and that patients with moderate dementia (sMMSE 10–13) have more benefit than patients with severe dementia (sMMSE 5–9). Conversely, the stopping of donepezil in patients with severe disease (1.3 points; 95% CI 0.2 to 2.4) did not have as much effect as discontinuing in those with moderate disease (2.6 points; 95% CI 1.5 to 3.7). All these are small with regards to the overall decline in the patients.

There is also a range of benefits, suggesting that the drugs work better for a subgroup of people than in others but the benefits are small with regard to the overall decline in cognition and function. There is no apparent benefit of adding memantine to a cholinesterase inhibitor for 52 weeks, so using monotherapy with a cholinesterase inhibitor is acceptable.

The study didn't comment on the secondary hypotheses of whether continuing the medications would be more cost effective than stopping them and that those who continued would be institutionalised later than those who stopped the drugs, as per the DOMINO-AD protocol published online 2009 July 24, doi: 10.1186/1745-6215-10-57. These are important outcome measures that do need to be addressed.

Efficacy and safety of donepezil in patients with more severe AD: a subgroup analysis from a randomised, placebo-controlled trial[47]

This study evaluated the benefit of donepezil in post hoc analyses of a subgroup of patients with more severe AD with an sMMSE score 5–12. These patients were all living in the community or in assisted living facilities, they were all ambulatory or ambulatory when aided with a walker or cane, and they received either placebo or donepezil for 24 weeks. The treated group of patients did better than the placebo group across global, cognitive, functional and neuropsychiatric measures, with the most sensitive measure being the Severe Impairment Battery. The mean treatment difference was 0.7 at week 24 last observation carried forward for the Clinician's Interview-Based Impression of Change (a 7-point scale). Donepezil was also well tolerated in the patient population.

Comment: This is another study that suggests patients with severe AD who are still living at home or with some support and who are mobile should be considered for treatment with cholinesterase inhibitors.
This study made the comment that the neuropsychiatric manifestations were markedly improved on donepezil treatment – this is important, as often it is these symptoms that prevent a patient from remaining safely at home. If these symptoms improve, then the caregiver will be able to continue looking after the patient at home. Once again, if the risk benefit ratio of the patient favours treatment, then it should be considered.

Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of AD: a systematic review and meta-analysis[48]

Hansen et al. searched MEDLINE, Embase, The Cochrane Library and the International Pharmaceutical Abstracts from 1980 through July 2007 looking for placebo-controlled and comparative trials assessing cognition, function, behaviour, global change, and safety. They found 33 articles on 26 studies.

Overall, the studies suggest that all the cholinesterase inhibitors have a modest benefit for AD, favouring treatment. The data on which drug is best is conflicting and there was no double-blinded head-to-head trial found funded by an independent investigator. Only 4 trials were found, and of these, 3 were open-label.

On average, across all the included trials, 76% (95% CI 70% to 81%) of participants randomised to active treatment reported at least one adverse event, most of which seemed to be related to the cholinergic side effects (nausea, vomiting, diarrhoea, dizziness, weight loss). Donepezil had the lowest side effect rate and rivastigmine the highest. Overall, 26% of participants randomised to active treatment withdrew from trials, approximately half of these patients withdrew specifically because of adverse events – this was lowest among donepezil trials (similar to placebo) and highest among rivastigmine trials – there is considerable heterogeneity within the data.

Comment: The results are consistent across the drug trials favouring treatment – the benefit is modest with a range of responses. This review again supports the contention that patients with AD should be offered treatment if it is clinically appropriate and that any of the 3 cholinesterase inhibitors are effective.

As donepezil is subsidised by the Government, then this is the drug I would recommend as first-line treatment. If an oral route is inappropriate, then self-funding rivastigmine is a viable alternative, as it comes in a patch formulation, as long as the patient is able to afford it.

Overall conclusions with regards to these medications and take home messages
– Dr Kiri Brickell

Once a patient has developed AD, all patients who are independent and living at home or in a rest home with some support should be considered for cholinesterase inhibitor treatment when the risk benefit assessment is thought to be positive. All the cholinesterase inhibitor drugs are considered to have similar benefits. If a patient cannot tolerate a cholinesterase inhibitor, then memantine is an alternative, although this medication is not subsidised.

I do not think these drugs should be offered in patients who are dependent on all cares and who have lost their mobility such as patients with severe AD in private hospitals, as the medications do come with real and significant side effects. The benefit of these drugs can be small and may not be clinically significant in all patients. These medications are not a 'magic bullet' and they are not lifesaving or disease-modifying. It is thought that only about 40% of patients benefit from these medications. It is important that the patient should have a formal diagnosis of AD and the prescriber should know why they are treating the patient.

If the assessment is that the side effects of the medications outweigh the benefits of the drug, then the medications should not be prescribed. The "missing out" of the cholinesterase inhibitor benefit is very small and there is no guarantee that the patient will receive benefit once the medication is started. Once the cholinesterase inhibitor is started, the patient needs to continue because of the suggested deterioration once the drug is stopped.

Lifestyle is a very important way to modify the risk for AD. The pathological process begins decades before the development of cognitive decline heralding the onset of AD. Everyday things such as exercise, good nutrition (such as fish, nuts, Mediterranean diet), ongoing cognitive stimulation and social activity beginning from an early age, and the addressing of cardiovascular risk factors such as hypertension, hypercholesterolaemia, obesity, and diabetes are essential in the early stages of AD, as these can modify the risk factors that contribute to AD. And best of all, they are free of side effects.

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